Leading article – Tropical infection of the gastrointestinal tract and liver series

Enterobius vermicularis infection

Enterobiasis (threadworm, or pinworm disease) is caused by the small nematode *Enterobius vermicularis*.[1 2] It is by no means limited to the tropics. It is probably the most common helminth to infect humans; prevalence rates of up to 100% have been recorded in north western Europe and the USA.[1 2] *E vermicularis* eggs have been visualised in a coprolite carbon dated to 7837 BC at western Utah.

While usually considered a nuisance, rather than a cause of serious disease, morbidity (especially in children) is significant. In an uncomplicated case, treatment is straightforward; however, elimination of the parasite from a family group or institution often poses significant problems – either because of incomplete cure, or reinfection.

Infection usually occurs by ingestion of eggs by contaminated hands, food, and less commonly water. Local irritation caused by migrating worms (or their eggs) produces the classic symptom – that is, pruritus ani. Further spread to the environment from finger contamination and autoinfection follows local scratching.

Epidemiological aspects

One estimate puts the total number of subjects infected at one billion.[3] Infection is most common in young schoolchildren (5–10 years) living in overcrowded conditions (it is unusual at <2 years); rates of infection of 80–90% have been reported at summer camps and various institutions. Sex incidence is equal. No social class is exempt, although personal hygiene and exposure to infected subjects is important. Transmission within families of infected children is common; handling of children's clothing or bedding can convey infection. High rates have been recorded in homosexual men[2 4]; there are no data suggesting this to be an 'opportunist' infection in the presence of HIV infection.

At Basrah, Iraq, 624 children were examined[5]; 56 infections were recorded (9%), most being in those <5 years old. Eighty five (4·2%) of 1167 faecal samples from 0·6–6 year old children at a hospital in Riyadh, Saudi Arabia yielded *E vermicularis*[6]; however, examination of faecal samples produces a low yield. In south western Puerto Rico, only two positive results were recorded in 852 faecal samples examined.[7] In Macao City, Taiwan (also using faecal samples), 39 (0·3%) of 1309 children were infected.[8] In a south Indian fishing community, infection rate was 74·3%[9]; after mass anthelmintic chemotherapy, some subjects reacquired a significantly higher level of infection, compared with others.[10] Figures are also available for prevalence in Malaysia.[11] Clearly, British, and other travellers to an unsophisticated developing country environment are often exposed to infection.

Pathogenetic mechanisms and pathology

E vermicularis (originally *Oxyuris vermicularis*) was probably first visualised by Linnaeus in 1758. It is normally confined to humans, although related species can infect other animals including chimpanzees, gibbons, and marmosets. In the United Kingdom and France *E vermicularis* lives sympatrically with a newly identified species, *E gregorii*[12]; the fact that the second organism was readily detected in a group of Liverpool University students suggested that both species are probably widespread in the United Kingdom.

Adult females measure 9–12 mm×0·5 mm. There are three labia, and a lateral pair of cephalic wing like alae; the muscular oesophagus terminates in a bulb and the posterior tip is attenuated. The reproductive system is T shaped; in cross section, characteristic eggs can be shown within the uteri. Adult males are smaller (length 2·5 mm) possessing a ventrally curved tail, with caudal alae, and a single large copulatory spicule.

The life cycle takes place within the lumen of the gastrointestinal tract,[1 2] no visceral component exists as with hookworm and *Ascaris lumbricoides*. After ingestion, eggs hatch in the stomach and upper small intestine; larvae (140–150 μm in length) migrate to the ileum, caecum, and appendix. After moulting twice en route they become adults. Infected patients harbour few to several hundred adults. Adult females (which move at approximately 6–7 cm per 30 min) settle in the lower ileum (where copulation occurs), caecum, appendix or ascending colon; minute ulcerations form at the site(s) of attachment; haemorrhage and secondary infection produce small ulcers and submucosal abscesses. Females survive for 37–93, and males about 50 days; oviposition begins at five weeks. When the uteri are loaded with eggs, the gravid worm migrates from the colon, through the anus; while traversing the perianal or perineal skin, eggs are expelled by uterine contraction(s), death, or disintegration of the worm, and by disruption during scratching. About 11 000 ovoid, asymmetrically flattened, and almost colourless eggs (50–54 μm×20–27 μm) are produced by a gravid female. The shell contains a thick, outer, albuminous layer (which adheres to environmental objects), a thin hyaline layer, and an embryonic membrane. At oviposition, larvae are immature and non-infective; atmospheric oxygen hastens development; they become infective – at body temperature – within six hours. Egg survival is optimal at low temperature and high humidity; in warm, dry conditions, infectivity declines after one to two days. The cycle takes between two and four weeks.

Four methods of transmission exist: (a) direct infection from the anal and perianal regions by fingernail contamination (autoinfection), and soiled night clothes; (b) exposure to viable eggs on soiled bed linen and other contaminated environmental objects; (c) by contaminated dust containing embryonated eggs (from bed clothes, pyjamas, toys, furniture, and cat and dog fur). No satisfactory evidence for a canine or feline reservoir exists[13]; and (d) retroinfection; after hatching on the anal mucosa, larvae migrate into the sigmoid colon, and caecum.

In one study, 119, 305, and 5000 eggs per sq foot were detected on the walls of a school hall, classroom, and lavatory, respectively.[14]

Aberrant infections

Rarely, adult worms migrate from the female genital tract to the peritoneum; they can also enter the peritoneal cavity through a perforated bowel wall, for example, appendicitis, diverticulitis, or intestinal malignancy. Haematogenous spread is unproved. Dead worms and eggs (identifiable long

after death of the adult) surrounded by a granulomatous reaction (lymphocytes and a few eosinophils predominate) have been shown in high vagina,[15] cervix, endometrium, fallopian tubes,[3 16 17] ovary, and peritoneum. Direct migration has been recorded after abdominal operation. Eosinophilic granulomas of the colon[18 19] and omentum have been described. It has also been detected in a perianal abscess.[20] Migration to an ectopic site(s) can give rise to diagnostic difficulty.[21] Sites of ectopic infection include: the liver,[22] spleen, kidney, and lung.[23 24] Chronic pelvic peritonitis has been described. At Seville, Spain, the presence of *E vermicularis* has been recorded in a macerated embryo removed after a miscarriage[25]; eggs were recoved from the vagina and endometrium. Rare sites at which *E vermicularis* has been located, include the external auditory meatus and conjunctival sac; infection was presumably by contaminated fingers. At laparotomy peritoneal involvement can be confused with tuberculosis or metastatic neoplasia. Granulomas are often mistaken for those produced by *Schistosoma spp.*

The occasional presence of *E vermicularis* in the appendix has been recognised since 1724[3]; it has been implicated in the pathogenesis of acute appendicitis since 1907. Whether *E vermicularis* is causatively related to acute appendicitis, however, remains controversial.[22 26–30] At Bristol, England, 1419 appendixes were resected for clinically suspected acute appendicitis, and a further 110 during the course of another surgical procedure, during a five year period[26]; *E vermicularis* was present in 38 (2·7%) of the first, but none of the second; it was most common in appendixes exhibiting chronic inflammation, and histologically normal ones, but rare in the presence of histologically confirmed acute appendicitis. The authors concluded that 'although *E vermicularis* may have a causal role in appendicular pain and chronic inflammation, it is rarely related to acute appendicitis'. At Leeds, England, examination of 199 appendixes containing *E vermicularis* showed male worms in 116 and females in 20,[27] while the remainder contained mixed infections; worm sex and appendiceal inflammation were not associated. This study suggested that the eggs released from female *E vermicularis* might predispose to luminal appendiceal obstruction. At Allahabad, India, 2921 appendicectomies (all specimens were subjected to histological examination) were carried out during a 25 year period[28]; in 153 (5%) a significant pathological abnormality was reported – in 75 (2·5%) a parasite: *E vermicularis* (41), *Entamoeba histolytica* (17), *Ascaris lumbricoides* (13), *A lumbricoides* and *Trichuris trichiura*(2), and *Taenia spp* (2). Using a toluidine blue staining technique, mast cell numbers were recorded in 22 histologically normal appendixes, and a similar number of those containing *E vermicularis*[31]; correlation between presence of mast cells and infection was not significant.

A report from China has reported fatal *E vermicularis* infection in a chimpanzee (*Pan troglodytes*)[32]; the nematode was present in mesenteric lymph glands and lymphatics, and hepatic and pulmonary vasculature. The authors concluded (from histological appearances) that *E vermicularis* gained access (to these organs) by a 'lymphatic or haematogenous pathway'.

Clinical aspects

The most common symptoms are either pruritus ani or perineal pruritus. Other symptoms include: local 'tickling' and acute pain. However, most infections are asymptomatic. Other symptoms (often worse at night), include insomnia, restlessness, and tiredness; children may become anorexic, lose weight, or suffer from impaired concentration, irritability, emotional instability, and enuresis, or all of these. Nail biting and thumb sucking have been associated. Seconday (eczematous) bacterial dermatitis and folliculitis[33] are complications. There may be local skin trauma, excoriation, and secondary infection.[34] In Israel *E vermicularis* induced pruritus has been considered more common in patients with an underlying dermatological condition[35]; 18 of 25 children with either pruritus ani or vulvae had psoriasis, atopic dermatitis, contact dermatitis, neurodermatitis, or seborrhoeic dermatitis; in most no evidence of local disease in the perianal or perivulval regions was detected. Abdominal pain (including colic) has been attributed to an *E vermicularis* infection.[36]

Vulvovaginitis is a recognised sequel to vaginal migration of adult worms[37] – especially in prepubertal girls; acute urinary tract infection, enuresis, and incontinence have also been associated with infection.[23] Vaginal discharge (with or without endometritis) is recorded.[38] Transfer of *Escherichia coli* (and other coliform organisms) by *E vermicularis* (perineal scratching might induce introital colonisation), into the female bladder and urinary tract is recorded, but the frequency and importance of this event remains unclear.[39] Chronic *E vermicularis* genitourinary infection has been recorded in India[40]; a 20 year old married Muslim woman experienced 'burning on micturition and crawling sensations in her vagina and urethra', and was shown to have profuse pyuria, with eggs and larvae of *E vermicularis* in both urine and vaginal discharge; various systemic and oral antimicrobial and anthelmintic regimens failed to improve her symptoms, but local applications of a piperazine solution (see below) for eight days produced a cure. These authors concluded that the focus of infection probably lay in the vagina. Other symptoms attributed to *E vermicularis* infection include nymphomania, keratoconjunctivitis, abdominal pain, nose picking, tooth grinding, and nightmares[14]; few investigators have recorded such exotic or bizarre symptoms.[23]

Parents (especially mothers) can become distraught at the thought that their child suffers from 'worms'.

Diagnostic methods

Diagnosis is dependent on accurate identification of adult worms or eggs, or both – which can be visualised in the perianal region (or less often vagina), usually at night.[41] Application of a strip of 'Sellotape' to the anus is of value; when adherent (sticky side downwards) to a microscope slide, visualisation of worms and eggs is straightforward (debris is cleared with a drop of toluene). The procedure is best carried out shortly after waking – before defecation or bathing; the buttocks are spread and the tape pressed several times against anal or perianal skin. Repeat investigation (on separate days) gives a higher yield of positive results. Three swabs detect 90% of infections; six consecutive negative results on separate days virtually excludes this diagnosis. Other diagnostic systems (using a glass or wool applicator, or cellophane) (some may be sent to the laboratory by post) are available; for example, Sterile pinworm collector, Starplex Scientific, Mississauga, Ontario, which uses a transparent adhesive strip and is examined microscopically after being placed across the anus. Eggs may also be detected in perianal scrapings or swabs, or from beneath the fingernails. At Cairo, Egypt, a 'modified perianal oil swab' technique was shown to be superior to several other methods[42]; after perianal swabbing adhesive Sellotape was applied, fixed on a clean glass slide, a drop of cedar oil added, and examination carried out under low power magnification.

Routine examination of a faecal sample gives a positive diagnosis in 5–15% of infected subjects. Faecal material obtained at rectal examination occasionally gives a positive result (see above); after mixing with normal saline, the specimen is examined under a coverslip. In a heavy infection, female worms may be adherent to a faecal bolus. Adult worms are occasionally visualised during colonoscopy.[43]

Rarely *E vermicularis* eggs are found incidentally in a Papanocolaou stained vaginal smear, or urine[40 43]; in a report from Kenya *E vermicularis* was shown in urine specimens obtained from three girls aged 5, 7, and 10 years.[44] Infection is not accompanied by a peripheral blood eosinophilia or iron deficiency anaemia.

Treatment of *E vermicularis* infection

The Table summarises some effective chemotherapeutic agents[45]; reinfection must be prevented during treatment. Careful handwashing and finger (nails must be kept short) scrubbing after defecation and before meals is essential. Ideally, bed covers, sleeping garments, and hand towels should be changed daily and the bedroom floor kept clean. Children should wear gloves while asleep. Eradication from a family circle may prove very difficult; repeated courses of chemotherapy (for up to a year or more) are sometimes necessary. An asymptomatic infection in another family member(s) (often a small child) can serve as a reservoir of infection; therefore, all should be treated simultaneously. In a geographical area with a high prevalence of infection, for example, southern India, chemotherapy at frequent intervals has been shown to achieve a longterm reduction within the community.[9] An antipruritic ointment often produces symptomatic relief.

The benzimidazole compounds (which inhibit microtubule function in the adult, and cause glycogen depletion) are most effective. Single dose mebendazole is usually effective; a repeat dose one week later is often recommended. It is poorly absorbed, and luminal concentration is high; there are no serious side effects, although abdominal pain and diarrhoea have been recorded. Results using albendazole – available in the United Kingdom on named patient basis only – is more effective (see below). Teratogenicity has been reported in some experimental studies, and these compounds are not therefore recommended during pregnancy.

Alternative chemotherapeutic agents (Table) are piperazine, pyrantel embonate, and viprynium (pyrvinium) embonate. In Peru, ivermectin has produced an 85% cure rate.[46] In Iraq, a herbal remedy – *Artemisia herba alba* extract – proved useful.[47]

Comparative trials of chemotherapeutic agents have been recorded.[1 2] In Egypt, 13 (81·5%) of 16 cases were cured with single dose mebendazole, compared with only 10 (62·5%) of 16 using piperazine.[41] In India, 58 (60%) of 97 patients responded to single dose mebendazole, and 95 (96%) of 99 were cured with pyrantel.[48] In a multicentre trial with 141 patients carried out in several different countries, albendazole produced a 100% cure.[49] A similar result was reported in 29 children in Brazil[50]; others have also reported a 100% cure rate.[51] Although the most effective chemotherapeutic agent, albendazole is not readily available in several countries (United Kingdom included).

Choice of chemotherapeutic agent in pregnancy has received attention.[51–53] When immediate eradication is important or natural cure (by scrupulous attention to personal hygiene, etc), or both unlikely, piperazine seems a reasonable choice; however, whenever possible this should be delayed until at least the second trimester. Parents, especially of young children, should be reassured that *E vermicularis* infection does not constitute a serious disease.

Some chemotherapeutic agents in use for E vermicularis *infection*

Drug	*Dose**	*Toxicity*
Mebendazole	100 mg	Abdominal pain/diarrhoea (rarely); contraindicated in pregnancy
Albendazole†	400 mg (or 10–14 mg/kg)	Abdominal pain/diarrhoea (rarely); contraindicated in pregnancy
Piperazine‡	Expressed as hydrate. Adults and children over 12 years 2 g; children <2 y, 50–75 mg/kg; 2–4 y, 750 mg, 5–12 y, 1·5 g Once daily for 7 days. Piperazine preparations are available for 'over the counter' treatment	Neurotoxicity, cerebellar ataxia, vomiting, diarrhoea, urticaria, tremor, dizziness, visceral disturbances, weakness; contraindicated in renal and liver disease and epilepsy
Pyrantel embonate	10 mg/kg (maximum 1 g). Repeat 6 weekly	Nausea, vomiting, diarrhoea, cramps, headaches, dizziness, drowsiness, transient rise in transaminase concentrations
Viprynium (pyvinium) embonate	5 mg base/kg (maximum 350 mg)	Nausea, vomiting, cramps, stains garments and skin

*A second dose after one to two weeks is often necessary. In recurrent or 'resistant' infections, repeat chemotherapy every two months is occasionally needed; in those subjected to constant exposure, for example, schoolchildren and teachers, a repeat dose every two to four months has been advocated. †Available only on a named patient basis. ‡Should not be used concurrently with a phenothiazine.

Control and prevention

Prophylaxis is dependent primarily on personal hygiene and cleanliness of living quarters (see above). As with head lice, the stigma attached to an *E vermicularis* infection is unjustified; infection occurs in the highest strata of society in which standards of hygiene, nutritional status, etc, are excellent. An increase in public health education might eventually erode the barrier. Meticulous attention to hygienic measures, especially in childhood, reduces the prevalence of *E vermicularis*, but also a potentially more serious infection – *Toxocara canis* – for which dogs form an important reservoir.[13]

Household detergents exert little impact on viability of *E vermicularis* eggs; cleaning a bathroom using a damp cloth moistened with an antibacterial agent or bleach merely spreads viable eggs.[54] Simple laundering of clothes and linen disinfects them; shaking disseminates infective eggs. Food should be covered to limit contamination with dust borne eggs.

Child sexual abuse is currently headline news; therefore, an increase in awareness of the importance of *E vermicularis* infection in the production of anal and vulval symptoms is of paramount importance.[54]

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