

Review Article

Hookworm infection: A neglected tropical disease of mankind

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ABSTRACT

Hookworm infection, a global problem of human, is caused by both *Ancylostoma duodenale* and *Necator americanus*. These parasites are considered as important blood feeding nematodes. Hookworm is usually prevalent among the people who live with low socio-economic status. However, this tropical disease is neglected in most cases. This review was aimed at investigating the insights of hookworm infection of human considering its epidemiology, pathogenesis, clinical manifestation, diagnosis, treatment, immune mechanism, prevention, and control. This study showed how hookworm infection poses a global burden and infects 438.9 million people around the world annually, and causes significant morbidity among the children and adult in endemic countries. Also, this review discussed how hookworm infection threatens the mankind causing serious health hazards.

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KEYWORDS

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INTRODUCTION

Hookworm infection which is caused by both *Ancylostoma duodenale* and *Necator americanus* are blood feeding nematode ([Yulan et al., 2009](#)) which has been documented globally, especially in people tropics with low socio-economic status ([Halpenny et al., 2013](#); [Furst et al., 2012](#); [Bethony et al., 2006](#)). Among the parasites soil-transmitted helminths (STHs) group hookworm is predominant. In an estimation reported 438.9 million people ([Pullan et al., 2014](#)) around the world are infected with hookworm and in Africa, Pacific Islands, India, Asia, America and Caribbean 576 million people infected by hookworm ([de Silva et al., 2003](#)). Nowadays hookworm infection is among the most important tropical diseases in humans; the use of disability-adjusted life years as a quantitative measure of the burden of disease reveals that this infection out ranks African trypanosomiasis, dengue, Chagas disease, schistosomiasis and leprosy ([Hotez et al., 2003](#)). Several studies ensured its continuous existence in Bangladesh ([Khair et al., 2016](#); [Hossain, 2015](#); [Sultana et al., 2012](#); [Gilgen et al., 2001](#)). *N. americanus* is more prevalent than *A. duodenale* ([Jiraanankul et al., 2011](#)). Children and pregnant women are at risk of hookworm infection ([Liabsuetrakul et al., 2009](#)). Human acquires hookworm infection via infective larvae (L₃) which penetrates intact skin ([Yulan et al., 2009](#); [Liabsuetrakul et al., 2009](#); [Tomono et al., 2003](#)). The larvae migrate to the heart and lung and then move to trachea whereby they have been swallowed. After two molts, larvae develop into blood feeding adult worms; whereas the female worms start to produce eggs that are excreted out through feces ([Cline et al., 1984](#), [Maxwell et al., 1987](#)). The eggs hatch in moist soil and produce larvae that develop into the L₃ stage and after two molts complete life cycle ([Craig and Scott, 2014](#)).

The hookworm infection mainly causes anemia, hypoalbuminemia and malnutrition, intellectual, cognitive impairment and stunted health of children ([Jardim-Botelho et al., 2008](#); [Bethony et al., 2006](#); [Brooker et al., 2006](#); [Ekiz et al., 2005](#); [Hotez et al., 2004](#)) and in pregnant women anemia supported by hookworm ([Ndyomugenyi et al., 2008](#)). Hookworm infection controlling was neglected worldwide because of its asymptomatic nature. Nowadays the control of hookworm infection is not beyond reach because of feasible and cost effective techniques are available. Periodic anthelmintic taking like benzimidazole anthelmintics is the main intervention strategy ([Hotez et al., 2005](#); [Bundy et al., 2005](#); [Awasthi et al., 2003](#)) and also need to pay heed on sanitation and hygiene ([Hossain et al., 2016](#); [Hossain and Bhuiyan, 2016](#); [Gruber et al., 2013](#); [Bartram and Cairncross, 2010](#)). Understanding

where at risk populations live is important for appropriate resource allocation and cost effective control. Particularly, it allows for reliable estimation of the overall drug needs of programs and efficient geographical targeting of control efforts ([Brooker and Michael, 2000](#)). Deworming programs at school level could efficiently help in the reduction the hookworm infection in children ([de Silva et al., 2003](#)) but could miss positive adult cases. Considerable efforts need to develop vaccine against hookworm and thus far more than 20 proteins have been explored as potential vaccine antigen targets ([Bungiro and Capello, 2004](#); [Hotez et al., 2008](#)). However, there is still a long way to go before an effective hookworm vaccine might eventually become available. Metabolic profiling pursues a systematic biological approach and can deepen our understanding of metabolic responses of an organism to stimuli, such as disease, physiological changes and genetic modification ([Nicholson et al., 1999](#)). This review will be focused on recent research on updated diagnosis techniques for hookworm detection and immunologic mechanism thought to be responsible for infection along with epidemiology, pathogenesis, clinical manifestation, diagnosis, treatment, prevention, and control.

ETHICAL APPROVAL

This whole study was approved by the Ethical Committee for public health research of Sylhet Agricultural University, Sylhet-3100.

GEOGRAPHICAL DISTRIBUTION

Hookworm is one of the important parasite of the soil-transmitted helminths group. Thus approximately one-half of the people of Southeast Asia living in poverty have one or more soil-transmitted helminths infection ([Hotez et al., 2015](#)). *Necator americanus* is the prevalent hookworm globally, but in some endemic areas where *A. duodenale* is predominant ([Hotez et al., 2004](#)). The distribution of worm burdens among different human hosts is highly over dispersed so that often only 10 percent of the infected population carries 70 percent of the worms ([Bundy, 1995](#)).

The endemic areas for *N. americanus* includes China ([Hotez, 2002](#)), India ([Yadla et al., 2003](#)), Asia, Central and South America ([Hotez et al., 2003](#)) (**Figure 1**). Coastal site of these areas are predominantly involved with *Necator* infection ([Lwambo et al., 1992](#)).

A. duodenale is prevalent in some provinces of China (Anhui, Sichuan Provinces) and India (Kanpur). *A. duodenale* have the capability to remain viable in odd

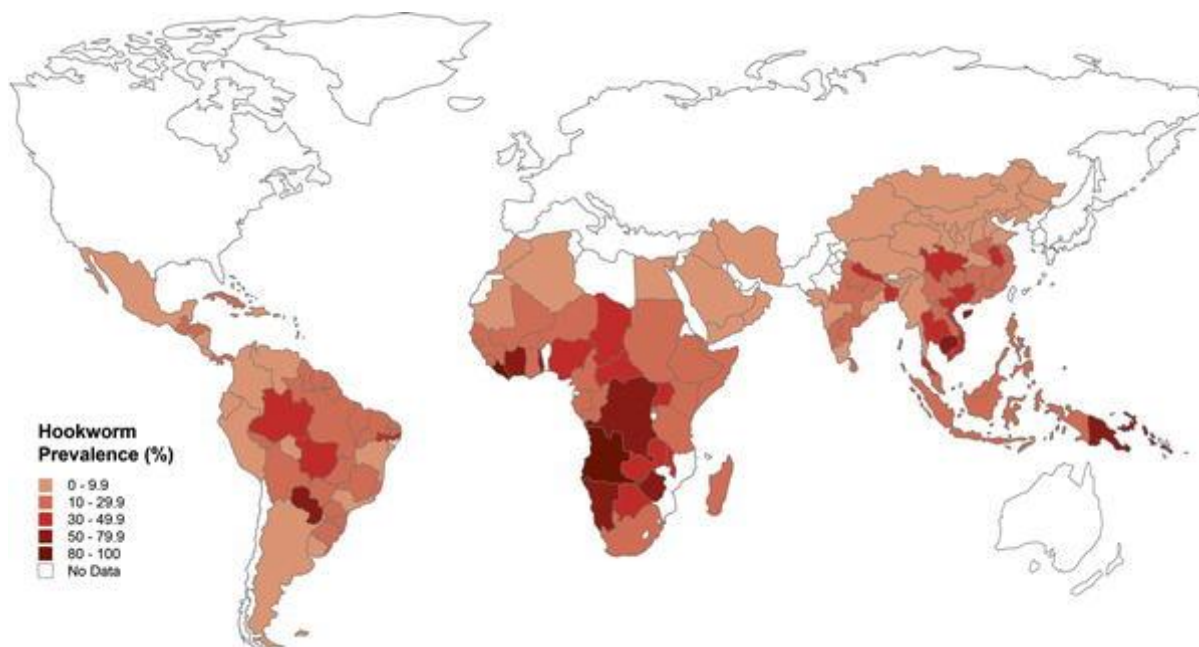


Figure 1: Global distribution of human hookworm infection [Illustration: Margaret Shear, Public Library of Science, adapted from ([de Silva et al., 2003](#))]

climates due to their undergoing ability of arrested larval development during desiccation or extreme hot. Hookworm infections also occur prevalent in some other parts of the world like Egypt, Australia and Latin America ([Labiano-Abello et al., 1999](#)), other regions like Peru and El Salvador, and Honduras ([Knight et al., 1981](#)).

HOST RANGE

There was belief that *N. americanus* is only can infect human beings but it also recovered from some other non-human primates ([Orihel, 1971](#); [Michaud et al., 2003](#)). In a finding, showed pig acts as the transport host for *N. americanus* ([Steenhard et al., 2000](#)). *A. duodenale* is the only significant human hookworm. *Ancylostoma ceylanicum* parasite of cat is infective to human as a zoonosis in Asia but it was not involved with blood loss in humans ([Carroll and Grove, 1986](#)), and it was remain as less important pathogen ([Hotez, 1996](#)). High proportion of cases with *A. ceylanicum* infections, an unique zoonotic hookworm infection found in ASEAN countries, especially Malaysia, Thailand, Cambodia and Lao PDR ([Nguu et al., 2012a, b](#)). The hookworm like *A. caninum* of dog can cause cause both eosinophilic enteritis and aphthous ileitis syndromes in human of Australia ([Landmann and Procriv, 2003](#)). The usual natural information of zoonotic *A. caninum* infection was extensively reviewed and was not found any significance to think of it further ([Procriv, 1997](#)). There is evidence

that some persons are predisposed to a heavy (or light) hookworm burden owing to either genetic or exposure factors ([Quinnell et al., 2001](#); [Williams et al., 1997](#)).

EPIDEMIOLOGICAL PATTERNS BY AGE AND SEX

Six month old children also can be infected with hookworm ([Brooker et al., 1999](#)). The prevalence of hookworm infection rises as age increasing ([Shiferaw and Mengistu, 2015](#); [Abossie and Seid, 2014](#); [Wegayechu et al., 2013](#)). Interestingly, the current information from studies in China and Asia suggest that highest prevalence is observed among the middle aged and even individuals over 60 years age ([Sengchanh et al., 2011](#); [Lili et al., 2000](#); [Gandhi et al., 2001](#); [Bethony et al., 2000](#)). Which is in contrast, it appears there is a noting variation in the age of host ([Bundy and Keymer, 1991](#)). In few areas like Africa, convex age intensity profiles for hookworm infection are observed ([Udonsi, 1984](#); [Behnke et al., 2000](#)) contrarily while in China intensity continues to rise throughout life and which is highest among the elderly ([Gandhi et al., 2001](#); [Bethony et al., 2002](#)).

In China and Malaysia, the hookworm burdens increases with age ([Ye et al., 1994](#); [Al-Delaimy et al., 2014](#)). This investigation find out the elderly are at higher risk of infection. Male is more prone to hookworm infection than female ([Bundy, 1988](#)) which was influenced by reflects of immune-suppression associated with male sex hormones ([Poulin, 1996](#); [Moore and Wilson, 2002](#)).

Occupation is an important risk factors for this worm infection and exposure to the sources of infection is proportional to infection rate, as male are involved in agricultural work so they are likely to get more infection than female ([Khair et al., 2016](#); [Behnke et al., 2000](#)). When male are getting incorporation of soil and get the touch of human stool as they try to increase the strength of house structure. Conversely, in few areas like China ([Sengchanh et al., 2011](#); [Gandhi et al., 2001](#); [Bethony et al., 2002](#)) and Vietnam ([Needham et al., 1998](#)) females shows prevalent of hookworm infection and intensities as elderly women are involved in soil work ([Humphries et al., 1997](#)). However, sex is not a parameter to judge infection intensity as occupational exposure is contributing in hookworm infection ([Abossie and Seid, 2014](#); [Gandhi et al., 2001](#); [Bethony et al., 2002](#)).

RISK FACTORS

Agent factors: Hookworms are parasites of under the family belonging to Ancylostomatidae, which is the part of Strongyloidea superfamily. The two important genera which infects human are Ancylostoma and Necator which are identified by their cutting plate or teeth ([Hotez, 1996](#)). *A. duodenale* and *N. americanus* is very host specific and occurs frequently in tropical areas ([Beaver et al., 1984](#)). Arrested larval development can be continued in soil even though there is no provision of larvae warmth, moisture and shade ([Brooker et al., 2004](#)). The surface protein of the organism is supposed to be antigenic and causes infection. The WHO identifies 2000-3999 eggs per gram of feces as moderate intensity of infections and 4,000 or more eggs per gram as heavy intensity infections ([Montresor et al., 2002](#)). Whereas the intensities for the former peak in childhood and adolescence, hookworm intensity usually either steadily rises in intensity with age or plateaus in adulthood ([Hotez et al., 2004](#); [Bethony et al., 2002](#)). The actual base of this findings is not known ([Olatunde and Onyemelukw, 1994](#)).

Household, socio-economic and occupational risk factors: As the transmission of hookworm engages contamination of the environment by hookworm eggs, it is expected that risk factors for infection may include poor personal hygiene ([Chin et al., 2016](#); [Strunz et al., 2014](#); [Traub et al., 2004](#); [Asaolu and Ofoezie, 2003](#); [Gunawardena et al., 2005](#)), low educational attainment ([Mihreshahi et al., 2009](#); [Liabsuetrakul et al., 2009](#)) and household sanitation ([Ensink et al., 2005](#)) and unfinished house floor ([Soares Magalhaes et al., 2011](#); [Pullan et al., 2010](#)), which is affected by socio-economic status ([Halpenny et al., 2013](#); [Furst et al., 2012](#); [Balén et al., 2011](#); [Brooker et al., 2004](#); [Traub et al., 2004](#)). Few studies have been demonstrated that hookworm

infection is associated with no facility of of hygienic toilet ([Hossain, 2015](#); [Wang et al., 2012](#); [Olsen et al., 2001](#); [Chongsuvivatwong et al., 1996](#)) and poor socio-economic status ([Holland et al., 1988](#)) (**Figure 2**). A study in Kenya showed that variation in household income and education level of the head of household were not associated with any helminths infection ([Olsen et al., 2001](#)), conversely a study in Nigeria exposed level of education is associated with hookworm infection ([Adeniyi et al., 2015](#); [Quihui et al., 2006](#); [Nematian et al., 2004](#)). The families who are involved in the use of feces as fertilizer in agricultural land, they got higher rate of infection ([Humphries et al., 1997](#)) and among vegetable growers and farmers ([Kirwan et al., 2009](#); [Conde et al., 2007](#); [Hotez et al., 1997](#)). As feces are used frequently as fertilizer they influences high level of infection by hookworm ([Schad et al., 1983](#)). Foot ware is also risk factors for hookworm infection ([Sandy et al., 2014](#); [Alemu et al., 2011](#); [Ratnayaka and Wang, 2012](#)) because walking in barefoot have high chance of hookworm infection ([Shiferaw and Mengistu, 2015](#); [Abate et al., 2013](#); [Alemu et al., 2011](#)). For example, in India, Bangladesh and Sri Lanka, the tea garden workers are getting high rate of infections ([Hossain, 2015](#); [Gilgen et al., 2001](#)).

Seasonal and environmental factors: The environmental humidity, temperature, ultra-violet light and geographical differences are greatly influencing the transmission cycle of hookworm and some other related factors like rainfall, soil type and altitude ([Ndokeji et al., 2016](#); [Bongi and Morel, 2005](#); [Chandler, 1929](#)) also contribute in the completion of cycle. 20-30°C temperature is thought to be optimal for reaching maturity. The above of temperature 35-40°C arrests development and even death occurs ([Nwosu, 1978](#); [Udonsi and Atata, 1987](#); [Smith and Schad, 1990](#)) and at temperature of 35°C larvae of *N. americanus* become dead, even though maximum rate obtained at 30°C ([Udonsi and Atata, 1987](#)).

In the tropics the lower temperature limit is often measured by altitude, in few areas of Africa coastal plain below 150 m above sea level ([Appleton and Gouws, 1996](#); [Appleton et al., 1999](#); [Mabaso et al., 2003](#)). Above these altitudes temperatures (<20°C) limit the growth of the parasite ([Yu et al., 1995](#)). *A. duodenale* can undergo arrested development which allows its survival in odd weather during winter ([Schad et al., 1973](#)). The relationship between spatial and rainfall and the prevalence of hookworm is well documented ([Anuar et al., 2014](#); [Brooker and Michael, 2000](#)). Hookworm infection often expresses seasonality ([Khanum et al., 2014](#); [Cook et al., 2009](#)). If *A. duodenale* undergo arrested development



Figure 2: Socio-demographic status of rural communities (A-D)

during the rainy season, new infections again appear after 8-10 months (Schad et al., 1973).

L₃ larvae are available during the rainy season (Udonsi et al., 1980) in Africa and fecal egg numbers are also highest 2-7 months after the rainy season (Knight and Merrett, 1981; Nwosu, 1981). However, seasonal fluctuations have little influence to the overall persistence of hookworm populations (Anderson, 1982). Soil type is an important influencing factor for hookworm larval development and transmission (Brooker and Michael, 2000). High prevalence of hookworm was involved with well drained sandy soil (Mabaso et al., 2003; Saathoff, 2002) conversely low rate of infection was associated with clay soils.

HISTORY AND MORPHOLOGY

In 1838, Dubini provided the detail description of the worm *A. duodenale* after examining sample taken from a woman. Hookworm infections were well established in the USA and in due course the Rockefeller Sanitary Commission for the eradication of hookworm disease was established (Hegner et al., 1938; Ettlting, 1990; Crompton and Whitehead, 1993). The overall information on hookworm given in (Table 1).

Table 1: Characteristics of human hookworm infections (Crompton and Whitehead, 1993)

Traits	<i>A. duodenale</i>	<i>N. americanus</i>
Adult worm size (mm)		
Male	8-11	7-9
Female	10-13	9-11
Adult life span (years)	1	3-5
Sex ratio (M:F)	1:1	1.5:1
Pre-patent period (days)	53	49-56
Fecundity (eggs/female/day)	10000-25000	5000-10000
Optimum temp (°C) for free living larval stages	20-27	28-32
Route of infection	O, P, T	P
Arrested development	Yes	No

Based on information from Hoagland and Schad (1978) and Beaver & Jung (1985). O:Oral route; P:Percutaneous route; T:Trans-placental route. Schad and Banwell (1984) review evidence to suggest that *A. duodenale* may also exploit the trans-mammary route of infection as does *A. caninum* (Miller, 1981).

The ova of hookworms (*A. duodenale* and *N. americanus*) are alike. They are colorless and oval in shape, measuring about 65x40 µm. The eggs contain an ovum which appears unsegmented. In stool more than 12 hours old, larvae may be seen inside the egg. The L₃ stage of larvae 600 microns of length (Brooker et al., 2004).

TRANSMISSION

The highest rates of hookworm transmission occur in the world's coastal regions, where infective third stage larvae can migrate freely in sandy soils and where the temperature and moisture are optimal for viability of larvae (Mabaso et al., 2003). Direct exposure of intact skin to the filariform larvae in soil initiates transmission of hookworm and even infection (Liabsuetrakul et al., 2009; Tomono et al., 2003; Traub et al., 2004) (Figure 3). Human gets hookworm when the infective larval stage

penetrate through the skin (Reichert et al., 2016; Haas et al., 2005) (both *N. americanus* and *A. duodenale*) or when they are swallowed (for *A. duodenale*) (Zechaida et al., 2011; Olsen et al., 2009; Brooker et al., 2004). It has also been reported that *N. americanus* L₃ will invade the buccal epithelium if they enter through the mouth (Nagahana et al., 1963). Exceptionally, larvae may be transmitted through fomites. For instance, if washed clothes are dried on the ground, larvae may creep on the textile from surrounding soil, resulting in an infestation when the piece of clothing is put on (Tomović et al., 2008).

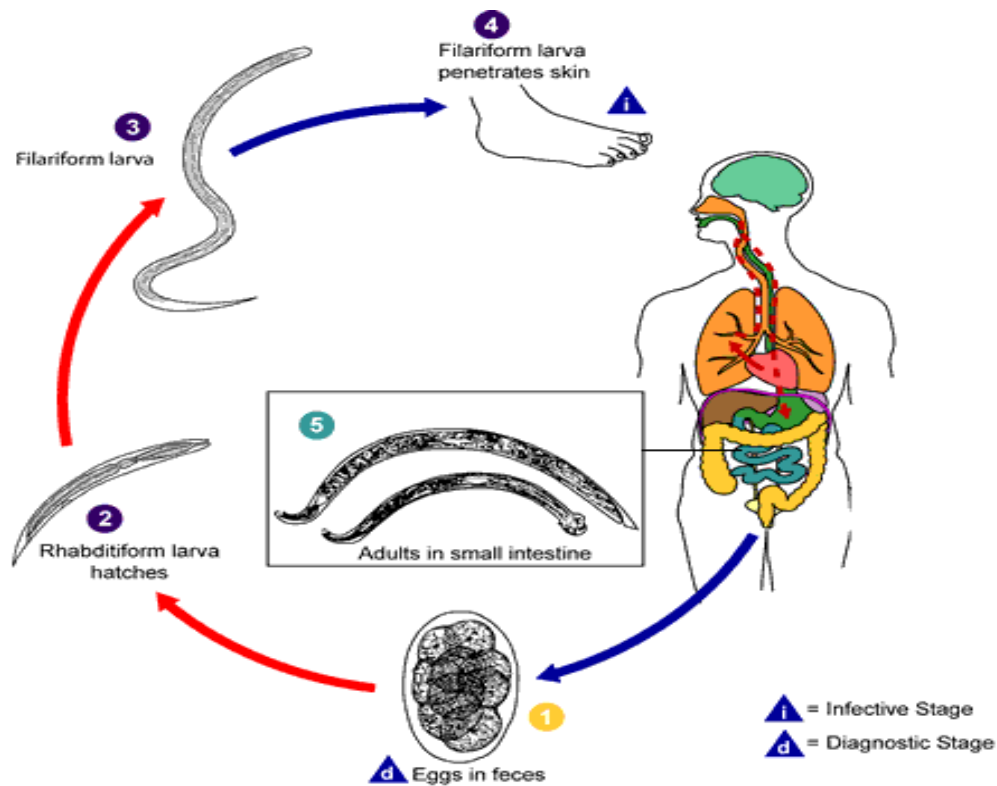


Figure 3: The biology of Hookworm (www.cdc.org)



Figure 4: More exaggerated vesicular skin eruption by cutaneous hookworm larvae (Despommier et al., 2000)

BIOLOGY OF HOOKWORM

A. duodenale life cycle was first expressed by (Looss, 1901), and *N. americanus* was identified for the first time in the Western Hemisphere (Chandler, 1929; Stiles, 1902). Hookworms follow direct life cycle (Hoagland and Schad, 1978). Hookworms remain in the SI and live on host mucosa and blood (Roche and Layrisse, 1966). Female worm produces eggs which are passed out through stool (Augustine, 1922) to be embryonated in the soil. Rhabditiform larvae grow in the soil contaminated with feces (Cline et al., 1984) and after 5 to 10 days (and two molts) they become filariform (third-stage) larvae that are infective (Cort and Payne, 1922) and feeds on organic debris and microorganisms.

When the infective larvae come in contact with skin and penetrate the skin (Logan, 2009) which further conveyed through blood vessels to the heart and then finally to the lungs. After few moult in the lung it pass down to the stomach to duodenum and take place final maturation (Craig and Scott, 2014; Maxwell et al., 1987). After entering in the host body larvae can resume its development (Hotez et al., 1993; Hawdon et al., 1996). Resumption of development can also be recovered (Hawdon et al., 2003). Of the proteins secreted by host activated hookworm larvae (Zhan et al., 2003) and which is belong to the pathogenesis (Hotez et al., 1993).

Between both hookworm species there is a major differences (Hoagland and Schad, 1978; Hotez, 1996). *A. duodenale* is larger than *N. americanus* and produces more eggs and causes high rate of blood loss (Albonico et al., 1998). Few researchers believe *N. americanus* can evade immune system and leads to parasitism (Hoagland and Schad, 1978; Pritchard and Brown, 2001). Hookworm can initiates iron deficiency anaemia (Albonico et al., 1998). Hookworm has the unique ability to undergo arrested development in body of final host (Ekiz et al., 2005; Schad et al., 1973) and during pregnancy it remain dormant in the mammary gland and initiates lactogenic transmission (Hotez, 1989; Yu et al., 1995). Neonatal Ancylostomiasis is prevalent in African and Asia (Yu et al., 1995).

CLINICAL FEATURES

Acute infection: The repeated entry of hookworm L₃ through skin result "ground itch" (Brooker et al., 2004). Sometime sleep disturbance because of intense itching (Jackson et al., 2006). This consists a pruritic erythematous papulo-vesicular rash. Ground itch seen often on the hand and feet (Figure 4). *A. braziliense* larvae results in cutaneous larva migrants appear on the

feet, buttocks and abdomen (Schuster et al., 2013; Blackwell and Vega-Lopez, 2001). Other animal hookworm such as *A. caninum* significantly causes CLM (Landmann and Prociw, 2003). The increased frequency of CLM among the travellers (Yosipovitch et al., 2002). A second form of CLM frequently associated with folliculitis (Reichert et al., 2016; Sakai et al., 2008; Caumes et al., 2002).

Following the entry of hookworm larvae into body, results respiratory problems (Miller, 1979). Circulating levels of IgE increase occurs in response to migrations of third stage larvae in the lungs and intestines (Maxwell et al., 1987). When the larval stage of hookworm enters into the gastrointestinal tract it results in epigastric pain (Anyaeze, 2003) and it causes the presence of parasitic egg in the feces (Maxwell et al., 1987). When human get *A. duodenale* infection through oral route sometimes it causes nausea, vomiting, pharyngeal irritation, cough, dyspnea (Harada, 1962).

Hypo-proteinemia caused by hookworm: The consequences of hookworm infection are loss of protein (Betson et al., 2012) by plasma as it is digested by mature worm (Smith and Schad, 1990; Albonico and Savioli, 1997). If the Hookworm burden occurs it leads to hypo-proteinemia because of continuous blood loss and sometimes it leads to edema (Hotez, 2002). If protein loss occurs because of hookworm infection it can be recovered by treatment even though it increases the chance of weight gain (Torlesse, 1999).

Hookworm induced anemia: The major clinical manifestation of human hookworm infection is intestinal blood loss (Roche and Layrissee, 1966; Miller, 1979; Crompton and Stephenson, 1990). Large scale of hookworm infections results in iron deficiency and microcytic hypochromic anaemia (Smith and Brooker, 2010; King et al., 2005; Lone et al., 2004; Beaver et al., 1984). When hookworm sucks blood via its buccal cutting plate it releases an antiplatelet agents which favors the continuous loss of blood (Stanssens et al., 1996; del Valle et al., 2003).

The hookworm ingested blood is easily digested by combined action of few enzymes (Jones and Hotez, 2002; Williamson et al., 2003a, b). A total number of 40 to 160 hookworms are good enough to cause anemia (Lwambo et al., 1992). The highest intensity of hookworm infection is associated with the burden of hookworm in the host body (Jackson and Jackson, 1987; Sill et al. 1987; Shulman et al. 1996; Egwunyenga et al., 2001). Previously hookworm was considered as the less important to cause anemia because it was thought to be

Table 2: Hookworm and loss of host blood. The data are extracted from [Holland \(1987, 1989\)](#), [Pawlowski et al. \(1991\)](#) and [Crompton \(2001\)](#) who give details of sources of information and techniques used to make measurements and estimates.

Traits	<i>A. duodenale</i>	<i>N. americanus</i>
Intestinal blood loss/mL/worm/day, mean (range)	0.15 (0.05-0.30)	0.03 (0.01-0.04)
Number (range) of worms causing a blood loss 1ml/day	5 (4-7)	25 (14-50)
Blood loss (mL/day) per 1000 epg stool mean±SD.	2.2 (1.54-2.86)	1.3 (0.82-2.24)
Iron loss (mg/day) per 1000 epg stool	4.4±2.16	2.2±1.01
Worm burden responsible for 1000 epg stool	0.76-1.35	0.45-0.65
	11	32

Table 3: Treatment of hookworm [Modified from the Medical Letter on Drugs and Therapeutics, Drugs for Parasitic Infections ([Anonymous, 2004](#)). In children of 1-2 years the dose of albendazole is 200 mg instead of 400 mg, based on a recommendation in the Report of the WHO informal consultation on the use of praziquantel during pregnancy and lactation and albendazole/mebendazole in children less than 24 months ([Kabaterine et al., 2007](#); [Koukouknari et al., 2006](#); [Montresor et al., 2003](#); [WHO, 2002](#))]

Infection	Drugs	Dose	
		Adult	Child
Hookworm	Albendazole	400 mg once	400 mg once
	Mebendazole	100 mg twice a day for 3 days	100 mg twice a day for 3 days
	Pyrantel pamoate	11 mg/kg (maximum dose 1 gm) for 3 days	11 mg/kg (maximum dose 1gm) for 3 days
	Levamisole	2.5 mg/kg once; repeat after 7 days in heavy infection	2.5 mg/kg once; repeat after 7 days in heavy infection

malaria is responsible for anemia in pre-school children ([Brooker et al., 1999](#)).

Perinatal hookworm infection: Hookworm infection consequences anemia of pregnant women causes adverse health problems like prematurity, low birth weight and impaired lactation ([Miller, 1979](#)). Lactogenic transmission to neonate has been seen in pregnant women ([Yu et al., 1995](#)). This happens because larvae of *A. duodenale* can arrest their own development in host tissues ([Schad et al., 1973](#)) and when parturition initiates larvae enter into mammary gland and become visible in milk. In neonate the hookworm infection results in profuse anemia ([Yu et al., 1995](#)).

School performance and productivity in adulthood: Heavy and longtime infection of hookworm during the period of child development causes less cognitive performance and educational achievement ([Jinabhai et al., 2001](#)). Lately, few studies observed child with hookworm infection shows poor cognitive function ([Shang, 2011](#); [Jardim-Botelho et al., 2008](#); [Watkins and Pollitt, 1997](#); [Drake et al., 2000](#)). Cognitive function problem because of anemia and retardation of growth ([WHO, 2006](#); [Grantham-McGregor and Ani, 2001](#); [Mendez and Adair, 1999](#); [Lozoff, 1990](#)). A recent study among Bangladeshi tea pluckers found that hemoglobin

and productivity of women were positively associated ([Gilgen et al., 2001](#)).

Effects of helminths in allergic patients: The global increase in allergy especially in urban areas ([Pearce et al., 2007](#)) has led researchers to a new path that when helminths infection reduces then chance of allergic diseases ([Rook, 2009](#)). A number of studies show that communities with helminths infection have reduced rates of allergy ([van den Biggelaar et al., 2000](#); [Cooper et al., 2003](#)) and the evidence that people with hookworm have less asthma problem ([Leonardi-Bee et al., 2006](#); [Flohr et al., 2010](#)) has stir up researchers to investigate a new approach to asthma patients ([Feary et al., 2010](#)). It is observed that if Th₂ response suppress by helminths it has an active influence on allergic response ([McSorley and Maizels, 2012](#)). There is another observation that if anthelmintics uses in the patients it increases the rate of allergic diseases ([van den Biggelaar et al., 2004](#); [Flohr et al., 2009](#)).

DIAGNOSIS

There is no gold standard for diagnosis of hookworm infection and diagnosis is often misunderstood or delayed because of the patients' non-specific verbal response. Nowadays widely taken samples for hookworm

diagnosis are blood and fresh stool. A great number of diagnostic methods have been compared to detect the presence of hookworm including stool examination by Harada Mori filter paper culture, Kato-Katz thick smear, sodium acetate-acetic acid-formalin (SAF) solution, ether concentration method and the FLOTAC technique and Polymerase Chain Reaction (PCR).

Direct smear: This method involves the identification of hookworm egg or larvae under microscope from fresh stool samples by normal saline, Eosin or Lugol's Iodine as emulsifying agents ([Cheesbrough, 1982](#)) and Kato-Katz smear was prepared from each and every stool sample on slides using 41.7 mg punched plastic templates ([Katz et al., 1972](#)), sodium acetate acetic acid formalin (SAF) solution ([Bogoch et al., 2006](#); [Marti and Escher, 1990](#)), ether concentration method ([Allen and Ridley, 1970](#)) and the FLOTAC technique ([Cringoli, 2006](#)).

Cultural techniques: Harada Mori culture techniques provide the morphological identification of hookworm larvae which first introduced by [Harada and Mori \(1955\)](#) then it is widely used ([Vonghachack et al., 2015](#); [Banu et al., 2013](#); [Steinmann et al., 2007](#)). This culture method better than direct saline smear and ether concentration techniques ([Sato et al., 2010](#); [Marchi and Cantos, 2003](#)). Harada Mori techniques require ten days cultivation for getting fully formed larvae.

Serology: Diagnosis of hookworm could be done by serological methods especially in patients with eosinophilia or mildly symptomatic patients. The serological methods widely used to determine the presence of hookworm antibody in the serum of the human hosts. The antibody could be determined by Enzyme Linked Immuno Sorbent Assay (ELISA) and Western Blot Analysis (WBA) ([Brooker et al., 2004](#)) as low titers of hookworm specific antibodies are noted in heavy infection along with a low or normal eosinophil count.

Polymerase chain reaction

DNA extraction: Bead beating technique a conventional method for DNA extraction ([Salonen et al., 2010](#)) from raw stool samples but now sophisticated methods like QIAGEN DNeasy Blood & Tissue Kit are developed and used widely (Qiagen Inc., Valencia, CA).

Nested and real time PCR: The nested PCR method established for detection of hookworm. DNA template which was purified was used for amplifying DNA in thermal cycler using a genus specific primer set as described by ([Yong et al., 2007](#)). The rDNA region comprising the first and second internal transcribed

spacers plus the 5.8S gene and near about 50 nucleotides of the 28S rRNA amplified using oligonucleotide primers NC5>: 5'-GTA-GGT-GAA-CCT-GCG-GAA-GGA-TCA-TT-3' (forward) and <NC2: 5'-TTA-GTT-TCT-TTT-CCT-CCG-CT-3' (reverse) designed to regions of the 18S and 28S genes, respectively ([Gasser et al., 1996](#)), and found to be conserved across a range of strongylid nematodes. A real-time PCR method developed by ([Verweij et al., 2009](#)) to detect hookworm DNA in fecal samples.

TREATMENT

Benzimidazole anthelmintics are the current corner stone of helminths treatment because of their wide range of activity against worm, low price, efficient efficacy and convenient route of administration ([Savioli et al., 2002](#)). Available anthelmintics for the treatment of hookworm are albendazole, levamisole, mebendazole and pyrantel pamoate (**Table 3**). A single oral dose of ivermectin (200 µg per kg body weight) kills the migrating larvae effectively ([Caumes, 2003](#)).

Levamisole and pyrantel pamoate have varying degree of cure and egg reduction rate ([Utzinger and Keiser, 2004](#)). The repeated round of pyrantel pamoate increases resistance to hookworm infection ([Black et al., 2010](#)). Anthelmintic treatment reduce load of hookworm infection and along with this increase unit of haemoglobin among children. Allergy of the patients misdirected anti-parasitic response of hypersensitive individuals ([Artis et al., 2012](#)). Anthelmintic treatment initiates benefits to pregnant women and children also ([Torlesse and Hodges, 2000](#)). Some other studies also reported anthelmintic treatment improves the health status of both child in the womb and bearing mother ([de Silva et al., 1999](#)). In endemic areas immediately after anthelmintic treatment reinfection occurs ([Albonico et al., 1995](#)). Treatments are required three times a year to improve the iron status of the host ([Stoltzfus et al., 1998](#); [de Silva, 2003](#)).

IMMUNE RESPONSE TO HOOKWORM INFECTION

The complex life cycle of the hookworm provides numerous benefits for both parasites and host. Helminths infections are known to exert strong immune modulatory effects on their hosts ([Danilowicz-Luebert et al., 2011](#)). Immunological responses to hookworm infection are reviewed both in human and experimental animal ([Behnke, 1991](#); [Loukas and Procv, 2001](#)) but poorly understood ([Forrer et al., 2015](#)). For example, *N. americanus* will become adult in hamsters but a wide range of changes observed in the way of their development to

adult ([Rose and Behnke, 1990](#); [Xue et al., 2003](#); [Rajasekariah et al., 1985](#); [Xue et al., 2003](#)). Likely, exogenous steroids help in the development of *A. duodenale* ([Leiby et al., 1987](#)). This variation occurs because *A. duodenale* and *N. americanus* is highly host specific ([Beaver et al., 1984](#)). Hookworm based immune therapy resulted suppression of pro-inflammatory anti-gliadin immune-response and induction of systemic and mucosal type 2 cytokine response ([Gaze et al., 2012](#)) although overt suppression of clinical disease was not observed ([Daveson et al., 2011](#)).

The immune response against hookworm infection is stimulated by the larvae and sometimes their excretory products ([Loukas and Prociv, 2001](#)); often hookworm secretory/excretory products suppress intestinal colitis ([Ferreira et al., 2013](#)). The methods used to identify antibody responses ([Sarles, 1938](#); [Otto et al., 1942](#); [Sheldon and Groover, 1942](#)). All the Ig isotypes accumulated in the site of infection to initiate immune response in naturally infected individuals ([Behnke, 1991](#); [Loukas and Prociv, 2001](#)). The biological properties of isotypes also differ ([Shackelford et al., 1988](#); [Dunne et al., 1993](#)).

The immunologic response to hookworm infection comprised of Th₂ antibody isotypes, IgG1, IgG4 and IgE where advanced concentration paid on IgE because during hookworm infection IgE in serum level increase several folds ([Jarrett and Bazin, 1974](#)). In IgE network IgE participates ([Sutton and Gould, 1993](#); [Garraud et al., 2003](#)) which activates this system against helminths ([Garraud et al., 2003](#)). The prediction for the high levels of IgE is involved in reduction in the risk of anaphylaxis ([Hagan, 1993](#)). IgE that gathered against *N. americanus* is highly specific to hookworm ([Pritchard and Walsh, 1995](#)).

In hookworm infection IgG1 and IgG4 level are increased in hookworm infection ([Palmer et al., 1996](#)) and, *A. duodenale* ([Xue et al., 2000](#)). The function of IgG4 is poorly understood ([Capron, 2011](#)). It was believed to down regulate the immune response ([Rihet et al., 1991](#)) and IgG4 is stronger among other immunoglobulin ([Geiger et al., 2011](#)).

The hookworm proteases function was reflexed mostly by IgA ([Loukas and Prociv, 2001](#)). Even though there is an extensive response to infection, but there is limited chance offers any protection ([Pritchard and Walsh, 1995](#)) reducing adult hookworm ([Hagan et al., 1991](#); [Dunne et al., 1993](#)) due to behavioral modifications ([Woolhouse, 1992, 1993](#)).

For initiating immune response to hookworm infection is eosinophilia present in peripheral blood ([Loukas and Prociv, 2001](#)) and which can be reflected in peripheral site ([Geiger et al., 2008](#); [Behnke, 1991](#)). Circulating eosinophils are functional in infected individuals ([White et al., 1986](#); [Maxwell et al., 1987](#); [Nawalinski and Schad, 1974](#)) were boosted greatly by the arrival ([Meeusen and Balic, 2000](#)). In response to IgE mast cell degranulation plays a crucial role ([Geiger et al., 2011](#)), because mast cell was thought to degrade collagens of adult necator ([McKean and Pritchard, 1989](#)). Therefore, the inherent ability of helminths to induce Th₂ responses lead to elucidation of the underlying mechanisms in lung, skin or gut ([Obata-Ninomiya et al., 2013](#); [Harvie et al., 2013](#); [Harvie et al., 2010](#)) which leads to Th₂ responses, interim mucus and fluid production increased ([Madden et al., 2004](#)). The high level of IL-10 along with other cytokines like (IL-4, IL-5 and IL-13) decline treatment ([Turner et al., 2013](#)).

Host protection to nematode infection is CD4+ T cell-dependent ([Oeser et al., 2014](#)). Hookworm antigen induces cell apoptosis by intrinsic mitochondrial pathway and induces generation of suppressor CD4+ and CD8+ T cells ([Gazzinelli-Guimaraes et al., 2013](#); [Cuellar et al., 2009](#)).

STRATEGIES FOR CONTROL AND PREVENTION

Hookworm infection removal or eradication from poor areas is difficult because of its transmission potentiality ([Brooker et al., 2004](#)). The interruption of transmission cycle is another key components of STH specially hookworm control ([Hawdon, 2014](#); [Strunz et al., 2014](#); [Anderson et al., 2014](#); [Truscott et al., 2014](#)). The current strategy to control hookworm is chemotherapy although it alone cannot remove hookworm infection ([Freeman et al., 2013](#)) but with support of health education ([Tomono et al., 2003](#)), improved water and sanitation ([Greene et al., 2012](#); [Freeman and Clasen, 2011](#); [Asaolu and Ofoezie, 2003](#)) and socio-economic status ([Mihirshahi et al., 2009](#)). Beyond saying Proper hygiene and sanitation is corner stone for control of hookworm infection ([Greenland et al., 2015](#); [Nasr et al., 2013](#)). However, feasibility of toilet facilities is involved in lowering the intensity of hookworm infection ([Sunderkotter et al., 2014](#); [Chongsuvivatwong et al., 1996](#)) and may not be completely effective. Hookworm infection and maintaining proper hygiene is crucial along with use of footwear in control strategy ([Kannathasan et al., 2013](#); [Albonico et al., 1998](#)). The long time required for improved sanitation and behavioral change to control helminths infection is chemotherapy ([Kabaterine et al., 2007](#); [Koukouknari et al., 2006](#); [Albonico et al., 1998](#)).

mentioned in (Table 3). The use of anti-hookworm vaccine with anthelmintic drugs brought benefits (Hotez et al., 2003). Promises led by the WHO have been counted in school-age children (World Bank, 2003). Treatment of potable water also can reduce the transmission of hookworm (Clasen et al., 2007).

CONCLUSION

Hookworm infection is still a topic of great concern because of its high morbidity. The public health importance is also a great concern if the hookworm infection is omitted. Interim it is warranted to investigate the risk factors involved in hookworm infection and screen patients from endemic areas prior to receiving chemotherapy. It is mandatory to highlight plethora of prevention effort in endemic countries like health education, proper sanitation, regular deworming and the use of protective footwear for reducing the occurrence of hookworm.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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AUTHORS CONTRIBUTION

M Hossain has designed the procedure of works and successfully written the whole manuscript and made all the relevant correction over the manuscript. MJU Bhuiyan thoroughly revised this manuscript and paid positive criticism to give it a quality shape.

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