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Intestinal Spirochetosis: Epidemiology, Microbiology, and Clinical Significance

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Abstract

First recognized in humans in the late 1800s, intestinal spirochetes are still poorly understood in their capacity to cause human disease. Though more commonly seen in developing than developed countries, the prevalence of intestinal spirochetosis appears to be growing in the Western world, particularly in the homosexual male and human immunodeficiency virus-infected populations. This change may also reflect increased recognition, as opposed to increased prevalence. Reported symptoms have ranged from asymptomatic colonization to watery, chronic diarrhea, abdominal pain, and fever, to the rare cases of fulminant hepatic failure and sepsis. The characteristic histological findings of a false brush border are distinctly unique, and while other methods of detection are being examined experimentally, they are not yet readily available. No specific guidelines for treatment exist. Although metronidazole is the most commonly employed means of therapy, cases of symptomatic remission have also been reported with penicillin, clindamycin, and erythromycin.

Introduction

Originally recognized as a disease of economic devastation in veterinary medicine, intestinal spirochetosis (IS) in humans and its clinical significance have been debated for years. The presence of intestinal spirochetes in human feces has been recognized since the late 1800s (1). In 1967, Harland and Lee (2) coined the term IS, recognizing adherence of spirochetes to colonic epithelium on electron microscopy, the characteristic histological appearance that is still considered pathognomonic for the disease. Despite improvements in the detection and identification of IS, it is still unclear whether this condition represents an actual disease process, or rather, the organisms represent interesting intestinal colonizers in humans.

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Epidemiology

In the veterinary world, IS has been linked to diarrheal illness in swine, poultry, dogs, cats, opossums, non-human primates, and guinea pigs. The disease causes significant economic losses when it affects large numbers of swine, leading to "porridge-like diarrhea," malnutrition, decreased food intake, and declining growth rates (3). Human disease is less well understood, though the presence of intestinal spirochetes in stool has been documented throughout Australia, India, Indonesia, and much of the Western world for decades. A large study in Chicago in the early 1900s revealed a 28% prevalence of intestinal spirochetes in the stools of healthy patients (4). Early studies in West Africa revealed close to a 100% rate of colonization by spirochetes (5). Prevalence rates in soldiers of the Western Command during the early 1900s reached 3.3% for those with previous bouts of dysentery (6).

In more recent times, the prevalence of colonization with intestinal spirochetes appears to correspond with habitation in a developing region. Prevalence rates of 32.6% are seen in Australian aboriginal children (7). Villages in India have shown rates as high as 64.3% in otherwise healthy individuals (6). A study looking at hospitalized and healthy patients in Oman found prevalence rates of 11.4 and 26.7%, respectively (8). A study in Bali in 2002 examined 992 fecal samples from people living in rural, urban, and suburban areas. In contrast to the rural predominance seen in earlier studies, prevalence in Bali varied from 3.3 to 23.4%, with the highest percentages in the suburban

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areas (9). Other studies reported rates from 1.1 to 5% in most developing countries (10-14).

The highest rates of colonization with intestinal spirochetes in developed countries are found in homosexual males and in human immunodeficiency virus (HIV)-infected individuals. In the United States, homosexual males have shown rates of colonization as high as 20.6 to 62.5% (15-17). The reason for this increased colonization in homosexual men is speculative at best but has caused proponents to ponder whether IS is sexually transmitted (17-20). For those with IS and HIV, there appears to be no correlation with degree of immunodeficiency and extent of disease (18). Colonization with intestinal spirochetes is not limited to the homosexual population in developed countries, as cases in heterosexual adults and children have been reported in the U.S., Denmark, Sweden, Norway, Japan, England, and France (7,11,13,14,16, 18,19,21-27). Intestinal spirochetes have even been documented in second trimester fetuses (28).

Microbiology

As the modern classification of bacteria came to rely on morphologic differences at the level of DNA and RNA, the spirochetes were divided into three phylogenetic groups. The family *Spirochaetaceae* includes *Borrelia, Spirochaeta, Spironema, and Treponema; Leptospiraceae* contains *Leptonema* and *Leptospira;* and the intestinal spirochetes of *Brachyspira* (*Serpulina)* are in the *Brachyspiraceae* family (Table 1) (29). Traditionally, *Brachyspira* and *Serpulina* were referred to as separate genera; however, a lack of significant phylogenetic differences has led to the unifying classification under *Brachyspira*, with the two genus names considered interchangeable (30).

Table 1. Classification of Spirochetes[a]

Spirochaetaceae	*Leptospiraceae*	*Brachyspiraceae*
Borrelia		
Spirochaeta		
Spironema		
Treponema	*Leptonema*	*Brachyspira*
	Leptospira	(*Serpulina*)

[a]See reference 29.

The two members of the *Brachyspiraceae* family most commonly associated with human disease are *Brachyspira aalborgi* and *Brachyspira pilosicoli*. *B. aalborgi* was first identified in the stool of a patient from Denmark in 1982 (31). In the years that followed, subsequent cases of IS were assumed to be caused by *B. aalborgi* on the basis of similar histological appearance. However, studies published in 1994 and 1996 reexamined the stools using multilocus enzyme electrophoresis and yielded a predominance of *B. pilosicoli* (32,33). Additionally, a study by Trivett-Moore et al. (34), published in 1998, looked at rectal biopsy specimens in homosexual men and found only *B. pilosicoli*. Following these studies, most subsequent cases of IS were attributed to *B. pilosicoli*. More recently, PCR-based assays have been used to identify these fastidious organisms.

Members of the family *Brachyspiraceae* are morphologically similar to other spirochetes. The characteristic of all spirochetes, movement through fluid environments, is performed by rotation of flagella. A central cylinder enclosed by a cytoplasmic membrane is the basic morphologic structure. The periplasmic space contains the axial fibrils, the number of which varies for individual species. Key features of each species can be found in Table 2.

Both *B. aalborg*i and *B. pilosicoli* are slowly growing fastidious anaerobes, with estimated growth times of 6 days for *B. pilosicoli* and up to 2 weeks for *B. aalborgi* (21,31,34). *B. aalborgi* is difficult to grow on artificial culture media. The first reported isolation of the organism from human feces was on brain heart infusion agar with 10% bovine blood and spectinomycin plus polymyxin B. Incubation in an anaerobic jar allowed growth of larger colonies, and growth was slightly improved at 38.5°C than at 37°C (38).

A report on antimicrobial susceptibility testing of *B. pilosicoli* was published in 2003 (39). Antimicrobial susceptibility was determined using Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards, or NCCLS) breakpoints for anaerobes, with isolates determined to be susceptible to ceftriaxone, chloramphenicol, meropenem, metronidazole, and tetracycline. An arbitrary breakpoint was established for ciprofloxacin, yielding a 60% resistance rate. A slightly better response rate to moxifloxacin was exhibited. Erythromycin was not active against *B. pilosicoli*, but approximately 30% of erythromycin-resistant isolates were susceptible to clindamycin.

Clinical Presentation, Diagnosis, and Treatment

In many cases, the histological findings of IS are simply an incidental discovery during a screening colonoscopy. Symptomatic IS is most commonly accompanied by complaints of chronic

