Journal of
TRAVEL MEDICINE

REVIEW

Post-Infectious Sequelae of Travelers' Diarrhea

Bradley A. Connor, MD* and Mark S. Riddle, MD†

*Weill Medical College of Cornell University, New York, NY, USA; †Naval Medical Research Center, Silver Spring, MD, USA

DOI: 10.1111/jtm.12049

See the Editorial by Herbert L. DuPont, pp. 273–274 of this issue.

Background. Travelers' diarrhea (TD) has generally been considered a self-limited disorder which resolves more quickly with expeditious and appropriate antibiotic therapy given bacteria are the most frequently identified cause. However, epidemiological, clinical, and basic science evidence identifying a number of chronic health conditions related to these infections has recently emerged which challenges this current paradigm. These include serious and potentially disabling enteric and extra-intestinal long-term complications. Among these are rheumatologic, neurologic, gastrointestinal, renal, and endocrine disorders. This review aims to examine and summarize the current literature pertaining to three of these post-infectious disorders: reactive arthritis, Guillain-Barré syndrome, and post-infectious irritable bowel syndrome and the relationship of these conditions to diarrhea associated with travel as well as to diarrhea associated with gastroenteritis which may not be specifically travel related but relevant by shared microbial pathogens. It is hoped this review will allow clinicians who see travelers to be aware of these post-infectious sequelae thus adding to our body of knowledge in travel medicine.

Methods. Data for this article were identified by searches of PubMed and MEDLINE, and references from relevant articles using search terms "travelers' diarrhea" "reactive arthritis" "Guillain-Barré syndrome" "Post-Infectious Irritable Bowel Syndrome." Abstracts were included when related to previously published work.

Results and Conclusions. A review of the published literature reveals that potential consequences of travelers' diarrhea may extend beyond the acute illness and these post-infectious complications may be more common than currently recognized. In addition since TD is such a common occurrence it would be helpful to be able to identify those who might be at greater risk of post-infectious sequelae in order to target more aggressive prophylactic or therapeutic approaches to such individuals. It is hoped this review will allow clinicians who see travelers to be aware of these post-infectious sequelae thus adding to our body of knowledge in travel medicine.

Travelers' diarrhea (TD) is a common and predictable illness in people traveling to developing countries.[1,2] The incidence of TD has been reported to be between 30 and 70% depending on travel destination and season of travel.[2] TD is caused by the ingestion of contaminated food or water.[3] The majority (80%–90%) of TD cases are caused by bacterial pathogens,[2] although protozoal and viral pathogens are also identified. Microbial pathogens which cause TD can vary with geography,[3,4] but generally speaking, enterotoxigenic *Escherichia coli* (ETEC), enteroaggregative *E coli* (EAEC), and norovirus appear to be the most important pathogens worldwide.[5] TD is typically an acute self-limited illness with symptoms resolving within 1 to 5 days but there has been increasing recognition of serious and potentially disabling enteric and extra-intestinal long-term complications of acute TD. This review will discuss three of these complications, reactive arthritis (ReA), Guillain-Barré syndrome (GBS), and post-infectious irritable bowel syndrome (PI-IBS), with a particular focus on their relationship with enteric infection. Although this review will highlight the relationship of these conditions with diarrhea associated with travel, much of the data are drawn from outbreaks of gastroenteritis which may not be specifically travel related. However, as the microbial pathogens are those commonly seen in TD it is hoped this review will allow clinicians who see travelers to be aware of these post-infectious sequelae thus adding to our body of knowledge in travel medicine.

Corresponding Author: Bradley A. Connor, MD, Division of Gastroenterology and Hepatology, Weill Medical College of Cornell University, 50 East 69th Street, New York, NY 10021, USA. E-mail: bconnor1@gmail.com

Reactive Arthritis

Symptoms

ReA was first described following gastrointestinal and genitourinary infections several decades ago. Review of

the literature suggests variable attack rates following gastroenteritis and TD. Much of this variability is due in part to a lack of standardization of the definition of ReA with some studies using only the ReA triad (eg, arthritis associated with urethritis and conjunctivitis) to make the definition and others using only certain microorganisms as triggers in order to calculate rates of ReA.[5]

The onset of joint symptoms is typically 1 to 4 weeks (most commonly 2 weeks) post-enteric infection with a reported range of 4 to 35 days. The joint disease may be monoarticular but is more commonly polyarticular and the clinical spectrum varies from slight transient arthralgias to long-standing debilitating arthritis. There is a predilection for joints of the lower extremities: knees and ankles, although small joints may be involved. Tenosynovitis may occur and the elbow, wrists, low back, and shoulder may be affected as well. Extra-articular manifestations of ReA may be mucosal, urethral, and cutaneous. Ocular manifestations include conjunctivitis, episcleritis, and uveitis.

The duration of arthritic symptoms is variable as well. Fifty percent of patients with ReA after enteric infection recovered in approximately 30 weeks in one study,[6] while in another study of an outbreak of *Salmonella* typhimurium infection, 60% had joint pains 4 to 5 months later.[7] Another study showed that the majority of patients with *Salmonella*-associated ReA were symptomatic 5 years after enteric infection.[8] In a review of *Campylobacter* infections, 5% of those with ReA had chronic or relapsing symptoms 5 years later.[9]

Incidence Associated With Enteric Infection

ReA has been reported to occur in 1%[10] to 62%[11] of people following an enteric infection caused by any one of a variety of microbes. The enteric bacterial species most often associated with ReA are *Salmonella enteritidis*, *Shigella* spp., *Campylobacter* spp., and *Yersinia* spp.[5] *Salmonella* spp. or *Yersinia* spp. were identified in 52% of patients with enteric ReA in one study.[9] Case reports linking ReA to *Cyclospora*,[12] *Giardia*,[13] *Clostridium difficile*,[14] and TD with unspecified etiology[15] have been reported, although no well-controlled studies implicating these pathogens have been published to date. Notably all of these organisms, with the exception of *C difficile*, are also common pathogens associated with TD. A recent report utilizing a case–control study design from data obtained from the Department of Defense Medical Encounter Database also highlights that the burden of post-infectious ReA may be underestimated in high risk populations such as travelers and deployed military service members.[16] In this study, not only was increased risk of ReA by at least two separate ICD-9 medical encounter visits (as measured by ReA triad or post-dysenteric arthritis) following an acute gastroenteritis episode identified (OR: 4.42, 95% CI: 2.24, 8.73), but other incidental acute ICD-9 visits related to non-specific arthalgia/arthritis (undifferentiated ReA) were also found to be increased following an episode of gastroenteritis (OR: 1.76, 95% CI: 1.49, 2.07). Interestingly, medical care visits for these ICD-9 codes persisted in approximately 40 and 12% of specific ReA and undifferentiated ReA, respectively.

Risk Factors

Predicting who is at risk is problematic but it is believed that host factors, pathogen factors, and host–pathogen interaction all play a role. ReA is frequently, but not always associated with HLA-B27. Whereas HLA-B27 is found in 6% of the general population, it is found in approximately 50% of patients with ReA related to enteric infection[5] and 70% of patients with the ReA triad.

The risk of ReA after enteric infection in HLA-B27-positive patients may depend on the pathogenetic organism; the risk of ReA was significantly associated with infection by *Salmonella*, *Shigella*, or *Yersinia*, but not with *Campylobacter* or *E coli*.[17] Despite the significant association of HLA-B27 with the development of ReA following *Salmonella* infection, HLA-B27-independent ReA after *Salmonella* infection has been reported.[18,19] However, some of the patients with HLA-B27-independent ReA expressed other class I major histocompatibility complex genes including the HLA-B27 crossreacting antigens B7, B22, and B40.[18] Two other studies have reported the presence of the related antigens B7 and further demonstrated the presence of HLA-Bw60 in a subset of patients with ReA.[19,20] Thus, the members of the HLA-27 cross-reacting antigen group may also be risk factors for ReA.

The genetic risk of contracting ReA is not limited to HLA genotypes. A genetic variant of the Toll-like receptor (TLR)-2 was recently shown to be associated with ReA after infection with *Salmonella*.[21] This TLR-2 polymorphism appeared to be specifically related to the development of ReA because it was not detected in controls infected with *Salmonella* but who had not developed ReA.

Pathophysiology

One model for the pathogenic mechanism leading to ReA associated with enteric infection is depicted in Figure 1.[5,22] During active infection, enteric bacteria invade the intestinal mucosa, enter the systemic circulation, and are transported to the joint. Transport to the joint may be mediated by monocytes (or other blood cells) that can carry the bacteria[22] and bacterial antigens [eg, lipopolysaccharide (LPS), heat shock protein].[23–25] Indeed, bacterial antigens[23,26–30] and evidence of direct synovial bacterial infection (ie, bacterial DNA or RNA)[26,31,32] have been detected in synovial fluid from joints of patients with ReA. *Salmonella* LPS appears to be an important virulence factor and may assist the organism in breaching the intestinal mucosa inciting this variety of immune and inflammatory events. LPS has been demonstrated in synovial cells and ReA joints.

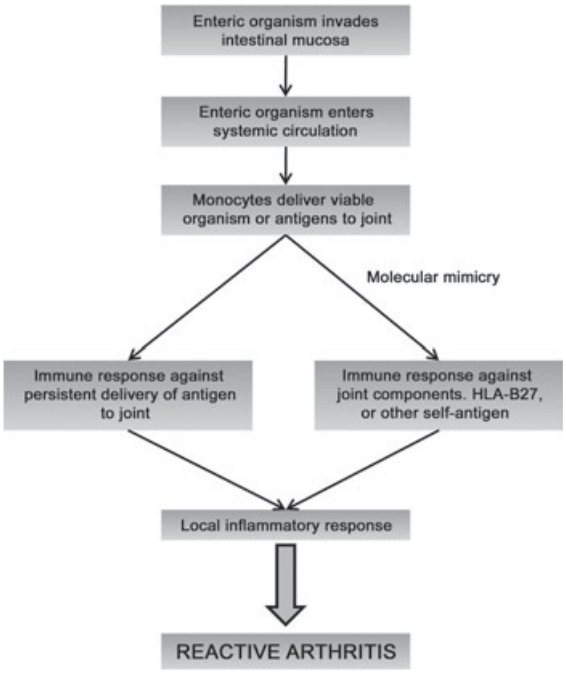

Figure 1 Proposed mechanism for molecular mimicry in the pathophysiology of reactive arthritis.[5,22]

Once in the synovial fluid of the joint, the bacterial antigens invoke a local and persistent immune response leading to the inflammation associated with ReA. This may occur via two possible mechanisms: (1) the immune system may be directly activated by recurrent infection or bacterial antigen delivery to the joint or (2) the immune response to the initial infection may result in production of antibody epitopes with cross-reactivity with bacterial and human antigens.[5] The latter of these two processes, known as molecular mimicry, may result in the activation of cytotoxic T lymphocytes with reactivity against HLA-B27, which contains protein sequences homologous to those detected in proteins of bacteria associated with ReA.[33–36] Indeed, antibodies with reactivity toward HLA-B27 have been detected in patients with ReA.[33,34,36] In addition, the novel finding of a variant TLR-2 in patients with ReA suggests that this receptor may also have a role in ReA pathogenesis.

An outcome of ReA following TD is more likely with a more severe enteric infection. ReA is more commonly associated with prolonged diarrhea (symptoms greater than 7 days), and there is a positive correlation with an emergency room visit or hospital admission for diarrhea. Antibiotics did not appear to decrease the risk for patients treated with fluoroquinolones for *S enteritidis* and ReA may be slightly increased in those treated with antibiotics.[37] Postulated reasons for this include: antibiotic-induced alteration of the microbe, prolongation in carriage of the microorganism, or it may simply be a marker of more severe disease. However in another study of patients who developed ReA after infection with *Salmonella hadar*, antibiotic therapy seemed to be protective.[38]

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a group of conditions in which an autoimmune response is mounted against the peripheral nerves,[39] leading to peripheral neuropathy and acute neuromuscular failure.[40] GBS is the most common cause of acute neuromuscular paralysis worldwide. There are three types of GBS: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN).[39,40] The overall incidence of GBS is approximately 1–2 per 100,000[41] The incidence of each type of GBS varies with geography, with AIDP being most common, occurring in 95% of GBS patients in the United States and Europe while 5% have the axonal form, which is more common among patients in Japan, northern China, and Central and South America.[41] Although all age groups are affected, peak incidence occurs in young adults and in the elderly and most, if not all, cases appear to have an infectious trigger.

Symptoms

GBS is characterized by global weakness affecting both proximal and distal limbs.[40,41] Numbness, pain, and paresthesias are also typically present.[41] Hyporeflexia may occur early on,[40,41] but 33% to 48% of patients with AMAN may have hyperreflexia.[42,43] The cranial nerves are often affected as manifested by facial weakness, bulbar palsy, and eye movement disorder.[40,41] Respiration may be weakened, requiring ventilation[40,41]; in one report, 33% of patients required ventilation.[44] Autonomic signs are commonly present and may include tachycardia, hypertension, orthostatic hypotension, urinary retention, and ileus.[40,41]

The symptoms of GBS usually begin between 1 and 3 weeks following an acute viral or bacterial infection,[39] and are acutely progressive, with the neuropathy peaking within 4 weeks.[41] After a plateau phase of variable duration, symptoms will begin to regress during a period of weeks to months. Most patients recover from GBS, but up to 20% may remain disabled, and 4% to 15% will die from GBS.[41] Symptoms of GBS reappear in 8% to 16% of patients after initial treatment,[41] with some patients eventually being diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy.[45]

Incidence Associated With Enteric Infection

Up to 72% of patients report having an infection preceding the onset of GBS.[46] GBS has been associated with preceding infection by several bacterial and viral pathogens (Table 1). The most common enteric pathogen associated with GBS is *Campylobacter* with approximately one case of GBS for every 1,000 cases

Table 1 Incidence of Guillain-Barré syndrome by pathogen*

Pathogen	Range of reported incidence, %
Campylobacter jejuni[46,58,59]	14–32
Cytomegalovirus[46,58,59]	7–18
Mycoplasma pneumoniae[46,59]	1–9
Epstein-Barr Virus[46,58,59]	1–7
Parvovirus[59]	4

**Based on data from studies examining the incidence of multiple pathogens by serology only.

of *Campylobacteriosis*.[47] *Campylobacter* is one of the most prevalent bacterial causes of food-borne disease in the United States with over 2.4 million cases a year[48] and it is a common cause of TD especially among travelers to Asia. Evidence for other enteric pathogens in GBS has also been reported. *Yersinia* infection was detected in stool samples in 1% of patients with GBS in one study[46] and there was a case report of a patient with *Cyclospora*-triggered GBS.[49]

Although *Campylobacter* is the single most common pathogen associated with GBS, the link was only first recognized in 1982,[50] and since then most epidemiologic studies have confirmed this association with up to 40% of GBS resulting from recent *Campylobacter* infections.[51] In a case–control study in the UK of 103 patients with GBS, 26% had evidence of recent *Campylobacter jejuni* infection compared with 2% of household and 1% non-matched controls.[52] The estimated risk of GBS from symptomatic *C jejuni* infections is 100 times that of the general population.[53]

Risk Factors

Unlike the association of ReA with HLA-B27, no strong link between HLA antigens has been reported for GBS.[39,40] Further, no strong link has been made between GBS and human immunosusceptibility genes in general, although some potential genetic factors have been identified.[39–41] However, other pathogen and host factors may impact the risk of development of GBS. Infection with the *C jejuni* strains with the HS:19 serotype and cstII polymorphism Thr51 may increase the risk for production of autoantibodies and development of GBS compared with infection by other enteritis-associated strains of *C jejuni*.[54] Increasing age and male sex also increased the risk of GBS in patients in one study.[55] Another study showed a bimodal distribution for increased incidence of GBS by age with peaks between 20 and 24 years and 70 and 74 years.[56]

A variety of factors may also influence the course of GBS. Infection by *C jejuni* is associated with significantly longer recovery time,[52] greater disability after 8 weeks, 6 months,[57] and 1 year,[52] and poorer outcome after 1 year[58] compared with infection by other organisms. Other factors significantly associated with poorer outcomes for patients with GBS include older age (≥50 years),[57,59] rapid onset of weakness,[57] being bedbound or on a ventilator,[57] severe arm weakness,[58] and diarrhea.[56,59]

Pathophysiology

Like the proposed mechanism for ReA (Figure 1), molecular mimicry is believed to be the mechanism for the pathophysiology of GBS[39–41] (Figures 2 and 3). In the case of AIDP, an inflammatory condition, activation of autoreactive T cells and production of autoreactive antibodies leads to attack on the myelin sheath and on Schwann cells leading to disruption of nerve transmission. In AMAN and ASMAN, both noninflammatory conditions, T cells are not involved, and autoreactive antibodies targeting the nerve axolemmal membrane lead to disruption of nerve conduction or axonal damage. Additional evidence for an immunologic rather than a toxic basis for disease production is the fact that the median interval from onset of diarrhea to neuropathic symptoms is approximately 9 days. This is more consistent with GBS as a consequence of an immune response rather than a direct effect of the organism or toxin.

Post-Infectious Irritable Bowel Syndrome

In most cases, the gastrointestinal effects of TD are self-limiting. In a subset of patients, however, persistent changes in GI function may occur following the infection.[60] These enteric changes, which often result in persistent diarrhea, may be related to several conditions including but not limited to persistent infection, co-infection with a second organism that was not targeted by initial therapy for TD, an underlying previously undiagnosed gastrointestinal illness, or PI-IBS.

Persistent diarrhea, chronic abdominal discomfort, and changes in bowel function in returned travelers have been commonly noted by clinicians who frequently see returned travelers. It was studies done in the past two decades, however, mainly follow-up of community-wide outbreaks of gastroenteritis, which showed that a percentage of those afflicted with acute enteric infection continued to have symptoms for months or even years after the inciting infection, a condition which has come to be known as PI-IBS. There is increasing evidence to support PI-IBS as a specific diagnosis. This requires a paradigm shift: a peripheral event, in this case an infection, leads to prolonged and permanent changes in GI function.

PI-IBS has been defined as the new onset of IBS symptoms as defined by Rome III Criteria for IBS (Table 2) following an episode of gastroenteritis or TD where the workup for chronic enteric infection and underlying organic gastrointestinal disease is negative.[60] In most cases, PI-IBS is characterized by diarrhea-predominant IBS but constipation-predominant IBS and mixed IBS have also been reported in PI-IBS.[61]

To put this in historical perspective, however, requires review of medical literature from more

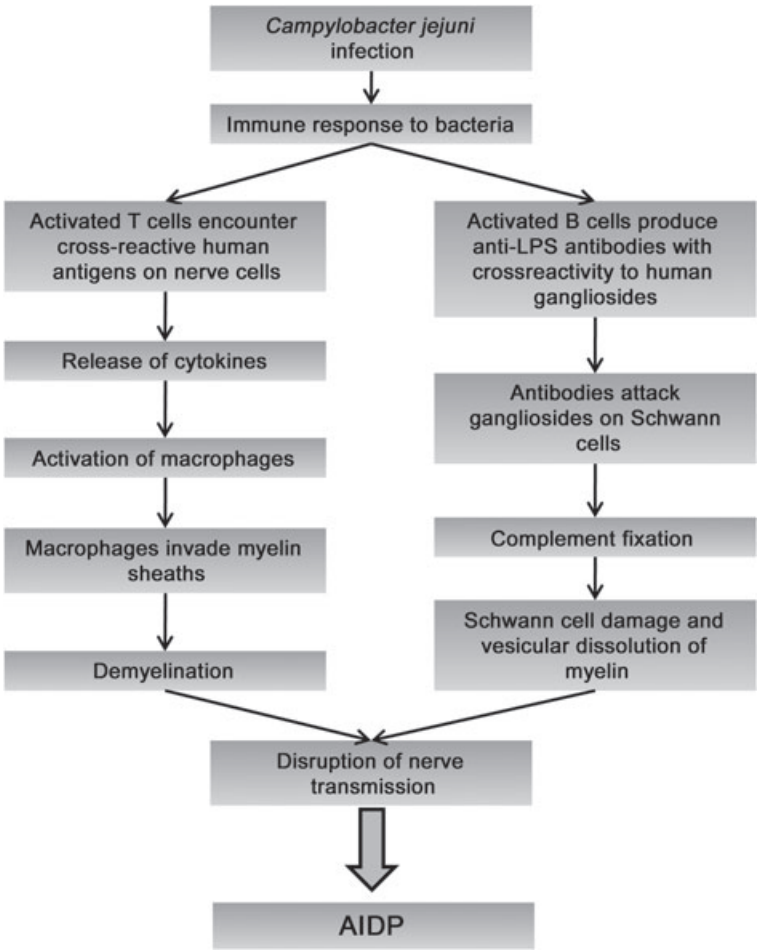

Figure 2 Proposed mechanism for molecular mimicry in the pathophysiology of AIDP (acute inflammatory demyelinating polyradiculoneuropathy).

than a half century ago when it was observed that post-dysenteric gastrointestinal symptoms occurred in British troops following successful treatment for amebic dysentery.[61] A common finding was functional non-ulcerative "colitis" with continued symptoms, but no obvious pathology. In more recent studies of IBS patients 20% retrospectively recalled diarrhea, vomiting, and fever at the onset of their symptoms and in other studies, 6% to 17% of IBS sufferers recalled acute diarrhea as a herald of IBS.[62]

Incidence

The incidence of IBS after any enteric infection has been reported to range from 4%[63] to 32%.[60,64,65] This wide range may be related to differences across studies in the definition of PI-IBS, the time between infection and follow-up, geography, and methods used for diagnosing IBS.[60] Further, most studies are retrospective, lack control groups, and rely on patients' recollection of previous gastroenteritis and on patients accurately reporting the severity of symptoms before and after their acute infections.[60] These limitations notwithstanding, PI-IBS appears to be a complication of enteric infection.

The incidence of PI-IBS specifically associated with TD has only been examined in four studies. The most recent study was reported among 121 US military travelers returning from routine deployment (>6 month follow-up) to the Middle East where it was reported that there was an over fivefold increase in incident IBS among those who experienced an episode of TD during travel compared to those that did not (17.2% vs 3.7%, $p = 0.12$).[66] Another study among travelers from Israel reported that significantly more people (14%) who had TD developed IBS after 6 to 7 months compared with only 2% of those who did not have diarrhea.[67] A third study reported an incidence of PI-IBS of 10% in patients who had acquired TD in Mexico.[68] The fourth study reported only a 4% incidence of PI-IBS after TD which was not statistically different compared with those who developed IBS who did not have diarrhea (2%).[69] However, this study may have been underpowered and unable to detect a statistical significance for such a small difference in incidence.

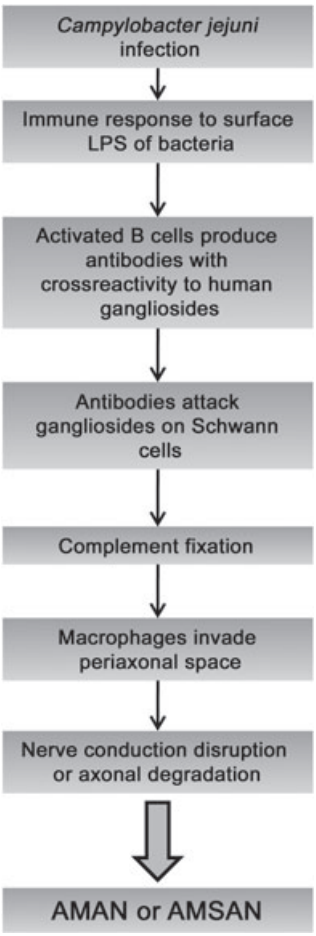

Figure 3 Proposed mechanism for molecular mimicry in the pathophysiology of AMAN and AMSAN.[39–41] AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; LPS = lipopolysaccharide.

Table 2 Post-infectious IBS (PI-IBS)

New IBS symptoms by Rome III criteria:
At least 3 months, with onset at least 6 months previously of recurrent abdominal pain or discomfort associated with 2 or more of the following features:
• improvement with defecation *and/or*
• onset associated with a change in frequency of stool *and/or*
• onset associated with a change in form (appearance) of stool
Following an episode of gastroenteritis or travelers' diarrhea where work-up for microbial pathogens and underlying gastrointestinal disease is negative.

Risk Factors

The risk factors for PI-IBS are only now beginning to be understood, but host factors, genetic factors, pathogen factors, and host–pathogen interaction are felt to serve as a basis for risk of PI-IBS. In a study of unselected patients with IBS versus controls, fewer patients with IBS were noted to have anti-inflammatory cytokines, IL-10, and TGF-b implying more susceptibility to prolonged and severe inflammation.[70] This is consistent with the increase in inflammatory cells such as enterochromaffin cells and T lymphocytes in the lamina propria in rectal biopsies of patients with PI-IBS. In addition, PI-IBS patients have increased post-prandial 5HT release compared to controls and those with standard constipation predominant IBS (IBS-C). PI-IBS patients also have an increased IL-1b both during and after infection compared to controls.[71]

Host risk factors for the development of PI-IBS have also been described. Psychological factors such as stress and anxiety have been shown to be associated with the development of PI-IBS in several studies.[72–75] Younger age has been shown to be a risk factor in some studies,[75,76] but not in another.[77] Host genetics may also be an important risk factor in PI-IBS; however, no studies to date have reported any relevant genes. Several studies suggest that individuals with a genetic background that results in the high production of the pro-inflammatory TNF-a and low production of the anti-inflammatory IL-10 may be more susceptible to prolonged inflammation following gastroenteritis, which may be important in the pathophysiology of PI-IBS.[78,79]

Pathophysiology

Similar to that of ReA and GBS, the pathophysiology of PI-IBS appears to be related to dysregulation

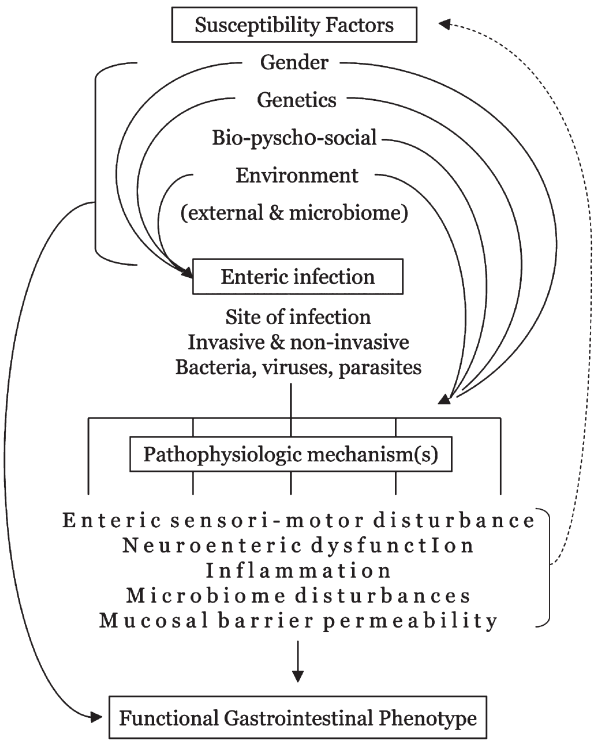

Figure 4 Proposed analytic framework for evaluating the pathogenesis of post-infectious irritable bowel syndromes and other functional disorders.

Table 3 Evidence for increased immune activation in intestines of patients with PI-IBS relative to controls*

Biopsy comparisons	EC cells	$CD3^+$ lymphocytes	Mast cells	IL-1b mRNA
Patients with PI-IBS vs healthy controls, rectal[71]	++	++	—	—
Patients with PI-IBS vs post-infection controls and healthy controls, rectal[70]	—	—	—	+++
Patients with PI-IBS vs post-infectious and non-infected controls, rectal[72]	+	+†	—	—
Patients with PI-IBS vs non-PI-IBS and non-infected family controls[83]				
Rectal	—	—	ND	+
Ileal	—	—	+†	+

EC = enterochromaffin; IL-1b = interleukin 1 beta; ND = no difference; PI-IBS = post-infectious IBS.
**Results shown if significantly different from all listed controls.
††Results only significantly greater than non-infected controls.

of an immune/inflammatory response (Figure 4). In contrast to the other two conditions, however, there is no compelling evidence to suggest PI-IBS is an autoimmune condition resulting from molecular mimicry. Instead, as described above, patients may be unable to downregulate intestinal inflammation caused by enteric infection.[60] The chronic intestinal immune activation in PI-IBS may be caused by low-grade inflammation and increased intestinal permeability, which leads to disrupted intestinal barrier function, altered neuromuscular function, chronic inflammation, and ultimately to the symptoms of PI-IBS.[80] The mechanistic significance of this is that once mucosal inflammation begins, an alteration of function of the enteric nervous system occurs leading to changes and excitability of muscle and nerves. A cascade starts in the mucosa and involves a series of mediators leading to activation of the visceral sensory system with visceral hypersensitivity and alteration in GI transit times with disturbed motor function. As a result of altered motility specifically decreased interdigestive Phase III waves, small intestinal bacterial overgrowth may occur resulting in changes in the intestinal microflora. Interestingly, recent data have emerged from an animal model which appears to link *C jejuni* infections with gut motor dysfunction, chronic inflammation, and small intestinal bacterial overgrowth.[81] A purported mechanism has been put forward which describes changes in the density of Interstitial Cells of Cajal (ICC) in the intestinal mucosa and subsequent aberrations in dysmotility.[82] While a number of questions regarding the potential patho-etiology and relevance to human PI-IBS exist, this finding, if confirmed, may prove to be an initial understanding of the mechanism by which acute enteric infections may trigger functional gastrointestinal disorders and be of great value in advancing our understanding of the genetics, immunology, and microbiomics behind this disease mechanism, as well as potentially evaluating mitigative host susceptibility factors and potential preventive interventions (eg, chemoprophylaxis, vaccination).

There is substantial evidence for inflammation in the gut of patients with PI-IBS. Significantly greater numbers of chronic inflammatory cells were detected in rectal biopsies from patients with PI-IBS than those from patients who had enteritis but did not develop PI-IBS.[74] Several other studies have also reported evidence of immune activation and inflammation in the GI system of patients with PI-IBS (Table 3).[70–72,83] Elevated levels of EC cells are relevant to the pathogenesis of PI-IBS because they produce serotonin, which can stimulate enteric secretions, activate visceral sensory nerves, and regulate peristalsis, thus playing a role in mediating the symptoms of PI-IBS.[60,84] Interleukin-1b may also be important in PI-IBS as it can affect enteric nerve function and contribute to diarrhea.[85]

In summary, potential consequences of TD extend beyond the acute illness. There is an increasing recognition of serious disabling and permanent sequelae of TD. As a result, this begs the need to reconsider strategies for treatment and perhaps prophylaxis of TD. Since TD is such a common occurrence it would be helpful to be able to identify who might be at greater risk of post-infectious medical sequelae in order to target more aggressive prophylactic or therapeutic approaches to such individuals. To this end, utilizing existing databases of ill-returned travelers (eg, GeoSentinel) to look at potential risk factors for post-infectious complications of TD and designing prospective studies from a geographically diverse selection of travel clinics might enable a more informed approach.

Disclaimer

The views expressed in this article by M. S. R. are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the US Government. There are no restrictions on its use. There were no financial conflicts of interests among any of the authors. This work was not supported by any work unit number.

This work was prepared as part of official duties. Title 17 U.S.C. §105 provides that "Copyright protection under this title is not available for any work of the US Government." Title 17 U.S.C. §101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person's official duties.

Declaration of Interests

M. S. R. is an employee of the US Government or military service members. B. A. C. states he has no conflicts of interest to declare.

References

1. Gascón J. Epidemiology, etiology and pathophysiology of traveler's diarrhea. Digestion 2006; 73(Suppl 1):102–108.
2. Connor BA. Travelers' diarrhea. In: The yellow book. CDC health information for international travel 2012. New York: Oxford University Press, 2012:56–60.
3. DuPont HL. New insights and directions in travelers' diarrhea. Gastroenterol Clin North Am 2006; 35:337–353 viii-ix.
4. DuPont HL, Ericsson CD, Farthing MJ, et al. Expert review of the evidence base for prevention of travelers' diarrhea. J Travel Med 2009; 16:149–160.
5. Hill Gaston JS, Lillicrap MS. Arthritis associated with enteric infection. Best Pract Res Clin Rheumatol 2003; 17:219–239.
6. Lauhio A, Leirisalo-Repo M, Lahdevirta J, et al. Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis. Arthritis Rheum 1991; 34:6–14.
7. Swerdlow DL, Lee LA, Tauxe RV, et al. Reactive arthropathy following a multistate outbreak of *Salmonella* typhimurium infections. Program and abstracts of the 1990 Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology; 1990. [abstract 916].
8. Thomson GTD, DeRubeis DA, Hodge MA, Rajanayagam C. Post-*Salmonella* reactive arthritis: late clinical sequelae in a point source cohort. Am J Med 1995; 98:13–21.
9. Pope JE, Krizova A, Garg AX, et al. *Campylobacter* reactive arthritis: a systematic review. Semin Arthitis Rheum 2007; 37:48–55.
10. Rohekar S, Tsui FW, Tsui HW, et al. Symptomatic acute reactive arthritis after an outbreak of *Salmonella*. J Rheumatol 2008; 35:1599–1602.
11. Fendler C, Laitko S, Sorensen H, et al. Frequency of triggering bacteria in patients with reactive arthritis and undifferentiated oligoarthritis and the relative importance of the tests used for diagnosis. Ann Rheum Dis 2001; 60:337–343.
12. Connor BA, Johnson EJ, Soave R. Reiter syndrome following protracted symptoms of *Cyclospora* infection. Emerg Infect Dis 2001; 7:453–454.
13. Carlson DW, Finger DR. Beaver Fever arthritis. J Clin Rheumatol 2004; 10:86–88.
14. Birnbaum J, Bartlett JG, Gelber AC. *Clostridium difficile*: an under-recognized cause of reactive arthritis? Clin Rheumatol 2008; 27:253–255.
15. Yates JA, Stetz LC. Reiter's syndrome (reactive arthritis) and travelers' diarrhea. J Travel Med 2006; 13:54–56.
16. Curry JA, Riddle MS, Gormley RP, et al. The epidemiology of infectious gastroenteritis related reactive arthritis in U.S. military personnel: a case–control study. BMC Infect Dis 2010; 10:266.
17. Schiellerup P, Krogfelt KA, Locht H. A comparison of self-reported joint symptoms following infection with different enteric pathogens: effect of HLA-B27. J Rheumatol 2008; 35:480–487.
18. Mattila L, Leirisalo-Repo M, Pelkonen P, et al. Reactive arthritis following an outbreak of *Salmonella* Bovismorbificans infection. J Infect 1998; 36:289–295.
19. Thomson GT, Chiu B, De Rubeis D, et al. Immunoepidemiology of post-*Salmonella* reactive arthritis in a cohort of women. Clin Immunol Immunopathol 1992; 64:227–232.
20. Inman RD, Johnston ME, Hodge M, et al. Postdysenteric reactive arthritis. A clinical and immunogenetic study following an outbreak of *Salmonellosis*. Arthritis Rheum 1988; 31:1377–1383.
21. Tsui FW, Xi N, Rohekar S, et al. Toll-like receptor 2 variants are associated with acute reactive arthritis. Arthritis Rheum 2008; 58:3436–3438.
22. Colmegna I, Cuchacovich R, Espinoza LR. HLA-B27-associated reactive arthritis: pathogenetic and clinical considerations. Clin Microbiol Rev 2004; 17:348–369.
23. Granfors K, Merilahti-Palo R, Luukkainen R, et al. Persistence of *Yersinia* antigens in peripheral blood cells from patients with *Yersinia enterocolitica* O:3 infection with or without reactive arthritis. Arthritis Rheum 1998; 41:855–862.
24. Kirveskari J, He Q, Holmstrom T, et al. Modulation of peripheral blood mononuclear cell activation status during *Salmonella*-triggered reactive arthritis. Arthritis Rheum 1999; 42:2045–2054.
25. Kirveskari J, Jalkanen S, Maki-Ikola O, Granfors K. Increased synovial endothelium binding and transendothelial migration of mononuclear cells during *Salmonella* infection. Arthritis Rheum 1998; 41:1054–1063.
26. Hill Gaston JS, Cox C, Granfors K. Clinical and experimental evidence for persistent *Yersinia* infection in reactive arthritis. Arthritis Rheum 1999; 42:2239–2242.
27. Granfors K, Jalkanen S, Lindberg AA, et al. *Salmonella* lipopolysaccharide in synovial cells from patients with reactive arthritis. Lancet 1990; 335:685–688.
28. Granfors K, Jalkanen S, Toivanen P, et al. Bacterial lipopolysaccharide in synovial fluid cells in *Shigella* triggered reactive arthritis. J Rheumatol 1992; 19:500.
29. Granfors K, Jalkanen S, von Essen R, et al. *Yersinia* antigens in synovial-fluid cells from patients with reactive arthritis. N Engl J Med 1989; 320:216–221.
30. Nikkari S, Rantakokko K, Ekman P, et al. *Salmonella*-triggered reactive arthritis: use of polymerase chain reaction, immunocytochemical staining, and gas chromatography–mass spectrometry in the detection of bacterial components from synovial fluid. Arthritis Rheum 1999; 42:84–89.
31. Siala M, Gdoura R, Fourati H, et al. Broad-range PCR, cloning and sequencing of the full 16S rRNA gene for detection of bacterial DNA in synovial fluid samples of Tunisian patients with reactive and undifferentiated arthritis. Arthritis Res Ther 2009; 11:R102.
32. Cox CJ, Kempsell KE, Gaston JS. Investigation of infectious agents associated with arthritis by reverse transcription PCR of bacterial rRNA. Arthritis Res Ther 2003; 5:R1–R8.
33. Tsuchiya N, Husby G, Williams RC Jr, et al. Autoantibodies to the HLA-B27 sequence cross-react with the hypothetical peptide from the arthritis-associated *Shigella* plasmid. J Clin Invest 1990; 86:1193–1203.
34. Lahesmaa R, Skurnik M, Vaara M, et al. Molecular mimickry between HLA B27 and *Yersinia*, *Salmonella*,

Shigella and *Klebsiella* within the same region of HLA alpha 1-helix. Clin Exp Immunol 1991; 86:399–404.
35. Stieglitz H, Fosmire S, Lipsky P. Identification of a 2-Md plasmid from *Shigella* flexneri associated with reactive arthritis. Arthritis Rheum 1989; 32:937–946.
36. Schwimmbeck PL, Yu DT, Oldstone MB. Autoantibodies to HLA B27 in the sera of HLA B27 patients with ankylosing spondylitis and Reiter's syndrome. Molecular mimicry with *Klebsiella* pneumoniae as potential mechanism of autoimmune disease. J Exp Med 1987; 166:173–181.
37. Locht H, Krogfelt KA. Comparison of rheumatological and gastrointestinal symptoms after infection with *Campylobacter jejuni/coli* and enterotoxigenic *Escherichia* coli. Ann Rheum Dis 2002; 61:448–452.
38. Arnedo-Pena A, Beltrán-Fabregat J, Vila-Pastor B, et al. Reactive arthritis and other musculoskeletal sequelae following an outbreak of *Salmonella hadar* in Castellon, Spain. J Rheumatol 2010; 37:1735–1742.
39. Yu RK, Usuki S, Ariga T. Ganglioside molecular mimicry and its pathological roles in Guillain-Barré syndrome and related diseases. Infect Immun 2006; 74:6517–6527.
40. Winer JB. Guillain-Barré syndrome. BMJ 2008; 337:a671.
41. Hughes RA, Cornblath DR. Guillain-Barré syndrome. Lancet 2005; 366:1653–1666.
42. Kuwabara S, Ogawara K, Koga M, et al. Hyperreflexia in Guillain-Barré syndrome: relation with acute motor axonal neuropathy and anti-GM1 antibody. J Neurol Neurosurg Psychiatry 1999; 67:180–184.
43. McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 1993; 33:333–342.
44. Winer JB, Hughes RA, Osmond C. A prospective study of acute idiopathic neuropathy. Clinical features and their prognostic value. J Neurol Neurosurg Psychiatry 1988; 51:605–612.
45. Mori K, Hattori N, Sugiura M, et al. Chronic inflammatory demyelinating polyneuropathy presenting with features of GBS. Neurology 2002; 58:979–982.
46. Van Koningsveld R, Van Doorn PA, Schmitz PI, et al. Mild forms of Guillain-Barré syndrome in an epidemiologic survey in The Netherlands. Neurology 2000; 54:620–625.
47. Tam CC, Rodrigues LC, Petersen I, et al. Incidence of Guillain-Barré syndrome among patients with Campylobacter infection: a general practice research database study. J Infect Dis 2006; 194:95–97.
48. Gilliss D, Cronquist A, Cartter M, et al. Vital signs: incidence and trends of infection with pathogens transmitted commonly through food—Foodborne Diseases Active Surveillance Network, 10 U.S. sites, 1996–2010. Morb Mortal Wkly Rep 2011; 60:749–755.
49. Richardson RF Jr,, Remler BF, Katirji B, Murad MH. Guillain-Barré syndrome after *Cyclospora* infection. Muscle Nerve 1998; 21:669–671.
50. Rhodes KM, Tattersfield AE. Guillain-Barré syndrome associated with *Campylobacter* infection. BMJ 1982; 285:173–174.
51. Allos BM. Association between *Campylobacter* infection and Guillain-Barré syndrome. J Infect Dis 1997; 176:S125–S128.
52. Rees JH, Soudain SE, Gregson NA, Highes RA. *Campylobacter jejuni* infection and Guillain Barré syndrome. N Engl J Med 1995; 333:1374.
53. McCarthy N, Giesecke J. Incidence of Guillain-Barré syndrome following infection with *Campylobacter jejuni*. Am J Epidemiol 2001; 153:610.
54. Koga M, Gilbert M, Takahashi M, et al. Comprehensive analysis of bacterial risk factors for the development of Guillain-Barré syndrome after *Campylobacter jejuni* enteritis. J Infect Dis 2006; 193:547–555.
55. Hauck LJ, White C, Feasby TE, et al. Incidence of Guillain-Barré syndrome in Alberta, Canada: an administrative data study. J Neurol Neurosurg Psychiatry 2008; 79:318–320.
56. Jiang GX, Cheng Q, Link H, de Pedro-Cuesta J. Epidemiological features of Guillain-Barré syndrome in Sweden, 1978–93. J Neurol Neurosurg Psychiatry 1997; 62:447–453.
57. Visser LH, Schmitz PI, Meulstee J, et al. Prognostic factors of Guillain-Barré syndrome after intravenous immunoglobulin or plasma exchange. Dutch Guillain-Barré Study Group. Neurology 1999; 53:598–604.
58. Winer JB, Hughes RA, Anderson MJ, et al. A prospective study of acute idiopathic neuropathy. II. Antecedent events. J Neurol Neurosurg Psychiatry 1988; 51:613–618.
59. Hadden RD, Karch H, Hartung HP, et al. Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. Neurology 2001; 56:758–765.
60. Connor BA. Sequelae of traveler's diarrhea: focus on postinfectious irritable bowel syndrome. Clin Infect Dis 2005; 41(Suppl 8):S577–S586.
61. Stewart GT. Post-dysentericcolitis. BMJ 1950; 1:405–409.
62. Spiller R. Irritable bowel syndrome. Br Med Bull 2005; 72:15–29.
63. Borgaonkar MR, Ford DC, Marshall JK, et al. The incidence of irritable bowel syndrome among community subjects with previous acute enteric infection. Dig Dis Sci 2006; 51:1026–1032.
64. McKendrick MW, Read NW. Irritable bowel syndrome—post salmonella infection. J Infect 1994; 29:1–3.
65. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. Gastroenterology 2009; 136:1979–1988.
66. Trivedi KH, Schlett CD, Tribble DR, et al. The impact of post-infectious functional gastrointestinal disorders and symptoms on the health-related quality of life of US military personnel returning from deployment to the Middle East. Dig Dis Sci 2011 Dec; 56:3602–3609.
67. Stermer E, Lubezky A, Potasman I, et al. Is traveler's diarrhea a significant risk factor for the development of irritable bowel syndrome? A prospective study. Clin Infect Dis 2006; 43:898–901.
68. Okhuysen PC, Jiang ZD, Carlin L, et al. Post-diarrhea chronic intestinal symptoms and irritable bowel syndrome in North American travelers to Mexico. Am J Gastroenterol 2004; 99:1774–1778.
69. Ilnyckyj A, Balachandra B, Elliott L, et al. Post-traveler's diarrhea irritable bowel syndrome: a prospective study. Am J Gastroenterol 2003; 98:596–599.
70. Gwee KA, Collins SM, Read NW, et al. Increased rectal mucosal expression of interleukin 1ß in recently acquired post-infectious irritable bowel syndrome. Gut 2003; 52:523–526.
71. Spiller RC, Jenkins D, Thornley JP, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute *Campylobacter*

enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000; 47:804–811.
72. Dunlop S, Jenkins D, Neal K, Spiller R. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. Gastroenterology 2003; 125:1651–1659.
73. Gwee KA, Graham JC, McKendrick MW, et al. Psychometric scores and persistence of irritable bowel after infectious diarrhoea. Lancet 1996; 347:150–153.
74. Gwee K-A, Leong Y-L, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. Gut 1999; 44:400–406.
75. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: the incidence and prognosis of post-infectious irritable bowel syndrome. Aliment Pharmacol Ther 2007; 26:535–544.
76. Parry SD, Barton JR, Welfare MR. Factors associated with the development of post-infectious functional gastrointestinal diseases: does smoking play a role? Eur J Gastroenterol Hepatol 2005; 17:1071–1075.
77. Neal KR, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study. Gut 2002; 51:410–413.
78. van der Veek PPJ, van den Berg M, de Kroon YE, et al. Role of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in irritable bowel syndrome. Am J Gastroenterol 2005; 100:2510–2516.
79. Gonsalkorale WM, Perrey C, Pravica V, et al. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? Gut 2003; 52:91–93.
80. Thabane M, Marshall JK. Post-infectious irritable bowel syndrome. World J Gastroenterol 2009; 15:3591–3596.
81. Pimentel M, Chatterjee S, Chang C, et al. A new rat model links two contemporary theories in irritable bowel syndrome. Dig Dis Sci 2008; 53:982–989.
82. Jee SR, Morales W, Low K, et al. ICC density predicts bacterial overgrowth in a rat model of post-infectious IBS. World J Gastroenterol 2010; 16:3680–3686.
83. Wang LH, Fang XC, Pan GZ. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. Gut 2004; 53:1096–1101.
84. Spiller RC. Postinfectious irritable bowel syndrome. Gastroenterology 2003; 124:1662–1671.
85. Spiller RC. Role of infection in irritable bowel syndrome. J Gastroenterol 2007; 42(Suppl 17):41–47.