

Postinfectious Functional Gastrointestinal Disorders: A Focus on Epidemiology and Research Agendas

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Abstract: Epidemiologic research is fundamental and complementary to our understanding of disease and development of primary, secondary, and tertiary interventions. To put the current evidence into context and identify gaps and research priorities in the areas of disease attribution, burden of disease, clinical characterization, and management of postinfectious functional gastrointestinal disorders (PI-FGDs), we took a multidisciplinary approach from the domains of infectious disease, gastroenterology, epidemiology, and public health. Our review of data from these disciplines found that, despite a complete understanding of pathoetiology, studies continue to accumulate and point toward evidence of a causal association for FGD. For some FGDs, Bradford Hill's criteria for causality yield more certainty than other criteria. In addition, the growing recognition of the impact of acute foodborne illness on economics and society is leading to exploration of the potential long-term health effects and disease burden of PI-FGDs, although a paucity of data exist in terms of pathogen-specific risk, disability duration, and relevant disability weights. Lastly, the understanding of PI-FGDs is changing the way research is approached and suggests a need for a more expansive exploration of biologic mechanisms and how FGDs are categorized. Areas of research priorities are catalogued in this paper and will hopefully provide inspiration for future studies and contributions to the field of gastroenterology.

A growing body of scientific literature is emerging that is commensurate with the recognized prevalence, on a global scale, of functional gastrointestinal disorders (FGDs) and their substantial attendant morbidity and economic costs.^{1,2} Furthermore, it is increasingly being recognized that acute gastrointestinal infections may play a role in triggering FGDs.³ Many parallel lines of investigation have been explored, including epidemiologic, psychosocial, immunologic, genetic, microbiomic, translational, and clinical research. Within the epidemiologic research domain alone,

Keywords

Functional gastrointestinal disorder, qualitative review, irritable bowel syndrome, dyspepsia, causation

a PubMed search including the terms “functional gastrointestinal disorders” and “prevalence” retrieves well over 100,000 hits. It is no surprise that there have been more than 15 systematic and qualitative reviews on the topic of postinfectious irritable bowel syndrome (PI-IBS) alone within the past 5 years.⁴⁻¹⁹

Paralleling the scientific discoveries about postinfectious FGD (PI-FGD) has been the emergence of numerous questions across disciplines. These questions address the need for methodologic standardization and novel avenues of research. Research across disciplines should be complementary and synergistic, providing reciprocal results that lead to further refinement that translate into treatments and cures.

The current paper reviews the emerging body of epidemiologic research on PI-FGD. Focus is specifically placed on the epidemiologic areas of disease attribution, burden of disease, and clinical characterization.

Attribution

A number of frameworks designed to elucidate the epidemiologic determination of causation have been advanced over the years.²⁰ The original Koch postulates were effective at establishing disease-pathogen relationships but fall short in the setting of more complex associations.^{21,22} In recent years, Bradford Hill's criteria have been more commonly used to describe complex relationships and their epidemiology.²³ Hill's criteria include strength of association, consistency of effect, specificity of effect, temporality, biologic gradient or dose response, and biologic plausibility and have been used successfully to establish the pathogenic roles of *Helicobacter pylori*, HIV, and toxins.²⁴ The association of causation between enteric infections and the development of FGDs was approached under this framework.

Strength of Association and Consistency of Effect

Numerous epidemiologic studies have consistently demonstrated a relationship between enteric infection and functional sequelae.^{19,25} The use of reference and comparator groups allows the ascertainment of the magnitude of association for the exposed (cohort) and risk factors (case-control) that are reported as rate or odds ratios. The magnitude and direction of these associations should be consistent across multiple populations to fulfill this criterion of magnitude of association.

Two recent meta-analyses evaluated available studies and estimated pooled risks for FGDs after acute infectious gastroenteritis (IGE).^{19,25} The pooled data showed a 6- to 7-fold increased risk of FGDs, with the majority of studies showing a positive association between IGE and development of FGDs across multiple geographic loca-

tions. Since publication of these meta-analyses, additional cohort studies that support these outcomes after bacterial and viral gastroenteritis have been published.^{26,27}

Sources of heterogeneity and bias must be considered when evaluating these types of studies. Challenges of heterogeneity and bias common in the FGD literature include the use of variable definitions for case ascertainment (ie, clinical, microbiologically confirmed, or both) and outcome classification (ie, Rome criteria; International Classification of Disease, 9th Revision [ICD-9] codes; or Talley's Bowel Disease Questionnaire).²⁸⁻³¹

Temporality

Temporality refers to documented evidence that the putative causal event precedes the outcome of interest. In the case of PI-FGD, the infectious insult must be noted to occur before the outcome. The best data to support temporality come from prospective cohort studies. Retrospective cohort studies can provide strong evidence of temporality as well, but the study design may not be able to separate out preexisting FGD among the exposed and the unexposed controls.

The majority of studies reviewed in the meta-analyses discussed above were prospective, although not all of them carefully excluded preexisting FGD and left open the question of whether FGDs could have predated the insult in some subjects.²⁵ Conversely, too brief a follow-up time would potentially undercount cases, as several studies have shown that risk remains elevated for months to a year from the inciting event.^{16,19,29,32} Such an “incubation period” makes it challenging to directly link the exposure with the outcome when intercedent causal events may occur. Furthermore, some studies have suggested that patients with FGDs (IBS in particular) are at increased risk for IGE³³ and that there may be a common genetic predisposition to infection susceptibility and development of IBS and also inflammatory bowel disease (IBD) pathophysiology.^{3,34-37}

The association between postinfectious functional dyspepsia and gastroesophageal reflux disease (GERD) also is problematic, given that patients with dyspeptic symptoms may be self-treating with acid-reducing medications without a clinical diagnosis, which makes them more susceptible to intestinal infections. These may be classified as incident cases due to an exacerbation of the disease state for which a patient seeks medical care. Additional prospective studies that include detailed baseline history and close follow-up in well-defined populations are needed to strengthen the evidence of temporality.

Specificity of Effect

Specificity describes the precision by which a factor will predict the occurrence of a single disease process. Among

Hill's criteria, specificity has been the least useful because it is based on the concept that a given exposure results in only one disease, a concept typified in the Koch postulates as well, but that loses validity as exposure and disease relationships become more complex. However, there has been considerable support from the epidemiologic literature to suggest that IGE can lead to a variety of functional outcomes beyond IBS and that a variety of pathogens can lead to a single functional disorder. For example, after a salmonellosis outbreak, cases of dyspepsia were common in addition to cases of IBS, and there was frequent overlap.³² Similarly, after a norovirus outbreak, an increase in reflux symptoms was seen among incident cases of IBS compared with nonexposed controls.²⁷ Thus, a major challenge to the study of PI-FGD is the lack of an all-encompassing case definition, such as with the Rome III criteria, which are often used to define FGD phenotypes and include criteria for PI-IBS, even though the phenotypes are not restricted to IBS subtypes.

All IBS subtype phenotypes, which include dyspepsia and GERD, have been documented after infectious insults.^{32,38-40} Bloating, a symptom often associated with small intestinal bacterial overgrowth (SIBO) and IBS, is not included in the Rome III criteria for postinfectious sequelae.⁴¹ Similarly, constipation risk was increased after *Clostridium difficile* infection and after IGE in a case-control study of military personnel.^{29,42} Broader definitions of these various manifestations would more completely encompass the widespread phenotypes described.

Research and validation of new diagnostic criteria for postinfectious sequelae would be a welcome addition and improve the quality of future epidemiologic and experimental studies. A recent study of the Walkerton, Ontario outbreak data analyzed functional outcomes and determined that the majority of cases were associated with abdominal pain with constipation or diarrhea and could be appropriately captured using Rome criteria.⁴³ However, it was notable that the phenotype changed over time and was unstable. More work must be done to describe the natural history of postinfectious functional sequelae and the spectrum of phenotypes encountered besides IBS.

Dose Response

Documentation of a dose response can constitute important evidence to support the validity of a proposed causal pathway. Prolonged antibiotic use during acute IGE—a possible marker of severity of disease but also a potential confounder—has been associated with incident sequelae in a retrospective study among outpatients.²⁶ Reported potential risk factors for the development of PI-IBS include the duration of infection (with PI-IBS rates increasing at least 2-fold if diarrhea persists more than 1 week), need for antibiotic therapy or presence of fever, and increased sever-

ity of disease.^{26,38,39,44} Studies that are designed specifically to examine disease markers of severity, disease duration, or risk after multiple infections are needed to add to our understanding of dose response. Such dose-response information is lacking for non-IBS FGDs.

Biologic Plausibility

In addition to a dose response, validation of novel causal pathways is further supported by the establishment of explanatory mechanisms rooted in biology. Establishment of these biologic underpinnings has increasingly become an essential part of elucidating causal pathways in complex disorders.⁴⁵ Studies describing animal models and patients with FGD reveal a number of pathologic findings at the microbial and molecular level that support a unifying theory that includes brain-gut-immune dysregulation, loss of epithelial barrier integrity, and innate immunity defects.⁴⁶⁻⁵¹ Elaboration of these mechanisms for both postinfectious and idiopathic diseases is beyond the scope of this review and is the focus of a number of recent reviews.^{3,5} However, some of the supporting evidence as it relates to disease mechanisms following enteric infection are briefly described in the following section.

Dietary Intolerance Protozoal and other infections of the small bowel may cause a malabsorptive syndrome.⁵² Hypolactasia, a transient deficiency of lactase that may manifest as new lactose intolerance and chronic diarrhea, is well characterized in children following IGE and may occur in adults.⁵³ More recently, evidence has emerged suggesting that celiac disease may be triggered by acute enteric infection. A number of case reports have described infectious diarrhea as a trigger for celiac disease with limitations in the ability to determine if the enteric infection was a trigger or somehow unmasked the symptom onset and diagnosis.^{52,54,55}

More recently, Riddle and Murray found a 3-fold increased odds of exposure to pathogens of nonviral etiologies among celiac disease cases compared with matched controls.⁵⁶ Although the odds of exposure were higher when looking at temporal proximity to diagnosis of celiac disease, exposure misclassification due to the use of non-specific ICD-9 codes could have biased the association. Beyond these preliminary epidemiologic associations, mechanisms of gluten sensitivity have been demonstrated in animal models.^{57,58} Further investigation is needed to explore mechanisms by which gastrointestinal infection may trigger or facilitate the onset of clinical celiac disease, either by disrupting the intestinal barrier^{34,59} and, hence, the uptake of antigen in a genetically susceptible host or by amplifying the immune response to gliadin.

Dysbiosis The intestine harbors a diverse ecosystem that is only now beginning to be characterized. Emerging non-

culture-based methodology has offered a glimpse of the vast numbers of species of bacterial and, more recently, viral organisms that inhabit the human and animal intestines. This microbiome is a necessary element and has a role in nutrient processing and immune system priming. As such, it contributes in yet-to-be understood ways to intestinal and overall health.^{60,61} Animal and human data demonstrate how changes in these microbial communities are evident in a number of pathologic states, including FGDs.^{62,63}

The common characterization of dysbiosis as an imbalance of proinflammatory and anti-inflammatory species may be too simplistic. Distinct pathogenic organisms or taxa have not emerged, and other evidence suggests that distinct microbial communities exist at the mucosal interface, the lumen, and the various portions of the intestine.⁶⁴ Prospective evaluation of microbiome changes during vaccine challenge studies and natural outbreak settings would help elucidate normal and abnormal patterns of microbiome homeostasis and whether these are causal themselves or merely the effects of other dysfunctional processes.

In addition to documenting changes in the microbiome, there needs to be a better understanding of the mechanisms by which the microbiota cause changes: whether by direct changes to the mucosa, interaction with the gut immune system, or by production of fermentation and other products.

Inflammation/Dysmotility/Hypersensitivity Animal models and human natural disease studies provide a biologic basis for infection and chronic gastrointestinal inflammation. Intestinal inflammation similar to that seen in IBS cases developed in mice infected with *Trichinella spiralis*, and at least one study documented incident IBS after a trichinellosis outbreak.⁶⁵ Similarly, animal models of *Giardia* infection and epidemiologic evidence from outbreak settings link chronic gastrointestinal symptoms to episodes of giardiasis.^{13,66} Lastly, it is well documented that a chronic atypical mycobacterial infection, Johne disease, causes a chronic granulomatous colitis in cattle that is similar to human Crohn's disease, although a clear connection between human disease and mycobacteria has not been made.⁶⁷

Studies in patients with suspected PI-FGD, specifically PI-IBS, have provided significant information regarding biochemical and histologic changes, which, in essence, may help guide future therapy. Data suggest that PI-IBS may actually be an inflammatory-mediated response and that a change in the mucosal humoral activity is responsible for the symptoms of FGD.

It has been shown that PI-IBS subgroups have a significant increase in enterochromaffin cells, mast cells, and lamina propria T lymphocytes compared with patients without PI-IBS. These changes seem to cause an increase

in the release of biologically active substances, such as histamine, serotonin, and cytokines, specifically tumor necrosis factor- α , interleukin (IL)-6, and IL-8. Such changes may alter gastrointestinal motility as well as influence the neurohormonal response to visceral hypersensitivity.^{5,68-70}

Intestinal Permeability/Gut Barrier Dysfunction Low-grade intestinal inflammation and enterochromaffin cell hyperplasia in PI-IBS are also accompanied by increased intestinal permeability, which may lead to increased antigenic load and further activation of the immune system.^{71,72} Animal models support such hypotheses, as shown by transient intestinal infection with the nematode *T. spiralis* in mice, which resulted in altered muscle contractility, gut dysmotility, and visceral hyperalgesia that persisted for up to 42 days after the infection had cleared.^{73,74} No overt mucosal damage is observed in the postinfectious state, but low-grade inflammation, mucosal mastocytosis, and intestinal barrier dysfunctions with altered permeability persist.⁷⁵ Interestingly, genes that encode proteins involved in epithelial cell barrier function and the innate immune response to enteric bacteria are also associated with the development of IBS following acute gastroenteritis, which may suggest a susceptibility to both an infectious trigger event and the development of chronic gastrointestinal dysfunction.³⁴

Genetics Familial aggregation of FGDs is evident, but the relative contribution of shared environment versus heritable factors has been challenging to elucidate. Twin studies have offered conflicting data, and studies of separated twins have not been performed.⁷⁶ Animal and some human data suggest that FGDs may be transmitted via complex genetic determinants, and several loci have recently been associated with PI-FGD.³⁴ Interestingly, genes involved in innate immunity, intestinal barrier function, and cytokine or serotonergic pathways have been included among those loci.^{5,34,36,76,77} One small study found that some mitochondrial polymorphisms were protective.⁷⁸ Larger studies are needed to confirm these findings.

Future study of the genetic contribution to PI-FGD and FGDs in general are needed. Assessment of genomics could be combined with the study of microbiome changes after natural and challenge infections. The use of endophenotypes in the study of the genetic contributions to FGDs—as has been used to study the genetics of mental health—has been advocated.⁷⁶

Animal Models Several animal models have been advanced that replicate some of the features of PI-FGD after bacterial, parasitic, or chemical insults. A review of the available models concluded that they are weakened by the fact that no one model has replicated all the features and durations of illness seen in human FGDs, and the

models often had different end results or lacked key clinical features (such as visceral hypersensitivity, consistent histologic changes, and altered bowel habits) common to similar models and human subjects.¹³

In one compelling model, investigators described how profound dysbiosis and evidence of mucosal immune activation mimicking immune activation seen in humans developed in one third of rats infected with *Campylobacter*.⁷⁹ Moreover, decreased numbers of interstitial cells of Cajal (ICC) postinfection predicted the development of SIBO. Two limitations of a *Campylobacter* infection animal model include a lack of acute illness and understanding of human versus animal pathogenesis.

Summary on Attribution

Evidence suggests that there is a high probability that IGE increases the risk of incident FGDs, although evidence for causation varies. Although evidence-based schema exist for the assessment of disease prevention and treatment guidelines, objective criteria are needed to critically evaluate epidemiologic evidence of causation.^{80,81} One such system—the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework—has recently been suggested as a system that might be adapted.⁸²

GRADE and similar frameworks provide an explicit description of the quality of data supporting treatment or prevention decisions, usually considering randomized controlled trials as the highest quality evidence. Although no such evidence exists for epidemiology, a GRADE framework that equally weights the quality of appropriate experimental and observational data has been proposed with application to Hill's criteria and may be suitable for use.⁸³ Table 1 summarizes the evidence of causation (based on the authors' interpretation) for the association between acute enteric infections (in general) and development of PI-FGD. As with any of these classification frameworks, the literature is open to interpretation and the field would benefit from an independent, thorough assessment that uses an appropriate framework.

From this review, a number of gaps remain and include the defining pathogen-specific risk, the spectrum of associated FGDs, and the biologic underpinnings to explain the mechanisms involved, which, in turn, can inform preventive and therapeutic efforts. One emerging theme that should guide future research is how risk of PI-FGD, as in other complex relationships, is influenced by host, environment, and agent factors. Furthermore, our knowledge of FGDs among populations in the developing world is considerably lacking, given the known high risk of enteric infection in these populations. Future epidemiologic research efforts are necessary and will complement animal and other clinic-based research.

In future epidemiologic studies, inclusion of microbiologic, immunologic, and genetic covariates may help

clarify the mechanisms involved. A central challenge will be the selection of controls that reliably represent the general population from where the studied cases originate. In addition, case definition and categorization need to be reconsidered, given the lack of specificity of current FGD diagnostic criteria. Important covariates of demographics/behavior factors (psychological comorbidities, family history of FGD, and stressful environments) should be evaluated as independent factors as well as effect modifiers.

Burden of Disease

Disease burden is defined as the impact of a particular disease on the health of a population. Two of the most common approaches to measuring disease burden are the disability-adjusted life-year (DALY) and the quality-adjusted life-year (QALY). Although related (each is, in theory, the inverse of the other), their relationship is more nuanced. Nonetheless, both measure disease impact by accounting for incidence and mortality rates, disease severity, and years lived with a disease.

The QALY is a measure of life expectancy and the quality of life during a given health state, whereby 1 represents perfect health and 0 represents death.⁸⁴ Frequently, this measure is placed in the context of cost, such that the impact of an intervention can be quantified as cost per QALY.

In contrast, the DALY is a summation of the years of life lost due to early mortality and the years lost to disability (YLD).⁸⁴ Other measures of disease burden include the amount of money spent toward treating and caring for those affected and the lost work productivity of those affected. QALY and DALY data often assist in the prioritization of research agendas.

Limited but compelling data suggest that postinfectious gastrointestinal disorders contribute to negative health consequences. A 2008 Dutch study used a panel of 105 individuals from the general population to calculate time-tradeoff (TTO) valuations transformed into a 0 (death) to 1 (perfect health) score under the annual profile method (APM).⁸⁵ The authors reported a mean TTO_{APM} of 0.958 (standard deviation [SD], 0.05) for IBS, and a mean TTO_{APM} of 0.928 (SD, 0.10) for yearly recurrent IBS. To place these scores into context with other conditions, similar TTO_{APM} scores were reported for chronic, permanent eczema and back/neck pain (0.950 and 0.928, respectively). Using those estimates, Haagsma and colleagues estimated that PI-IBS cases diagnosed in 2006 in The Netherlands and attributed to infection with 3 common bacterial enteropathogens (*Campylobacter*, *Salmonella*, and *Shigella*) accounted for over 2,000 YLD.⁸⁶ Using identical measures of PI-IBS risk (9%), duration (5 years), and disability weight (0.042), those same 3 pathogens were estimated to cause just

Table 1. Evidence of Causal Association Between Gastrointestinal Infection and Functional Gastrointestinal Disorder

	Strength and consistency of effect	Specificity of effect	Biologic gradient or dose response	Temporality	Biologic plausibility	Overall assessment of evidence for causation
IBS	++++ Multiple studies (and meta-analyses) on a variety of populations showing a strong effect in absence of heterogeneity	+++ Diarrhea-predominant IBS is most common; however, inconsistency and instability over time are noted. Many pathogens are associated.	+++ Well-designed studies demonstrate severity of illness and duration of disease in association with increased risk.	+++ Well-designed cohort studies have been reported. RCTs of chemoprophylaxis for TD could be conducted and supportive.	+++ Clinical and animal model data exist, suggesting that inflammation, microbiome, and gut barrier dysfunctions through multiple mechanisms are likely.	Strong Establishment of causality can influence health economics, policy related to the reduction of foodborne illness, and the exploration of biologic mechanisms and novel treatments.
Dyspepsia/ GERD	+++ Multiple studies (no meta-analyses) on a variety of populations showing a strong effect	++ Studies evaluating causation lack strict outcome assessment definitions. Unique pathogen-specific differences for outcome are noted.	++ Few studies have reported severity of illness and duration of disease in association with increased risk.	++ Few well-designed cohort studies have been reported. Association may be confounded by preexisting symptoms and use of acid blockers.	+++ Clinical and animal model data exist that suggest the presence of inflammation and neuroendocrine mechanisms.	Moderate Establishing the causal association of the situations described will require substantial debate and involvement of various stakeholders.
Constipation	++ Limited studies with mixed results	++ Pathogens that primarily cause colitis seem to be associated with functional constipation, although counter examples exist.	+ Studies showing dose response are currently lacking.	+ Few well-designed cohort studies have been reported.	+ Clinical and animal model data on possible disease mechanisms are lacking.	Weak Establishing the causal association of the situations described will require substantial debate and involvement of various stakeholders.
Functional bloating	++ Bloating is a common postinfectious symptom. Studies prospectively evaluating functional bloating are lacking.	+ More studies are needed.	+ More studies are needed.	+ Prospective cohort studies are needed.	++ Animal model data exist that suggest dysbiosis. SIBO may be caused by mechanisms associated with such symptoms.	Weak Establishing the causal association of the situations described will require substantial debate and involvement of various stakeholders.

GERD=gastroesophageal reflux disease; IBS=irritable bowel syndrome; RCT=randomized controlled trial; SIBO=small intestinal bacterial overgrowth; TD=traveler's diarrhea.

Grading definitions:

++++ High quality: Further research is very unlikely to change confidence in the criteria being met.

+++ Moderate quality: Further research is likely to have an important impact on confidence in the criteria being met and may change the overall assessment of causal association.

++ Low quality: Further research is very likely to have an important impact on confidence in the criteria being met and is likely to change the overall assessment of causal association.

+ Very low quality: Confidence in the criteria being met is very uncertain.

under 50,000 IBS-associated YLD in the United States annually in relation to recent estimates of infectious diarrhea incidence.⁸⁷

The fiscal impact of IBS has been described in several reports, and the relative increase in direct annual medical care costs among those with IBS compared with a non-IBS reference population has ranged from several hundred⁸⁸ to well over 1,000 US dollars.⁸⁹ Variability in these estimates likely arises from the use of unique study populations and designs. Also, it is important to note that there is likely variability in PI-IBS disability and care-seeking behavior across numerous demographic characteristics (such as gender) as well as concurrent medical conditions.⁹⁰ Importantly, Levy and colleagues noted that a significant proportion of medical costs among patients with IBS were associated with nongastrointestinal complaints.⁸⁹

Although these studies provide a snapshot of the costs associated with all-cause IBS, it is unclear whether these estimates are similar for PI-IBS. Future studies should attempt to stratify costs regarding IBS episodes following IGE. These direct medical costs are in addition to the economic and societal costs associated with acute foodborne illnesses, which have been estimated at \$133 billion.⁹¹

Recent studies estimate that approximately 33% of all cases of IBS in the United States are attributed to antecedent IGE.⁹² Given that historic estimates for the total annual cost of IBS in the United States is in the billions of dollars,⁹³ primary prevention of IGE through modification of food policy or vaccines in high-risk groups or tertiary prevention through better treatments could provide significant cost savings in the future.

Although these studies provide an initial assessment of the IBS burden of disease, they also highlight important gaps in our understanding. First, the use of PI-IBS-specific parameter estimates is complicated by their scant availability. The majority of studies describing PI-IBS burden have relied on estimates of idiopathic IBS. One parameter that has been inconsistently reported in PI-IBS research is the duration of symptoms following initial onset. Confounding point estimates of symptom duration are variations in study methodology and duration of follow-up. For example, Marshall and colleagues initiated long-term follow-up of subjects following a large waterborne outbreak of enterohemorrhagic *Escherichia coli* and *Campylobacter jejuni*.⁹⁴ Due to the initial efforts to define the affected cohort and an unexposed reference population, investigators have been able to detail the initial risk of PI-IBS and follow IBS persistence and changing disease phenotypes up to 8 years of the initial outbreak using standardized methodology.

In contrast, Ji and colleagues identified a much smaller number of subjects sickened by a foodborne outbreak of *Shigella sonnei* and reported IBS symptoms

in these subjects for 1 year postexposure.²⁸ Due to the temporal nature of the 3-, 6-, and 12-month surveys, the authors used separate definitions for IBS symptoms (Rome I: 3- and 6-month surveys) and IBS (Rome II: 12-month survey only). Table 2 includes a listing of cohort studies in which data on disease persistence following initial infection can be extracted and highlights some of the heterogeneity among studies. Importantly, studies to date seem to indicate that approximately 50% of patients with PI-IBS have persistent symptoms up to 5 years following the instigating infectious episode; however, more studies are needed to improve estimates of PI-IBS and other PI-FGD durations.

Another important component in the calculation of disease burden, specifically the DALY, is the disability weight used to characterize the severity of disease on a scale of 0 (perfect health) to 1 (death). At present, only a single disability weight, 0.042, has been published for IBS.⁸⁵ Although the utility of the disability weight is that it allows a fixed measure of disease severity across populations, such a fixed measure has been criticized as being overly simplified and may over- or underestimate the true burden in a given population.^{95,96} Furthermore, the lone published estimate is not specific for PI-IBS, and comparisons of idiopathic IBS and PI-IBS severity are limited.

In comparing patients with PI-IBS and idiopathic IBS, DuPont and colleagues reported differences in the clinical presentation and impact on daily activities, indicating that IBS is not a homogeneous disorder and that efforts to quantify PI-IBS burden should use PI-IBS-specific parameter estimates.⁹⁷ This is further compounded by the development of other FGDs, including dyspepsia and constipation, following IGE.^{29,30,98,99} Often, these outcomes present as a disease complex with multiple symptoms and diagnoses that may further modify disability weight estimates. Finally, comprehensive cost-of-illness studies are needed that are inclusive of both economic and societal costs for the wide range of FGDs and other sequelae (eg, reactive arthritis, Guillain-Barré syndrome, and IBD) and are specific to particular pathogens and/or food sources. Such studies are needed to prioritize policy and research efforts related to foodborne illness relative to other major public health problems.

Clinical Characterization and Disease Management

Previous attempts at a unifying hypothesis to explain the cause of FGD have acknowledged that there is no known mechanism to explain the overlap of symptoms in IBS, functional dyspepsia, chronic abdominal pain, or chronic fatigue.¹⁰⁰ FGDs are currently defined by the Rome III criteria as a group of symptoms without obvious struc-

Table 2. Cohort Studies Reporting the Persistence of PI-IBS Following Acute Infection

Study	Year	Exposure	Number exposed	Observation time point from exposure					
				First		Intermediate		Last	
				Time (mos)	n (%) [*]	Time (yrs)	n (%) ^{**}	Time (yrs)	n (%) ^{**}
Gwee KA, et al ¹²²	1996	Acute gastroenteritis	75	3	22 (29)	0.5	20 (91)	1	9 (75) [†]
Neal KR, et al ¹²³	2002	<i>Shigella</i>	413	6	25 (6)	–	–	6	8 (57) [‡]
Ji S, et al ²⁸	2005	<i>Shigella sonnei</i>	101	3	20 (20)	0.5	7 (35)	1	10 (50)
Marshall JK, et al ³¹	2007	Norwalk-like virus	91	3	21 (24)	1	9 (43)	2	7 (41) [§]
Jung IS, et al ⁵¹	2009	<i>S. sonnei</i>	87	12	12 (14)	3	9 (75)	5	5 (42)
Marshall JK, et al ⁹⁴	2010	EHEC, <i>Campylobacter jejuni</i>	742	24–36	210 (28)	4	159 (76)	8	114 (54)

EHEC=enterohemorrhagic *Escherichia coli*; IBS=irritable bowel syndrome; PI-IBS=postinfectious IBS.

^{*}Percent is reflective of the percent of subjects with IBS following documented exposure (with the denominator reflective of the total exposed population).

^{**}Percent is reflective of the patients with persistent IBS among those with IBS at the first observation.

[†]The number of patients with PI-IBS completing follow-up decreased from 22 to 12 at the 12-month time point.

[‡]The number of patients with PI-IBS completing follow-up decreased from 25 to 14 at the 6-year time point.

[§]The number of patients with PI-IBS completing follow-up decreased from 21 to 17 at the 2-year time point.

tural or biochemical explanation.⁹⁹ However, as previously described, research over the past decade has yielded considerable advancements in the understanding of the biologic plausibility of PI-FGD. Although these data are encouraging, they do not provide a complete explanation of who may be at risk for development of a chronic gastrointestinal disorder, and there is little understanding of how such patients are best managed. The prediction of which patients are at greatest risk after the resolution of the index infection may allow for more rapid and cost-effective treatment. It would also help to streamline care of those with similar symptoms and infections, thus enabling more comprehensive disease models and a basis for therapeutic interventions.

Risk Assessment

The identification of independent risk factors may elucidate subpopulations at increased risk for FGD following infection. Reports have indicated an increased prevalence among females over males, with a relative risk ranging from 1.47 to 2.86.¹⁶ Stressful life events and psychiatric disorders—specifically anxiety disorders, depression, neuroticism, stress, and a negative perception of illness—have been identified as potential triggers for development of IBS following a gastrointestinal infection.¹⁰¹ These host risk factors, although not present in all cohorts examined, have some overlap with FGD

in general. A clear understanding of how these factors interact and contribute to changes in the host that then lead to symptoms is speculative at this time.

Unlike other gastrointestinal conditions, such as pancreatitis, acute gastrointestinal bleeding, and cirrhosis, there is no certified risk score that can identify or predict the severity and likelihood of long-term complications for those individuals in whom suspected PI-IBS develops.¹⁰²⁻¹⁰⁴ Thabane and colleagues devised a scoring system that demonstrated good predictive accuracy between derivation and validation models through logistic regression analysis, in which gender, duration of diarrheal illness lasting more than 7 days, maximum number of stools per day, presence of abdominal cramps, fever, and weight loss of more than 10 lbs were used as independent variables to create a scoring system of low-, intermediate-, and high-risk probability of development of long-term PI-IBS.³⁹ Although this is a fairly comprehensive scoring system, it does not include age or psychological or physical comorbid conditions, all of which are independent risks that have been associated with PI-IBS in other studies.^{7,17,105} It also does not account for other concurrent PI-FGDs in the absence of altered bowel habits, such as dyspepsia, bloating, or chronic abdominal pain. This underscores the points that there remains disparity about who truly is at risk for the development of PI-FGD and that more controlled studies are needed to further characterize the disease.

A Problem with Definition

PI-IBS is currently defined as the acute onset of new IBS symptoms in an individual who has not previously met criteria for IBS immediately after an acute illness characterized by 2 or more of the following: fever, vomiting, diarrhea, or a positive bacterial stool culture.¹⁰⁶ However, with the overlap of symptoms among PI-FGDs and the current available research on unique genetic risks, changes in the microbiome, neuroendocrine abnormalities, and histologic inflammation, it is reasonable to assume that our current definitions of PI-IBS and PI-FGD are outdated. For example, there currently are separate Rome criteria to diagnose the distinct entities of IBS and functional dyspepsia; however, the definitions do not account for symptom overlap, not to mention the possibility that infectious agents act as disease triggers.^{107,108}

Hanevik and colleagues noted a significant overlap in patients with both IBS and dyspepsia after *Giardia* infection, with abdominal bloating, nausea, and diarrhea being the most common symptoms.⁶⁶ Wang and colleagues confirmed the findings that significant overlap exists, specifically noting that abdominal bloating and postprandial fullness were independent risk factors for the development of both IBS and dyspepsia rather than either one alone, but, unfortunately, the study did not include a postinfectious cohort.¹⁰⁹

A more ideal definition of postinfectious bowel dysfunction is needed. Such a definition should identify specific infectious causes and the myriad gastrointestinal symptoms that can include epigastric pain or discomfort (which may be distinct), bloating, and nausea, all of which may be alone or in combination with stool changes, and lower abdominal cramping. Immunologic and histologic changes would preferably be included along with response to specified treatment strategies; however, large prospective studies among varied populations with detailed exposure information and ascertainment of preexisting bowel dysfunction with long-term follow-up would be needed.

To better define the condition, it may be initially helpful to differentiate patients with primarily dyspeptic symptoms from those with altered bowel movements and independently analyze risk factors, histopathologic changes, and response to treatment. These data could be used to formulate a more comprehensive definition of PI-FGD and help differentiate it from other functional conditions. Finally, with the additional understanding of disease mechanisms and refinement of symptom classifications, especially among those conditions triggered by enteric infection, it may be time to move beyond the “functional” disease classification that presents an often dysfunctional paradigm to both patient and physician.

Disease Management

Successful therapies specific to PI-FGD are lacking, and the majority of published data strictly relate to IBS. Generalized PI-IBS treatment is based on idiopathic IBS therapy and is targeted toward symptom relief. The current rationale supports lifestyle modification through dietary changes, better sleep hygiene, increased regular physical activity, and cessation of the use of potential environmental triggers such as alcohol, caffeine, and tobacco products.¹¹⁰ Recent data suggest that a diet low in fermentable complex sugars and avoidance of gluten, even in those who do not meet the definition for celiac disease, result in reduced bloating, gas, and altered bowel habit symptoms.¹¹¹ Antispasmodics, such as dicyclomine, have been shown to improve abdominal pain and quality of life in some patients with IBS with diarrhea (IBS-D) or alternating IBS, whereas the use of supplemental dietary fiber has shown little promise in treating pain, bloating, or overall symptoms.¹¹² Additionally, loperamide with dose titration to the optimal effect is used to decrease the frequency of bowel movements for those with diarrhea-predominant symptoms.¹¹³

In contrast, laxatives and stool softeners may be beneficial for the subset of patients who have IBS with constipation. Several trials have also evaluated the use of tricyclic antidepressants (TCAs) and have found significant improvement in pain relief and decreased stool frequency compared with placebo¹¹⁴; however, no specific trials using TCAs have been done in the PI-IBS population. One placebo-controlled trial evaluating the use of prednisolone in PI-IBS demonstrated reduced numbers of T lymphocytes in rectal mucosa; however, it did not reduce symptoms of abdominal pain, diarrhea, or fecal urgency.¹¹⁵ There are data to suggest that serotonin metabolism is altered in both PI-IBS and non-PI-IBS and that stimulation of 5-HT₃ receptors increases visceral hypersensitivity and alters intestinal motility.⁶⁸ Alosetron (Lotronex, Prometheus), a 5HT₃ receptor antagonist, has been proven to be effective in female patients with IBS-D.¹¹⁶ However, this has not been studied in PI-IBS or male patients; thus, the utility of the therapy in these populations is unknown. It stands to reason that many of the same medications and dietary changes can be used in the PI-IBS population as well; however, more trials need to be conducted in this specific population.

An area of increasing interest in PI-IBS treatment is the manipulation of intestinal flora. Because certain bacteria are commonly associated with the development of PI-IBS symptoms, it is reasonable to consider that the index infection not only triggers mucosal inflammation but also alters the gut flora. As previously described, one animal model evaluated the density of ICC in *C. jejuni*-exposed rats compared with control rats. Those rats exposed to *C. jejuni* had decreased intesti-

nal ICC and were at higher risk for development of SIBO 3 months after recovery from the infection.⁷⁹ Interestingly, rats given rifaximin (Xifaxan, Salix) had a greater rate of stool shedding and decreased duration of *C. jejuni* colonization, as well as more normal-appearing stools at 3 months postinfection.¹¹⁷ Histologic changes in the mucosa after prophylactic treatment were not evaluated. These data suggest that dysbiosis may play an important role in pathology and provide a potential target area for therapeutic intervention. The use of probiotics has shown promising results in decreasing abdominal pain/discomfort, bloating, and bowel movement frequency; however, no studies have been performed in the PI-IBS subgroup.¹¹⁸

The most interesting medical therapy to come along in recent years is rifaximin for treatment of IBS. Rifaximin is an oral, nonabsorbable, broad-spectrum antibiotic that targets the intestines and has a low resistance profile. A recent trial by Pimentel and colleagues has shown that oral rifaximin 550 mg 3 times daily for 2 weeks was significantly better than placebo in providing global relief of IBS symptoms.¹¹⁹ Unfortunately, no distinction between PI-IBS and non-PI-IBS subpopulations was described in this trial.

Despite promising animal studies in which rifaximin seemed to decrease the rate of development of chronic bowel changes after an infection, as previously noted, no data in human studies that demonstrate the prevention of PI-IBS with this specific antibiotic have been published. Theoretically, rifaximin chemoprophylaxis for enteric infection in high-risk groups, such as travelers, could reduce both the risk and cost of acute illness and the chronic long-term consequences.¹²⁰ Further research in this area would be of value.

Although novel therapeutic strategies are needed, epidemiologic studies may be of value. Specifically, large registry studies that include patients with PI-FGD and controls, along with specific information on treatment modalities used, diet modifications, and changes in functional bowel symptoms may be useful. Furthermore, future studies on vaccines and also chemoprophylactic interventions against acute enteric infections might consider the collection of data on the prevention of FGD as well as primary acute disease endpoints.

Conclusion

Nearly one century has passed since chronic bowel changes were observed after an acute dysenteric episode of diarrhea, with one of the earliest instances being among British soldiers during World War I.¹²¹ This observation prompted a series of basic epidemiologic studies to further determine the existence of a true asso-

Table 3. Epidemiologic Research Gaps Identified

Attribution
<i>Strength and consistency of effect</i>
<ul style="list-style-type: none"> • Studies exploring functional gastrointestinal disorder (FGD) after diverticulitis or appendicitis may be complementary to the understanding of consistency of effect. • Studies evaluating postinfectious risk of constipation and functional bloating are needed.
<i>Temporality</i>
<ul style="list-style-type: none"> • Additional prospective studies with detailed baseline history and close follow-up are needed in well-defined populations to strengthen the evidence of temporality. (Emphasis is needed on microbiome changes and genetic markers or risk.)
<i>Dose response</i>
<ul style="list-style-type: none"> • Studies that are designed specifically to examine disease markers of severity or risk after multiple infections are needed. • Further characterization and standardization of the various animal models are needed.
Burden of disease
<ul style="list-style-type: none"> • Studies of patients with well-defined postinfectious FGD (PI-FGD) are needed to provide estimates of illness-associated disability and symptom duration. • Cost-of-illness studies are needed to elicit estimates of direct and indirect medical care costs specific to PI-FGD.
Clinical characterization and disease management
<ul style="list-style-type: none"> • To improve definitions of postinfectious irritable bowel syndrome (PI-IBS), large prospective studies among varied populations with detailed exposure information, ascertainment of preexisting bowel dysfunction, and inclusion of widely available biomarkers are needed. • A more comprehensive definition may help separate PI-IBS from other FGDs and make identification of those at increased risk easier. • Current treatment for PI-IBS does not significantly differ from that of other FGDs; however, normalization of the intestinal flora may be of some benefit. Additional studies are needed to better define symptom response between PI-IBS and idiopathic IBS groups of patients.

ciation between gastrointestinal infections and FGD. Although it is our opinion that the strength of evidence supports such an association, with suggestive evidence of causation, further research is needed, particularly in the area of non-IBS FGDs and pathogen-specific attribution. The value of such study extends beyond the critical question of disease attribution, and findings gleaned will encourage research in other scientific domains. For example, the strength of evidence for the link between *Campylobacter* and PI-IBS based on the Walkerton,

Ontario outbreak led researchers to initiate clinical studies as well as studies in animal models that advanced our understanding of disease pathogenesis. Epidemiologic research gaps are identified in Table 3.

A critical role of epidemiologic research is to describe the burden of particular diseases and health conditions relative to others. This is important at the societal level for the purpose of optimizing resources to preserve the health of the greatest proportion of the population at a modest cost expenditure. A number of factors beyond strict enumeration of relative disease burden are needed to better clarify the relative importance of disease categories. Well-designed studies on cost of illness and burden of disease could increase focus on FGDs, which greatly contribute to increased disability and loss of quality of life.

Finally, epidemiologic research plays an important role in helping to better classify particular subgroups affected by PI-FGD. The development of agreed-upon standard case definitions and control section criteria that are used prospectively would greatly improve the quality of data and help make findings comparable across multiple population types.

Although it is likely that pathogenic mechanisms of PI-FGD are varied, a prospective study evaluating the natural disease history and effectiveness of differing treatments, diets, and therapies could be developed through a multi-site registry/cohort study. Given the prevalence of acute gastroenteritis and the absolute risk of PI-FGD based on current data, such a study would be able to enroll adequate numbers of subjects across a variety of patient and FGD subtypes. The addition of select biologic specimens would add considerable richness to these data and provide a platform for novel exploration of disease characterization and pathogenesis.

The opinions and assertions herein should not be construed as official or representing the views of the Department of the Navy, the Department of Defense, or the US Government. This is a US Government work. There are no restrictions on its use. There were no financial conflicts of interest among any of the authors. This work was not supported by any work unit number.

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