Significance of post-infectious Irritable Bowel Syndrome?

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Ask any patient with Irritable Bowel Syndrome (IBS) when their condition began and most will struggle to answer but the occasional patient will cite a specific date, saying " I was fine until..". Such patients who relate onset of their IBS to an episode of infectious gastroenteritis appear to be rather different from the others, or are they? As the current review[1] shows this has been a very active area of research whose implications are both clinical, mechanistic and therapeutic.

Clinically it is important to recognise this condition to provide the patients with a rational explanation for symptoms and to reassure them that the prognosis is relatively benign with recovery rates of around one quarter by 1 year [2] and one half by 6-8 years[3;4]. Mechanistically it offers important opportunities to understand the causation of IBS and has stimulated a wealth of research focused on features associated with infection including impaired barrier function, immune activation and altered microbiota. The therapeutic implications will be discussed in the second half of this commentary.

The authors report that the incidence of PI-IBS is highly variable worldwide. We should perhaps not be surprised, since the infecting pathogens have evolved different strategies to overcome host defences. Some, like *Vibrio cholera,* secrete a toxin which binds to a specific receptor, ganglioside GM1, causing chloride secretion from enterocytes greatly amplified by serotonin (5-HT) released from enteroendocrine cells (EEC). This causes profuse intestinal secretion and diarrhoea without much inflammation, in contrast *Shigella flexneri* causes extensive immune activation and ulceration followed by increases in substance P and 5-HT positive nerve fibres along with mast cells, particularly those surrounded by enteric nerves, changes which are more prominent in patients that develop PI-IBS [5]. *Campylobacter jejuni*, one of the commonest causes of PI-IBS in Europe, also causes a striking increase in gut permeability with associated increase in the proportion of EEC which stain for 5-HT along with evidence of long lasting immune activation [6]. The nature of the pathogen influences the risk for developing PI-IBS, the hazard ratio being 4.3 for *E coli* , 2.9 and 2.5 for *C. jejuni* and *Salmonella spp*. respectively and just 2.2 for viral gastroenteritis [7]. This is in keeping with the lesser mucosal damage[8] and typically more rapid recovery after viral enteritis [9]. The importance of pathogen toxicity is best seen by comparing within a single species such as *C jejuni* where it can be seen that the expression of a cytotoxin increases the risk of developing persistent bowel dysfunction [10].

Giardiasis differs from the above, being a protozoan which affects predominantly the upper small bowel [11] while *C jejuni* cause ileal and colonic ulceration. While C jejuni increases 5-HT containing enteroendocrine cells Giardia decreases them but causes an increase in cholecystokin (CCK) containing cells[12]. While both types of infection are associated with PI-IBS, Giardia is associated with a much higher rate of postinfectious functional dyspepsia, being 25.9% after 3 years [13] compared to just 13% 1 year after Salmonellosis [14]. This may relate to the higher postprandial CCK levels which correlate with dyspepsia scores[12].

Host immune status is important with older age protecting against infection[15] and also PI-IBS [16], possibly reflecting greater immunity gathered over a longer lifetime or less hygienic conditions when they were young which may increase the risk of PI-IBS [2].

Given this marked variability in initial insult and host response it is perhaps not surprising that PI-IBS is, like other sorts of IBS, heterogeneous both in its symptoms and underlying mechanisms. Indeed perhaps the greatest discovery of the last decade has been that PI-IBS is remarkably similar to other sorts of IBS, both in the importance of a psychological predisposition [7], as well as the changes in the gut including immune activation, impaired barrier function and altered serotonin metabolism.

This raises the important issue of how much of all IBS is post-infectious? One small early study reported that the proportion ranged from 6-17% [17], a figure similar to the 13.3% reported in a recent much larger survey[2].

One key question remains, have these insights lead to specific therapies targeted at underlying mechanisms rather than the current symptom directed therapies? The observations of immune activation in PI-IBS encouraged a small pilot study of prednisolone in PI-IBS which however showed no benefit [18]. An RCT of the anti-inflammatory agent mesalazine in IBS-D showed no benefit overall, however *post hoc* analysis showed that a small subgroup with PI-IBS appeared to respond [19]. Furthermore, open label treatment of *E. coli* O147 infection with mesalazine appeared to reduce the risk of developing PI-IBS[20] but this needs confirming by RCT. Against this small pilot study of mesalazine in PI-IBS failed to show any difference from placebo though it was undoubtedly underpowered[20;21]

More encouragingly Keating et al showed that Trichinella infection in mice was followed by increased 5-HT availability in the small intestine and visceral hypersensitivity which could be blocked by a 5-HT receptor antagonist, ondansetron [22]. This and evidence that PI-IBS patients have exaggerated postprandial 5-HT release encouraged a randomised placebo controlled trial (RCT) of ondansetron in IBS with diarrhoea (IBS-D) which showed relief of IBS symptoms, particularly urgency [23]. Small intestinal bacterial overgrowth (SIBO) has been shown in rodent models of PI-IBS after Campylobacter infection [24]and recent studies in India have suggested that PI-IBS may overlap with tropical sprue in which SIBO is common[25]. Trials with rifaximin targeting SIBO have shown a benefit in about 1 in 11 of IBS-D patients.

As can be seen, most of the literature to date on PI-IBS has been descriptive, what is now needed (see Figure 1) are large randomised trials in PI-IBS of specific treatments in which participants are subdivided according to the underlying mechanisms. The response of each subgroup will allow more accurate definition of what is the main driver of symptoms and what is mere epiphenomena. Only then will we achieve the precision medicine we all aspire to.

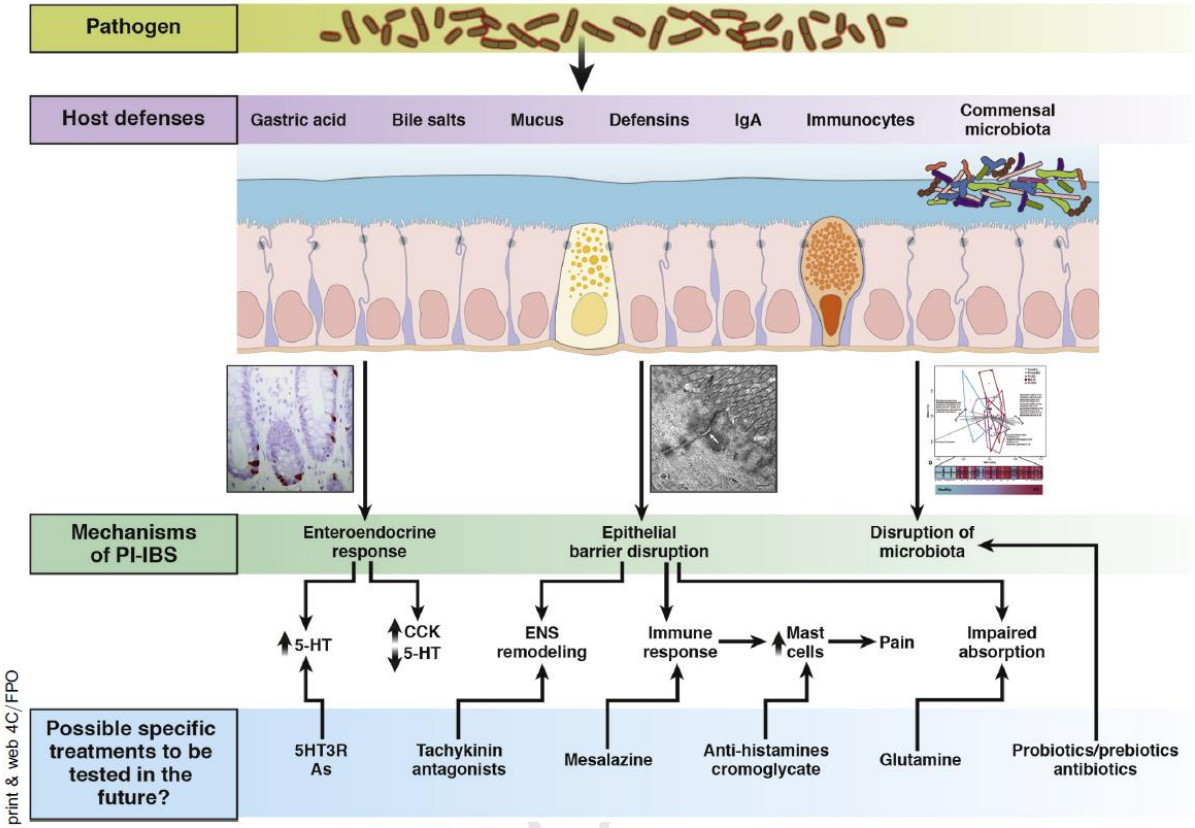

Figure 1. ■■■

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