Altering the gastrointestinal flora in patients with functional bowel disorders: a way ahead?

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Abstract: Functional gastrointestinal disorders are very common in the Western world, but unfortunately the underlying mechanisms behind these disorders are incompletely understood. Treatment options are limited and the economic consequences for society are profound. Recent data suggest an involvement of bacteria in the pathogenesis of functional gastrointestinal disorders. Probiotics are promising new treatment alternatives, which will be reviewed in this supplement.

Keywords: functional gastrointestinal disorders, probiotics, irritable bowel syndrome

Introduction

Functional gastrointestinal (GI) disorders are defined as a variable combination of chronic or recurrent GI symptoms, attributed to different parts of the GI tract, which is not explained by structural or biochemical alterations; that is, without clear explanation found on routine investigations [Drossman, 2006]. Irritable bowel syndrome (IBS) – one of the functional bowel disorders – is one of the most common functional GI disorders, affecting 10–15% of the general population [Vandvik *et al.* 2006; Agreus *et al.* 1995] and constitute a significant part of the workload for both gastroenterologists and primary care physicians [Thompson *et al.* 2000; Harvey *et al.* 1983]. IBS is characterized by abdominal pain and/or discomfort related to an abnormal bowel pattern [Longstreth *et al.* 2006]. Other prominent symptoms often seen in these patients are bloating, visible abdominal distension, incomplete bowel emptying, urgency and excessive straining. Moreover, overlap with upper GI symptoms, as part of a more widespread functional GI symptom complex, is very common [Corsetti *et al.* 2004], as well as coexisting extraintestinal symptoms such as muscle pain, headache, sleep disturbances, urogenital symptoms and fatigue [Maxton *et al.* 1991]. Health-related quality of life in IBS patients is reduced [Simrén *et al.* 2004] and is often more severely impaired in patients with a functional GI disorder than in groups of patients with an organic GI disease [Simrén *et al.* 2006]. Unfortunately, the understanding of the pathogenesis and pathophysiology of these disorders

is limited and there are few effective treatment options [Spiller *et al.* 2007]. Moreover, health-care consumption in this group of patients is high, and since IBS is a very common, chronic disorder with severe symptoms, the economic consequences of the disorder are profound [Wells *et al.* 1997].

In order to improve the management of these patients, a better understanding of disease mechanisms involved in the generation of symptoms in IBS patients is needed. This will potentially lead to new treatment alternatives. Recent studies suggest a potential role of altered gut flora in IBS and there are promising treatment trials using probiotics. In this supplement, presentations given at a recent symposium exploring the potential role of bacteria in the pathophysiology of IBS and the usefulness of treatment with probiotics are summarized.

Aetiology and pathogenesis of IBS

The causes of IBS are largely unknown, which is an obvious dilemma in the search for new therapeutic options. However, there are some known risk factors for developing IBS, but for the individual patient it is often impossible to give information about the cause of their specific symptoms. One of the most well-established risk factors for developing IBS is having an infectious gastroenteritis [Halvorson *et al.* 2006], especially if the subject has psychological symptoms at the time of the infection [Gwee *et al.* 1999]. Moreover, psychological factors and stress *per se* seem to be a risk factor for developing IBS, as many patients

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report onset of their disorder during a period in their life with stress or poor psychological well-being [Ford *et al.* 1987]. There also seems to be a genetic component of IBS, as suggested by aggregation of symptoms compatible with a functional bowel disorder in families [Saito *et al.* 2008] and the fact that concordance for IBS is greater in monozygotic than in dizygotic twins [Levy *et al.* 2001]. However, social learning has also been proposed to contribute to the development of IBS and can partly explain the aggregation of IBS in families [Levy *et al.* 2000].

Pathophysiology of IBS

The pathophysiology of IBS is complex and most probably multifactorial [Ohman and Simrén, 2007]. Historically, IBS has been considered to be a disorder of altered GI motility, but even though motility alterations do exist in a subset of IBS patients [Camilleri *et al.* 2008; Chey *et al.* 2001; Simrén *et al.* 2000], no uniform motility pattern has been found and a clear relationship with the different symptoms has been hard to demonstrate. Visceral hypersensitivity is probably one of the most important pathophysiological factors in IBS [Mertz *et al.* 1995], even though its relevance has to some extent been questioned recently [Naliboff *et al.* 2006]. However, recent studies have demonstrated an association between the presence of visceral hypersensitivity and severity of IBS symptoms, especially pain and bloating [Kanazawa *et al.* 2008; Posserud *et al.* 2007], but it also seems clear that other factors are equally or even more relevant for the symptom pattern. Psychosocial factors, stress and maladaptive coping styles are most certainly of great importance for the symptom severity of IBS patients [Drossman *et al.* 2000; Whitehead *et al.* 1992], and recent studies indicate differences between IBS patients and healthy controls in activation of different pain processing regions in the brain [Hobson and Aziz, 2004]. Taken together, much of the current evidence points in the direction of IBS being a disorder of dysregulation of the brain–gut axis, with peripheral alterations probably dominating in some patients and disturbed central processing of signals from the periphery dominating in others [Ohman and Simrén, 2007; Posserud *et al.* 2006].

Treatment options for IBS

As stated above, effective treatment options for IBS are limited. There are treatment alternatives for individual symptoms such as diarrhoea, constipation and abdominal pain, but none of the

Figure 1. Number of articles found on PubMed when using the search terms 'bacteria' and 'IBS'.

available treatment options target the overall symptoms of IBS [Jailwala *et al.* 2000]. Moreover, due to unexpected side effects of recently developed IBS drugs [Pasricha, 2007; Thompson, 2001] several pharmaceutical companies have stopped their development of drugs for functional GI disorders. Moreover, nonpharmacological treatment alternatives such as different psychological treatment options [Lackner *et al.* 2004], which seem to be very effective, are hampered by limited availability. Therefore, there are great unmet medical needs for patients with functional GI disorders today.

Inflammation, permeability, bacteria and IBS

During recent years, studies exploring new pathogenetic and pathophysiological factors have been presented. These include low-grade inflammation within the GI tract [Ohman *et al.* 2005; Barbara *et al.* 2004], altered intestinal permeability [Piche *et al.* 2009] and alterations in the bacterial flora of the GI tract [Kassinen *et al.* 2007; Posserud *et al.* 2007]. In particular, the latter has attracted many researchers, which can be seen in the increasing number of publications found on PubMed exploring the role of bacteria in IBS in recent years (Figure 1). Future studies will most certainly be valuable in order to clarify the role of bacteria in IBS and the possibilities to do so are tremendous given the fact that new sophisticated techniques to analyze the composition of the gut flora more accurately have been developed [Furrie, 2006].

Probiotics and IBS

Probiotics are defined by the World Health Organization as 'live micro-organisms which when administered in adequate amounts confer a health benefit on the host' [WHO]. Several groups have performed studies assessing the effect of different probiotic products on IBS symptoms, with somewhat conflicting results, but the overall impression is that probiotic products are promising treatment alternatives for functional GI disorders,

Figure 2. Number of articles found on PubMed when using the search terms 'probiotic' and 'IBS'.

which is supported by recent meta-analyses [McFarland and Dublin, 2008; Moayyedi *et al.* 2008]. However, today there is limited knowledge about mechanisms behind improvement with probiotics and if some probiotic products are better than the others. Therefore, more research within this area is needed, even though the number of articles published assessing probiotics in IBS is steadily increasing (Figure 2).

Conclusion

There are tremendous unmet medical needs in IBS and other functional GI disorders. The available treatment options are limited and the pathogenesis/pathophysiology is poorly understood. Better understanding of mechanisms behind symptoms in IBS is needed, as well as new effective treatment alternatives. Today, there is evidence that bacteria within the gut will turn out to be major players in the pathogenesis/pathophysiology of IBS and other functional GI disorders, and probiotics are certainly promising treatment alternatives for these patients. This will be thoroughly evaluated in the papers in this supplement, which are summaries of presentations given at a satellite symposium at the 2nd Joint International Neurogastroenterology and Motility meeting in Lucerne, Switzerland, November 2008.

Conflict of interest statement

Advisory Board: AstraZeneca, Novartis, Albireo, Danone, Movetis, Succampo, Addex, Research support: AstraZeneca, Danone, ArlaFoods, Alimenta, Novartis, Speaker: AstraZeneca, Novartis, Danone.

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