

## LEADING ARTICLE

## Dysbiosis in inflammatory bowel disease

C P Tamboli, C Neut, P Desreumaux, J F Colombel

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Abundant data have incriminated intestinal bacteria in the initiation and amplification stages of inflammatory bowel diseases. However, the precise role of intestinal bacteria remains elusive. One theory has suggested a breakdown in the balance between putative species of “protective” versus “harmful” intestinal bacteria—this concept has been termed “dysbiosis”. Arguments in support of this concept are discussed.

**A**bundant data have incriminated intestinal bacteria in the initiation and amplification stages of inflammatory bowel diseases (IBD).<sup>1–2</sup> The role of the NOD2/CARD15 Crohn’s disease (CD) susceptibility gene in bacterial peptidoglycan recognition strengthens the links between enteric bacteria and mucosal inflammation.<sup>3–5</sup> Despite these advances, the precise role of intestinal bacteria remains elusive. Non-mutually exclusive theories have included: an unidentified persistent pathogen; an abnormally permeable mucosal barrier leading to excessive bacterial translocation; an immune system abnormality of effector cell activation or insufficient regulatory cell activity in response to intestinal bacteria<sup>6–7</sup>; or a breakdown in the balance between putative species of “protective” versus “harmful” intestinal bacteria—this concept has been termed “dysbiosis”.<sup>8–9</sup> Here we will focus on arguments to support this concept.

## EXPERIENCE FROM EXPERIMENTAL MODELS OF COLITIS

The presence of intestinal bacteria is essential in several animal models of colitis. These models exist on varied genetic backgrounds, including mice that are deficient in interleukin (IL)-10,<sup>10</sup> T cell receptor alpha beta,<sup>11</sup> T cell receptor alpha,<sup>12</sup> and also CD3-epsilon transgenic mice<sup>13</sup> or HLA-B27 transgenic rats.<sup>14</sup> By nature of their design however, these studies have not examined the natural relationships of intestinal flora before or during intestinal inflammation. Experiments have employed the entire undefined native intestinal microflora, excluded certain known pathogens (specific pathogen free), or selectively colonised animals with defined bacterial species under germ free conditions.<sup>15–16</sup> In these models, the appearance of colitis depends on highly individualised host-microbe relationships. For example, Waidmann *et al* have recently shown that colitis occurs in IL-2 deficient germ free mice with a non-pathogenic strain of *Escherichia*

*coli mpk* but not with *Bacteroides vulgatus*.<sup>17</sup> Colitis did not develop with coadministration of both species, suggesting that *B vulgatus* has a protective role in this model. Interestingly, *B vulgatus* induces inflammation in carrageenan induced guinea pig colitis,<sup>18</sup> T cell receptor alpha knock-out mice,<sup>12</sup> or HLA-B27 transgenic rats,<sup>15</sup> even without other microflora. Also interesting is that in Waidmann’s experiment, *E coli mpk* lacked commonly recognised virulence traits such as adhesiveness whereas other more adhesive strains of *E coli* (strain Nissle) remained incapable of inducing colitis.<sup>17</sup> These observations suggest that the bacterial virulence factors essential for inducing inflammation are not yet well characterised, and that microbe-microbe interactions vitally influence expression of disease.

On the other hand, probiotic therapies have attempted to modify disease expression by favourably altering bacterial composition, immune status, and inflammation. The rationale for administering strains of live “beneficial” bacteria for IBD is based largely on the premise of dysbiosis. The strain *Lactobacillus* subspecies *reuteri* was shown to reduce mucosal permeability, prevent the onset of colitis, and attenuate established inflammation in IL-10<sup>-/-</sup> mice.<sup>19</sup> Successful probiotic strategies have not been limited to bacteria: helminthic parasites also induce immunomodulatory T cell responses in the host. Exposure to eggs of *Schistosoma mansoni* has been shown to attenuate excessive Th1-type inflammation in the trinitrobenzene sulphonic acid colitis mouse model.<sup>20</sup> *Schistosoma* egg exposure diminished interferon  $\gamma$  levels, enhanced IL-4 production and IL-10 mRNA expression, and protected these mice from lethal inflammation.<sup>20</sup> Of great interest will be studies exploring which components of probiotic organisms are important disease modifiers and how these components interact.

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In summary, experimental animal models have greatly contributed to our understanding of IBD pathogenesis. They have shown us that certain organisms and strains may be protective

**Abbreviations:** IBD, inflammatory bowel disease; CD, Crohn’s disease; IL, interleukin; PCR, polymerase chain reaction; UC, ulcerative colitis

See end of article for authors’ affiliations

Correspondence to:  
Dr C P Tamboli, Division of Gastroenterology, Department of Internal Medicine, University of Iowa Hospitals and Clinics, 4544 JCP, 200 Hawkins Drive, Iowa City, Iowa, USA; cyrus-tamboli@uiowa.edu

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while others are aggressive, but the models have not yet explored the issue of dysbiosis.

## DYSBIOSIS IN IBD

In IBD, intestinal microflora have been analysed repeatedly. Although methodologies and results may differ, some generalisations are possible (for an overview see Linskens and colleagues<sup>21</sup>). Earlier studies utilised conventional faecal based or mucosal bacterial isolation and culture techniques. These have often shown increased concentrations of anaerobes, particularly Gram negative anaerobes, including *Bacteroides* species in CD,<sup>22–25</sup> ulcerative colitis (UC),<sup>26–27</sup> and pouchitis.<sup>28–29</sup> The pouchitis studies found increased numbers of *Clostridium perfringens* and other species not found in controls. Other studies incriminate *Enterobacteriaceae*, especially *E coli*, in CD.<sup>25–30–31</sup> Many studies have also noted reductions in presumably beneficial bacteria, such as *Bifidobacteria* species in CD,<sup>24–30–32</sup> UC,<sup>33</sup> and pouchitis.<sup>28</sup>

Several points require emphasis regarding studies on the intestinal flora in IBD. Firstly, most studies have used conventional bacteriological techniques that are inadequate for complete enumeration of the intestinal flora. Only up to 30% of the total microflora can be recovered in this way, and so molecular techniques analysing bacterial 16S ribosomal RNA components may improve the overall detection rate.<sup>34</sup> Molecular techniques include polymerase chain reaction (PCR), in situ hybridisation, flow cytometry, and DNA microarray/chip analysis. However, even the use of molecular probes may leave significant numbers of bacteria undetected.<sup>35</sup> Secondly, many strains in CD do not belong to major phylogenetic groups represented in healthy individuals.<sup>34</sup> Even in healthy subjects, up to 75% of the total bacteria remain unclassified species.<sup>36–37</sup> The possible contribution of these strains to IBD remains unknown. Thirdly, a distinction should be made between mucosal flora and faecal flora. The compositions of these two domains are unique<sup>38</sup> and this may be of significance in IBD. Indeed, it is a reasonable assumption that the dysregulated immune response of IBD is targeted towards mucosal associated flora.<sup>39</sup> As in faecal culture studies, mucosal analyses in IBD have found increased concentrations of anaerobes,<sup>25–27–35–40–41</sup> *E coli*,<sup>25–31–35–40</sup> and decreased concentrations of *Bifidobacteria* species,<sup>35–41</sup> including in the neoterminal ileum following ileocolonic resections for CD.<sup>31</sup> There is also evidence to suggest an overall increase in mucosal concentrations of other bacterial species. Schultz *et al* used 16S rRNA probes with in situ non-fluorescent hybridisation to demonstrate increased bacteria localised to the rectal mucus layer.<sup>42</sup> Most of the patients studied had UC. Similarly, Swidsinski and colleagues<sup>40</sup> demonstrated thick layers of adherent mucosal associated bacteria in both UC and CD. Higher bacterial concentrations were found in Crohn's subjects. By simultaneous culture, quantitative PCR, and fluorescent in situ hybridisation analysis, 50% of CD patients had either *E coli* or *Bacteroides* species as the predominant group. Kleessen and colleagues<sup>35</sup> used 16S rRNA probes to demonstrate increased mucosal concentrations of many species in UC but particularly *E coli* and *Bacteroides* species in CD. It should be noted that mucosal studies using molecular techniques do not always concur: Swidsinski and colleagues<sup>40</sup> found overall mucosal bacterial concentrations to be higher in CD than UC and higher in the ileum than in the colon, whereas Kleessen and colleagues<sup>35</sup> found the reverse. Neither Schultz and colleagues<sup>42</sup> nor Swidsinski and colleagues<sup>40</sup> found bacterial colonisation in control specimens or any relationship between bacterial invasion and the degree of mucosal inflammation but Kleessen and colleagues<sup>35</sup> did demonstrate bacteria in control specimens and increased penetration in areas of inflammation. Patient selection and complex processing requirements may account for some of these discrepancies.

“Certain intestinal strains may be overrepresented in IBD, both in proportion and in immune responsiveness towards them”

Also worth considering are data from serological studies. Specific antibodies and T cell subsets have been demonstrated in serum and intestinal tissues of IBD patients.<sup>26–27–43–46</sup> Reactivity to bacterial antigens is not unexpected with increased mucosal permeability or intestinal inflammation, and thus does not by itself add weight to the argument for dysbiosis. In this issue of *Gut*, Furrie and colleagues<sup>41</sup> describe their simultaneous quantitative analysis of immune responsiveness to over 35 intestinal bacterial isolates in IBD subjects [see page 91]. Significantly higher systemic antibody responses were mounted in UC towards *Peptostreptococcus anaerobius*, in parallel with higher recovery rates of this strain from the colonic mucosae. This analysis provides evidence that certain intestinal strains may be overrepresented in IBD, both in proportion and in immune responsiveness towards them. Similarly, Landers *et al* have described heterogeneity of immune responsiveness to selected bacterial antigens in a large cohort of CD patients.<sup>47</sup> The proportions of seroreactive patients varied towards four microbial antigens, and cluster analysis of the seroreactivity patterns defined distinct patient subgroups. Although speculative, this raises the question of whether such antibody profiles might represent important differences in the composition of the mucosal flora or dysbiosis.

Emerging therapies for IBD include probiotics and prebiotics. There is good animal data to support the beneficial effects of many commensal bacteria on immune function and mucosal integrity. However, there remain very few well designed randomised clinical trials of probiotics in IBD. The most positive results have been for pouchitis prevention with a mixture of strains, VSL#3 (Yovis; Sigma-Tau, Pomezia, Italy).<sup>48</sup> VSL#3 also prevents relapse of chronic pouchitis.<sup>49</sup> As mentioned earlier, dysbiosis has been proposed as a key feature of pouchitis.<sup>28</sup> Prebiotic therapy—manipulation of diet to promote growth of beneficial intestinal microflora—is becoming increasingly studied and could prove to be particularly useful in improving dysbiosis. Colonic growth of *Bifidobacteria* strains is promoted by regular consumption of certain indigestible carbohydrates such as fructooligosaccharides and inulin, which are found at high concentrations in specific vegetable foods.<sup>50–51</sup>

“How some bacteria may exert an inflammatory effect and others a protective role in IBD is as yet uncertain”

How some bacteria may exert an inflammatory effect and others a protective role in IBD is as yet uncertain. Strains of *Bacteroides* and *Clostridia* species can produce enterotoxins and/or possess proteolytic properties that enhance mucosal permeability and bacterial uptake.<sup>52–53</sup> There may also be detrimental effects of sulphide producing bacterial species in UC<sup>35–54</sup> or pouchitis.<sup>29</sup> Hydrogen sulphide blocks epithelial cell utilisation of short chain fatty acids, the preferred nutrient source for colonocytes. However, one animal model has shown sulphide production to be unimportant in DSS induced colitis.<sup>55</sup> Other investigations are focusing on the role of peptidoglycans, lipopolysaccharides, and bacterial CpG DNA motifs.<sup>56</sup> Studies from our group have shown that adherent and invasive *E coli* often colonise ileal lesions of CD. These strains appear to have all of the virulence factors required to colonise intestinal mucosa, cross the epithelial barrier, interact with resident macrophages, and induce the synthesis of proinflammatory cytokines by infected epithelial cells and macrophages.<sup>57–59</sup>

"Is dysbiosis just a secondary phenomenon of IBD, or is it actually a cause of IBD?"

Assuming dysbiosis is indeed a key element in the pathogenesis of IBD, perhaps the most vexing question is: what is the origin of dysbiosis? It was proposed many years ago that determination of our intestinal flora may be partly under genetic control.<sup>60</sup> Alterations in faecal flora have also been found among healthy relatives of patients with IBD,<sup>23</sup> suggesting that this may be an important a priori genetic risk factor for developing IBD. However, close family members also share their environment and the relative contributions of genetics and environment to one's intestinal flora makeup are unclear. Environmental factors thought to be influential in determining the type (and rate of establishment) of normal intestinal flora include: mode of childbirth, maternal intestinal and vaginal bacterial colonisation patterns, weaning practices, and local environmental variables (hospital bacteria, level of hygiene, etc). Most studies of neonates show that intestinal colonisation progresses rapidly after childbirth, although factors determining the ultimate composition are unclear. Another key question related to this issue is: at what time does the intestinal flora of a person with IBD become dysbiotic? Is dysbiosis just a secondary phenomenon of IBD, or is it actually a cause of IBD? In favour of the former argument are animal data which suggest that the host's immune phenotype may strongly influence the composition of the intestinal microflora.<sup>61</sup> However, older literature suggesting that the bacterial profile is stable throughout life has been challenged by suggestions that a Western diet, modern infant nutrition, antibiotic use patterns, and public health measures may favour the growth of relatively aggressive resident bacteria at the expense of beneficial commensals.<sup>9</sup> Future IBD research endeavours should focus on developing testable hypotheses for each of these proposed risk factors.

#### Authors' affiliations

**C P Tamboli**, Division of Gastroenterology, Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA  
**C Neut**, Laboratoire de Bacteriologie, Faculté de Pharmacie, Lille and INSERM EPIO114, CHU Lille, France  
**P Desreumaux**, **J F Colombel**, Service d'Hepatogastroenterologie, Hopital Huriez and INSERM EPIO114, CHU Lille, France

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## GI SNAPSHOT.....

### Self inflicted rectal ulcer: hearing is believing

#### Question

A 54 year old woman presented with haematochezia of two weeks duration. She gave no history of straining at defecation or taking non-steroidal anti-inflammatory drugs. Physical examination was unremarkable. A colonoscopic image, showing a shallow longitudinal ulcer involving the anterolateral wall of the lower rectum and anal canal, is depicted in fig 1. Biopsies showed non-specific inflammation without the presence of fibromuscular obliteration. What further information should be obtained to make a definitive diagnosis? What is the most likely diagnosis?

See page 20 for answer

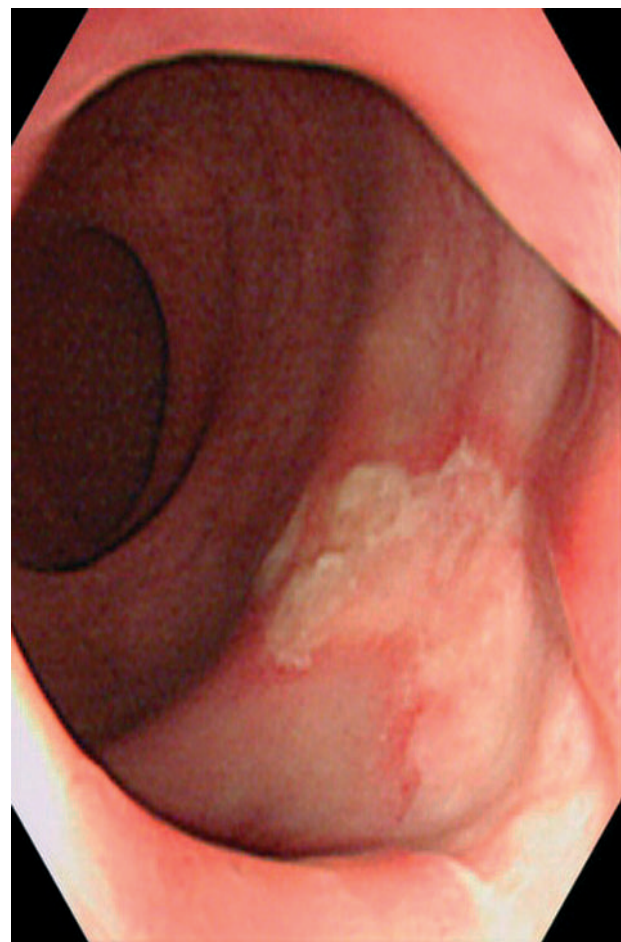
**A Hokama  
F Kinjo  
R Tomiyama  
A Saito**

First Department of Internal Medicine, University of the Ryukyus, Okinawa, Japan

**H Kikkawa  
H Miyazato**

Department of Psychiatry, University of the Ryukyus, Okinawa, Japan

Correspondence to: Dr A Hokama, First Department of Internal Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan; hokama-a@med.u-ryukyu.ac.jp



**Figure 1** Colonoscopic image, showing a shallow longitudinal ulcer involving the anterolateral wall of the lower rectum and anal canal.