Treatment, follow-up and microbiota in acute diverticulitis
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Citation for published version (APA):
Daniels, L. (2015). Treatment, follow-up and microbiota in acute diverticulitis

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PART 3

MICROBIOTA
A hypothesis: 
Important role for gut microbiota in 
the etiopathogenesis of diverticular disease
BACKGROUND

Epidemiology, Terminology, and Pathophysiology of Diverticular Disease

Diverticular disease (DD) inflicts a high socioeconomic burden on Western and industrialized countries because of an increasing incidence worldwide and, consequently, increasing admission rates and costs. DD is composed of a spectrum of conditions. Patients with diverticulosis have asymptomatic colonic diverticula. Uncomplicated DD is defined as symptomatic disease, associated with mild symptoms, such as abdominal pain and/or change in bowel habit. Complicated DD is diverticulitis with severe clinical symptoms and evidence of inflammation. Complicated diverticulitis is accompanied by an abscess, perforation, peritonitis, fistula, bleeding, stricture, or obstruction.

The epidemiology and pathophysiology are assumed to be clear and well understood. However, theories are currently shifting away from the traditional dogma stating that low dietary fiber predisposes to diverticulosis and fecalith obstruction of a diverticulum causes acute diverticulitis. DD was once regarded as a relatively asymptomatic disorder hampered by acute, often self-limited, attacks of diverticulitis.

More recently, the chronic component in some patients with symptomatic DD received attention, and it was suggested this condition should be regarded as a form of inflammatory bowel disorder. New research implicates a role for low-grade inflammation and alterations of gut microbiota in this group of diseases. Other than known factors, such as age, diet, fecalith entrapment, and bacterial overgrowth, gut microbiota may play a role in the development of diverticula and (complicated) DD.

Microbiota as a New Player in the Field

A new hypothesis encompasses the roles of altered gut microbiota and low-grade chronic inflammation leading to periods of symptomatic DD and perhaps even as triggers of acute diverticulitis. Several lines of indirect evidence support a potential association between these factors and DD. The initial hypothesis by Painter and Burkitt with a key role for fiber deficiency in the etiology of DD, as well as outdated views on the pathogenesis of inflammation, needs some revision. Based on current literature, we aim to integrate known factors and the new player in the field, gut microbiota, and propose a valid hypothesis on the etiopathogenesis of DD in which an important role is reserved for the microbiome factor.

Gut Microbiota Function and Characterization

A symbiotic relationship exists between intestinal microbiota and the host. The gut microbiota have a direct impact on the morphology of the gut and are involved in protective functions. The microbial layer in the gut mucosa contributes to the gut barrier function. The gut mucosal barrier effect causes resistance to pathogens, thereby controlling epithelial cell proliferation and homeostasis of the immune system. Moreover, the gut mucosal barrier has a metabolic function in the fermentation of non-digestible dietary residues into short-chain fatty acids.
Characterization of gut microbiota was formerly performed almost exclusively by cultivation methods. However, the large majority of organisms are refractory to cultivation, and the true diversity of the microbial communities is not reflected. Presently the highly conserved 16S ribosomal RNA gene is used for taxonomic purposes. Nowadays nucleic acid sequencing methods allow for differentiation of bacteria at species and subspecies levels.

**Normal Gut Microbiome Composition**

The initial colonization after birth is very important with respect to the final composition of the permanent flora in adults. A healthy intestinal microbiome can be defined as the normal individual microbiota that maintain and propagate wellbeing and absence of disease. The intestine harbors a complex bacterial community that consists almost entirely (>95%) of 2 bacterial phyla, Bacteroidetes and Firmicutes. The genera *Bacteroides, Bifidobacterium, Eubacterium, Clostridium, Peptococcus, Peptostreptococcus, and Ruminococcus* are predominant. The intestinal tract of every individual contains several hundred different species belonging to these genera. Each individual has a particular combination of predominant species that is distinct from that found in other individuals, the microbiome fingerprint.

Gut microbiota stability is controlled by several factors, among others: pH, temperature, microbial interaction, peristalsis, bile acid, drug therapy, and immune responses. An individual’s microbiome composition can fluctuate under some circumstances, for instance, with acute diarrheal illnesses, antibiotic treatment, or, to a lesser extent, dietary interventions.

**Changes in Gut Microbiome in Relation to Disease**

Disease-specific variations in the composition of the colonic microbiome have been found as well. A descriptive study in humans has mapped fecal flora composition and has found a high risk for colon cancer in the presence of *Bacteroides vulgatus* and *B stercoris* and a low risk with *Lactobacillus acidophilus, L S06*, and *Eubacterium aerofaciens*. Although the evidence is not conclusive, colonic flora could play a part in initiation of colon cancer through the production of carcinogens, cocarcinogens, or procarcinogens. In sections of acute appendicitis, Fusobacteria are a specific component of epithelial and submucosal infiltrates in 62% of patients, and its presence positively correlates with the severity of the appendicitis. For conditions with some similarities to DD, such as irritable bowel syndrome (IBS) and IBD, and also for obesity, a known risk factor for diverticulitis, intestinal microbiota shifts have been observed.
IBS and Gas-Related Syndrome

IBS is a disorder with a multifactorial and largely undetermined pathophysiology. A changed composition of microbiota is thought to be the underlying causative factor for nonspecific gastrointestinal symptoms, such as bloating, borborygmus, flatulence, abdominal distension, and discomfort. This so-called gas-related syndrome is caused by overproduction of gastrointestinal gas and may be related to an altered gut microbiome. Decreased \textit{Clostridium}, \textit{Lactobacilli}, and \textit{Bifidobacteria} have been demonstrated in the feces of IBS patients.\textsuperscript{6} In terms of symptomatology, there is considerable overlap between DD and IBS.

Obesity, Microbiome, and Diverticulitis

Obesity has been established as a major risk factor for diverticulitis. The exact mechanism that links these 2 conditions is unclear. An altered cytokine profile, increased intra-abdominal pressure, altered diet, and altered gut microbiome may play a role.\textsuperscript{2} Ley et al.\textsuperscript{11} showed that the relative proportion of Bacteroidetes is decreased in obese people in comparison with lean people and that this proportion increases with weight loss on 2 types of low-calorie diets. Therefore, obesity may affect inflammatory responses either directly or indirectly, and thereby contribute to the development of diverticulitis.

IBD and Changes in Intestinal Microbiota

IBD is a spectrum of diseases characterized by chronic gastrointestinal inflammation. Compositional and functional changes in the intestinal microbiota, host genotype, and immune disequilibrium may play a role in the development and progression of disease. Comparison of clone libraries has revealed significant differences between the microbiota of patients with Crohn’s disease (CD) and ulcerative colitis and those of non-IBD controls.\textsuperscript{12} Patients with IBD have higher amounts of bacteria attached to their epithelial surfaces and a predominant colonic phenotype of anaerobic commensal enteric microbiota compared with healthy people.\textsuperscript{5} Direct interaction between commensal microflora and intestinal mucosa can stimulate inflammatory activity in the gut lesions. After induction of colitis, some anaerobes invade the mucosa. Intestinal microflora of patients with IBD produce greater amounts of metabolic products than the microflora of healthy controls.\textsuperscript{6} Uninhibited activation of the intestinal immune system by elements of the gut flora could be a causative factor in the pathophysiology of IBD.\textsuperscript{5}

Inflammatory Similarities Between IBD and DD

The interest in similarities between IBD and DD is growing. The coming and going of symptoms in DD is similar to periods of exacerbation and remission in IBD. A possible overlap between chronic diverticular inflammation and IBD has been suggested more than once. Studies in biopsy material indicate that DD is associated with degrees of chronic inflammation. Floch\textsuperscript{3} demonstrated that diverticula are associated with an increase in microscopic colitis. Biopsy material of left-sided diverticula showed mild-to-moderate lymphocytic infiltrates and chronic inflammation in areas of diverticula.\textsuperscript{3} Gledhill
and Dixon\textsuperscript{13} have found histologic features of CD and diverticulitis in colonic resection specimens of 11 patients. All of the cases demonstrated mural thickening, hypertrophy of the muscularis propria with diverticula, and peridiverticular abscesses typical of DD. Microscopy revealed transmural granulomatous inflammation and ulceration typical of CD, with crypt abscess formation and fissuring ulceration in most cases. The authors concluded that a CD-like inflammatory response can be a localized reaction to diverticulitis and does not necessarily indicate chronic IBD.\textsuperscript{13} A small subset of patients with DD may develop segmental colitis associated with diverticulosis. This is recognized as a unique form of chronic colitis limited to areas of the colon with diverticular formation that is often mistakenly diagnosed as IBD.\textsuperscript{14} It is generally accepted that segmental colitis associated with diverticulosis is a distinct clinicopathologic entity that has much in common with idiopathic IBD.

**Altered Microbiota and Inflammation in DD**

Chronic diverticular symptoms, such as abdominal pain, bloating, tenesmus, and diarrhea, may be caused by low-level mucosal inflammation similar to that occurring in chronic idiopathic IBD. Chronic inflammation is related to relatively increased levels of proinflammatory cytokines. This may be triggered, at least in part, by altered peridiverticular microflora. *Bifidobacterium longum* and *B. animalis* are found to be significantly more frequent and more abundant in patients with diverticulitis than in patients with colon cancer or IBD. *B. adolescentis* is only found in the mucosa of patients with colon cancer and not in patients with diverticulitis.\textsuperscript{15}

Some anaerobes induce immune responses that are associated with accumulation of collagen in the tissue. Moreover, increased elastin deposition is found in the colonic wall of patients with DD.\textsuperscript{2} These findings could lead to the assumption that inflammation causes weakness of the colonic wall and results in diverticula formation.

**Fiber Deficiency Causes Both Diverticula and Microbiome Changes**

Fiber deficiency, attributed to a Western diet, is seen as a crucial pathogenic factor of DD. In this widely accepted hypothesis, the resulting smaller-volume stool is said to cause alterations in colonic motility and to increase segmental contractions of the colonic circular muscle. Resulting increased intracolonic pressure then generates increased outward force on the colonic wall. At areas of potential weakness, where penetrating arteries are localized, mucosal herniation results in a diverticulum.\textsuperscript{4}

Studies comparing cultures of gut flora in a rural African population eating a high-fiber diet with an English population eating a low-fiber diet found much higher levels of *Bacteroides* and lower levels of *Bifidobacteria* within the population eating the low-fiber diet.\textsuperscript{16} Indeed, DNA sequencing confirmed that fecal microbiota composition is affected by consumption of supplemental fibers.\textsuperscript{17}
Therapeutic Advances in DD
The presence of chronic inflammation suggests that some patients may benefit from treatment with nonabsorbable enteral antibiotics, anti-inflammatory medications, probiotics, or a combination of these.

Rifaximin, a poorly absorbable antibiotic, decreases the metabolic activity of the intestinal bacterial flora and the degradation of dietary fiber. Cyclic administration of rifaximin with dietary fiber supplementation is more effective in reducing both symptom and complication frequency than simple dietary fiber supplementation in patients with DD.\textsuperscript{18}

The 5-aminosalicylic acid mesalazine is an anti-inflammatory drug typically used in IBD.\textsuperscript{19} Probiotics are ingested living microorganisms which, when administered in adequate concentration, should confer a health benefit on the host. Probiotics antagonize the inflammatory effect triggered by an altered bacterial microenvironment because they have competitive metabolic interactions with proinflammatory organisms and downregulate proinflammatory cytokines. Mesalazine significantly improves patient symptoms and a global sense of wellbeing and is highly effective in obtaining and maintaining remission of symptoms. Probiotics improve abdominal symptoms and prolong the remission period. Patients receiving a combination of mesalazine and the probioticum \textit{L. casei} are more likely to remain in remission compared with patients receiving a single treatment.\textsuperscript{20} Hence, based on these therapeutic effects, it can be concluded that low-grade inflammation is associated with DD symptoms and plays a role in the progression to acute diverticulitis.

Composing a Hypothesis
Figure 1 displays the hypothesis that changes in intestinal microbiota composition play a role in the development of DD and its complications because of uninhibited activation of intestinal immune responses. Interestingly, a chronic low-grade inflammation can be found in patients with asymptomatic diverticulosis. Changed stability control factors or genetic variations could have led to these changes in intestinal microbiota composition. The onset of inflammation in diverticulitis shows similarities to the induction of inflammation in IBD. Deficiencies of host immune defenses and dysfunction of the barrier effect result in increased mucosal adherence of bacteria and promote translocation. A pathogenic immune response is activated and inflammation induced by the formation and topical release of proinflammatory cytokines. Inflammatory and/or functional changes lead to abdominal symptoms, such as lower abdominal pain/discomfort, bloating, tenesmus, and diarrhea. Evidence that supports the assumption that microbiota and low-grade inflammation play important roles in DD derives from studies demonstrating the efficacy of rifaximin, 5-aminosalicylic acid, and probiotics in achieving symptom relief and disease remission.
A changed microbiota composition can cause diverticulitis without the presence of an inspissated fecalith, in contrast to what generally is hypothesized. When diverticula are present, microbiota are able to cause diverticulitis. However, it is assumable that the presence of a fecalith accelerates the onset of diverticulitis because of stasis or obstruction in the narrow-necked diverticulum resulting in bacterial overgrowth and local tissue ischemia.

One could even speculate on a role for microbiota in the development of diverticula. Most risk factors for this are indirectly related to microbiota composition or even directly able to influence the microbiota composition. For instance, consider the mentioned differences in microbiota composition between people with a low-fiber and high-fiber diet. A disturbed anaerobic/aerobic bacteria ratio can induce immune responses associated with accumulation of collagen resulting in structural colonic alterations. Furthermore, a low-fiber diet not only causes colonic motility changes but can inflict a change in microbiota composition that can lead to small-bowel overgrowth and induction of gas-producing bacteria. These could alter the colonic pressure leading to a diverticulum and, additionally, could even cause symptomatic DD. Changes in microbiota composition could be the result of a known risk factor. A plausible explanation is that the microbiota composition can also make the host more vulnerable to DD risk factors. When a risk factor then occurs, a person with aberrant intestinal microbiota will develop a diverticulum because of an abnormal response. It is likely that a changed microbiota composition and risk factors for DD interact with each other, which may even lead to additive effects.
Healthy colon

Initial bacterial colonization, at birth

Final adulthood microbiota

Defect in host (genetics)

Stability control factors
  > Diet
  > Rate passage nutrients
  > Luminal pH
  > Pancreatic secretion
  > Temperature
  > Acidity stomach contents
  > Peristalsis
  > Microbial interaction
  > Drug therapy
  > Probiotics
  > Bile acid
  > Immune responses

Risk factors
  > Matity changes
  > Inactivity
  > High refined carbohydrates diet
  > Obesity
  > High intracolonic pressure
  > Constipation
  > Genetic differences
  > Age
  > Structural colonic alterations
  > Low fiber

Changed intestinal microbiota composition

Translocation
  > Pathogens
  > Viable enteric bacteria
  > Immunologically active adjuvants

Defect in host (genetics)

Defect in host (genetics)

Elastin deposition

Gas-producing bacteria

Low-grade inflammation

Activation immune response

Protective and trophic functions
  > Immunologic stimulation
  > Epithelial dysfunction
  > Enhanced mucosal permeability

Risk factors
  > NSAIDs
  > Smoking

Complicated diverticulitis

Insipissated fecalith

Symptomatic diverticula

Diverticulosis

Diverticulitis

Healthy colon

Accumulation of collagen

Figure 1 | A proposed hypothesis: important role for changed microbiota composition in the etiopathogenesis of diverticular disease. NSAID = nonsteroidal anti-inflammatory drug.
CONCLUSION

A changed microbiota composition is a plausible etiopathogenetic factor in DD. A solitary role for microbiota is not likely, however; the pathogenesis is more likely multifactorial and the result of complex interactions. There may well be some missing links, yet to be discovered, other than a changed microbiome and subsequent activation of immune responses that are necessary for the development of DD and/or its complications. The pathophysiologic significance of these changes in gut microbiome is still uncertain. Importantly, it needs to be determined whether changes in the gut microbiome indeed are a cause or just a consequence of DD. If the exact role of gut microbiota in DD is determined, this could be of great clinical value in the diagnosis and prevention of disease, treatment options, targeting of treatment, and in measuring the effect of therapy.
REFERENCES


