# The GI Microbiome and its role in Chronic Fatigue Syndrome: a Summary of Bacteriotherapy

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*Thomas J. Borody has a pecuniary interest in the Centre for Digestive Diseases where fecal microbiota transplantation is a treatment option and has filed patents in this area.*

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## ABSTRACT

Introduction: Chronic Fatigue Syndrome (CFS) has a complex and multifactorial etiology making treatment and definitive diagnosis, currently made through exclusion, difficult. Current therapies, such as cognitive behaviour therapy and graded exercises, are inadequate and targeted to address symptoms, rather than the underlying disease pathology. Increasing evidence implicates the microbiota of the gut in a number of conditions previously thought distinct from the gastrointestinal system. Previous work with bacteriotherapy in CFS has suggested a link between the condition and the composition and health of the gut microbiota. Here, we review and further examine a larger cohort of CFS patients who had undergone bacteriotherapy for their CFS.

Method: A total of 60 patients from the Centre for Digestive Diseases presented with CFS. Of these, 52 patients had concurrent IBS and 4 patients additionally had constipation. All underwent initial transcolonoscopic infusion of 13 non-pathogenic enteric bacteria. 52/60 patients undertook an additional rectal infusion a day later and 3/60 undertook an additional 2 rectal infusions.

Results: 35/60 patients who underwent initial bacteriotherapy responded to treatment. 10/15 patients who failed this course were offered a secondary transcolonoscopic infusion followed by a rectal infusion or an oral course of cultured bacteria. Of these 7/10 responded, giving a total of 42/60 (70%) patients who responded to treatment. Contact was achieved with 12 patients after 15-20 year follow-up. Complete resolution of symptoms was maintained in seven of the twelve patients and 5/12 did not experience recurrence for approximately 1.5-3 years post bacteriotherapy.

Conclusion: Bacteriotherapy achieves initial success rate of 70% in CFS and a 58% sustained response. Given that manipulation of the colonic microbiota improved CFS symptoms, bacteriotherapy for CFS warrants further investigation and may provide further insight into a possible etiology of CFS.

## INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating disorder, affecting over 150,000 Australians[1] and accounting for over $4 billion annually in direct and indirect costs[2,3].

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Chronic fatigue syndrome frequently occurs following either viral or bacterial infection, leading to the synonymous terms post-viral fatigue syndrome, myalgic encephalomyelitis and chronic fatigue immune dysfunction syndrome, with an immune mechanism previously suggested.

CFS is characterised by disabling fatigue of unknown origin, which persists for six months or more. While prolonged fatigue may be present in 10 – 25% of primary care cases in Australia[1], a diagnosis of CFS also requires four or more of the following symptoms to fulfil the criteria[4]: impaired short-term memory or concentration; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain without arthritis; headaches of a new type, pattern or severity; unrefreshing sleep; post-exertional malaise lasting for more than 24 hours. CFS also frequently co-exists in the presence of gastrointestinal symptoms. In a study of 25 CFS patients, Aaron et al. (2000) reported 92% of CFS patients also had IBS[5]. In another study, Nisenbaum et al. (1998) found a 22.4% prevalence of constipation in patients with severe fatigue lasting for more than 6 months[6].

Due to its complex and multi-factorial etiology, CFS is largely a diagnosis of exclusion, occurring only when known causes of fatigue such as hypothyroidism and anaemia cannot be found. There is considerable debate and confusion as to the cause of CFS, with no single, widely-accepted theory prevailing. While CFS has traditionally been thought of as a neurological disorder or, in some cases, merely hypochondria, recent literature has proposed a new theory to explain the development of CFS: that of an infectious etiological agent. Bacterial and viral species, including B. burgdoferi, Coxiella and Brucella species, Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6), have long been thought to trigger CFS symptoms, possibly acting in conjunction with various genetic and biological factors[7]. Additionally, the gastrointestinal tract has been proposed as an important but under investigated reservoir of potential pathogens that may be involved in CFS development[8].

Current treatments are unfortunately lacking and are largely limited to symptom-specific therapies such as cognitive behaviour therapies and graded exercises. These treatment options generally fail to provide a significant benefit to patients, with less than 10% of

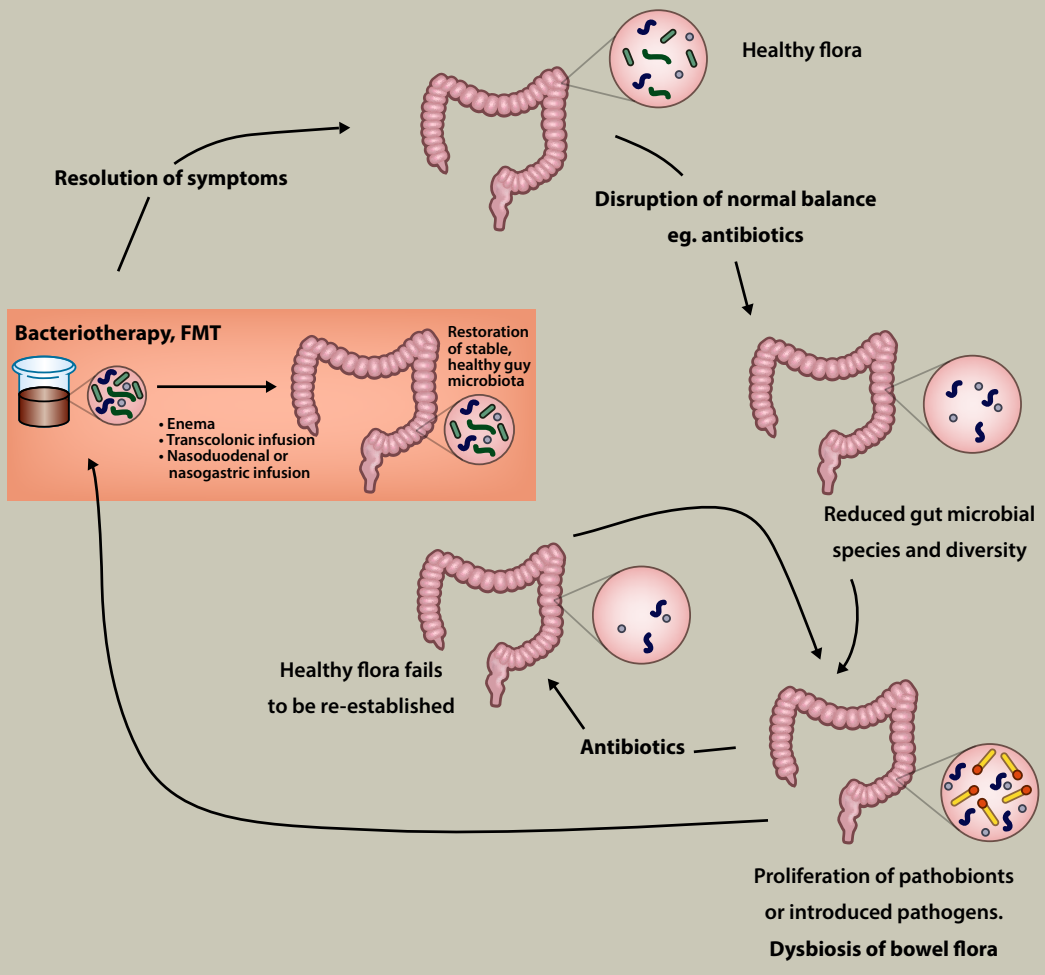


*Figure 1: Disruption of the normal balance of bowel flora can lead to the proliferation of pathogenic organisms. Bacteriotherapy and faecal microbiota transplantation (FMT), unlike antibiotics, are capable of restoring the healthy bowel flora and thus protecting against recurrent infection. Adapted from Borody & Khoruts (2012)[14]*

patients recovering fully and 10-20% of patients worsening during follow-up[9]. More effective, targeted therapies are therefore needed, which not only treat the CFS symptoms but also aim to address the etiological cause.

## THE GUT MICROBIOTA AND MICROBIOME

The human gastrointestinal tract is home to between 1 and 100 trillion bacterial cells, comprised of an estimated 1000-plus unique species[10]. This bacterial community is collectively known as the gut microbiota and can be thought of as the largest organ of the human body – indeed, there are approximately 9 times more bacterial cells in the colon than human cells in the entire body[10]. The bowel flora serves a number of important functions, fulfilling metabolic (fermentation of non-digestible dietary residue, production of Vitamin K, ion absorption), trophic (control of epithelial cell growth and differentiation) and protective roles.

Critical to the maintenance of human health, a delicate balance exists between the bacterial species which make up the composition of the gut microbiota. Disruption of the native microbiota, by antibiotics for example, can lead to the development of a number of disease states. Perhaps the best known example is Clostridium difficile infection (CDI). CDI most commonly develops following antibiotic exposure, as the disruption of the microbiota facilitates colonisation and proliferation of the Clostridial species[11]. The intestinal microbiota has been identified as a rich source of protective probiotics which produce novel antimicrobial and, more specifically, anti-pathogenic bacteriocins. However, in cases of high-level or long-term antibiotic exposure, this protective ecosystem is disrupted, allowing the proliferation of the potentially pathogenic Clostridia species. Rising outbreaks of CDI in North America and Europe, coupled with the emergence of new, epidemic, hypervirulent strains has resulted in significant morbidity and mortality, with over 300 deaths occurring in the US each day from Clostridium difficile infection[12]. The Sydney Morning Herald recently reported the 'arrival' of CDI in Australia from Europe and the United States, with 14 deaths in Victoria alone over a 15 month period in 2010-11[13]. Antibiotic treatment is generally ineffective in CDI, as it fails to eradicate the C. difficile spores while further damaging the underlying microbiota, further contributing to the pathogenesis of the disease (Figure 1).

## CLINICAL EXPERIENCE OF BACTERIOTHERAPY IN CFS

Bacteriotherapy involves the infusion of a mixture of 13 non-pathogenic enteric bacteria (a combination of Bacteroidetes, Clostridia, and E. coli), in attempt to correct imbalances in the composition of the flora. However, the majority of native bacterial species cannot be cultured and so cannot be included in bacteriotherapy, meaning not all of the microbiota imbalances can be corrected. Previous research conducted by Centre for Digestive Diseases (CDD) used bacteriotherapy in a sub group of constipation-predominant IBS patients with concurrent CFS[15]. Results for 55 patients demonstrated a 40% improvement in their CFS. These observations led to speculation of an enteric flora-derived, causative bacterial agent for CFS.

In recently presented work, 60 patients attended CDD (36 female, 24 males; average age 55 ± 11.5yrs) with Chronic Fatigue Syndrome. Of these, 52 had IBS in conjunction with their CFS and another 4 presented with constipation. All underwent bacteriotherapy for their CFS. The results of this were presented at the annual American College of Gastroenterology conference in Las Vegas by CDD and examined the use of bacteriotherapy as a treatment for CFS. The goal of this work was to provide further insight into the pathophysiology of CFS, by demonstrating that bacteriotherapy can improve CFS and simultaneously associated gastrointestinal (GI) symptoms.

All patients received a single transcolonoscopic (TC) infusion of 300cc of anaerobic bacterial culture. Fifty-two of the 60 patients then underwent a single, rectal infusion the following day while 3/60 patients underwent two days of rectal infusions (Figure 2).

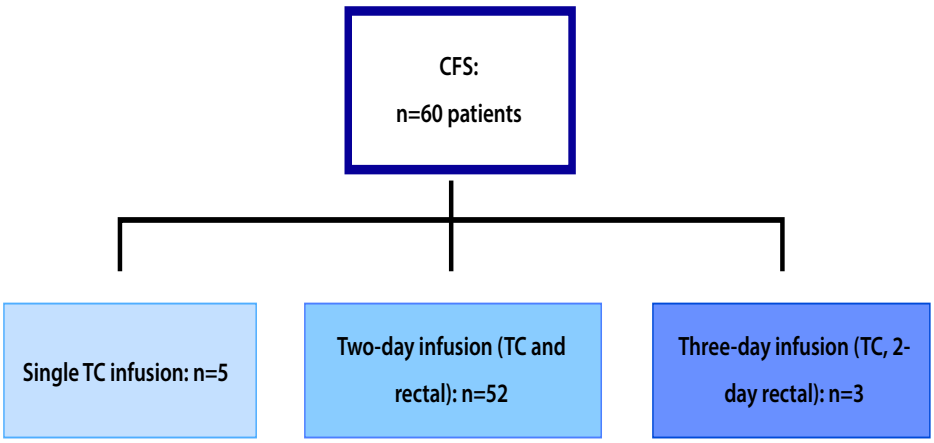


*Figure 2: Schematic of bacteriotherapy treatment in 60 CFS patients. TC: transcolonoscopic.*

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Response was defined as a resolution of CFS symptoms (sleep deprivation, lethargy/fatigue) and non-response was defined as a return of CFS symptoms (sleep deprivation, lethargy/fatigue) at 4 week follow-up, despite improvement in bowel symptoms (diarrhoea, constipation, abdominal pain).

Of the 60 patients who underwent bacteriotherapy, 35 responded to initial treatment. Ten of the patients who failed initial therapy underwent a second TC infusion followed by either a rectal infusion (n=4) or an oral course of cultured bacteria (n=6). Of these patients, 7/10 responded to therapy (Figure 3A).

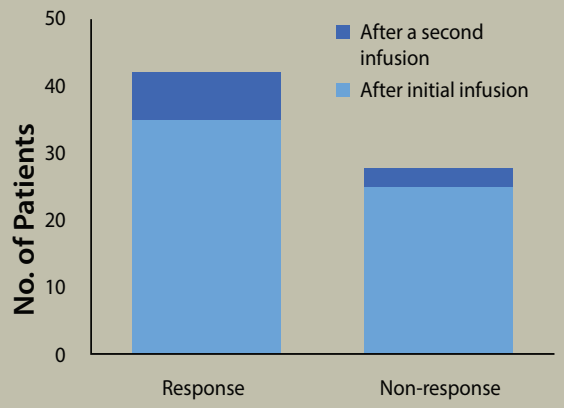


*Figure 3A. Response to treatment after initial transcolonoscopic infusion, and after second transcolonoscopic infusion in CFS patients.*

A total of 42/60 (70%) patients achieved clinical response post-bacteriotherapy. Resolution of associated gastrointestinal symptoms was seen in 37/42 (88%) responding patients. Of the 18 non-responders, 10 attained improvement of associated GI symptoms despite persisting CFS symptoms (Figure 3B).

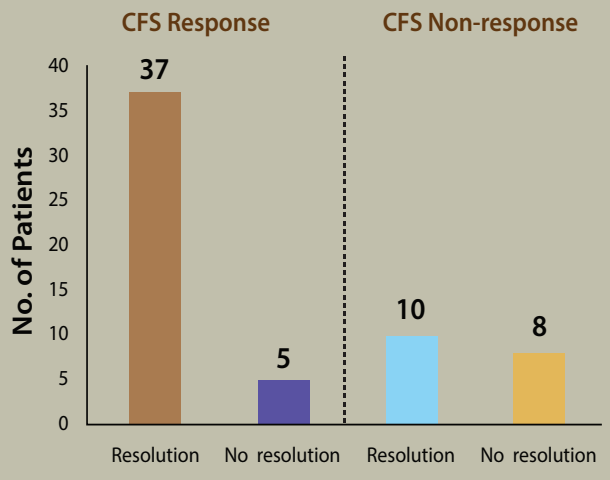


*Figure 3B Comparison of GI symptom resolution in responders and non-responders to bacteriotherapy for CFS.*

At 15-20 year follow-up, 12/60 patients were contactable and 7/12 (58%) remain CFS-free. The remaining 5 experienced a recurrence of CFS approx 18 months to three years post-bacteriotherapy (Figure 3C).

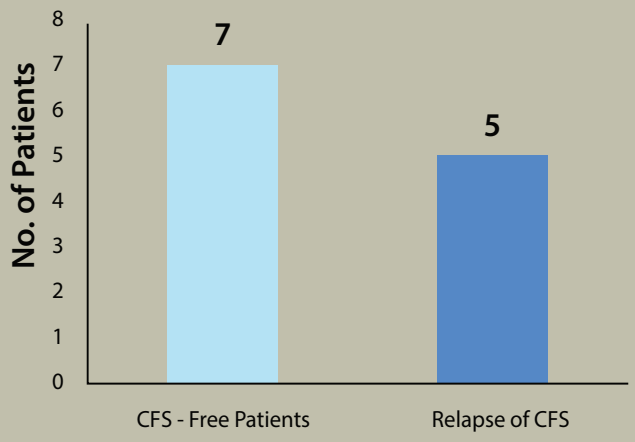


*Figure 3C. Longevity of CFS recovery in patients at 15-20 year follow-up.*

## THE SIGNIFICANCE OF THESE FINDINGS

Bacteriotherapy resulted in a resolution of CFS symptoms in 70% of patients. Of these patients, 58% achieved a sustained response lasting almost two decades to date. Such prolonged and widespread success is virtually unheard of in the treatment of CFS. As mentioned previously, current therapies are at best symptomatic treatments which do not address the underlying possible etiological cause/s of the condition. In addition, while some improvement may be observed in between 17-64% patients undergoing traditional therapies, very rarely is the recovery complete or sustained[9]. Bacteriotherapy represents a new approach to the treatment of CFS and, given the outcomes of this research, one that will potentially greatly benefit the world of CFS treatment.

This work also provides further evidence for a role of the gastrointestinal system in CFS. The incidence of gastrointestinal complaints such as IBS and constipation in CFS has been mentioned previously, and was similarly represented in the patient population here. Indeed, almost 94% (56/60) of the CFS cases examined exhibited either concurrent IBS or constipation symptoms. The link between the resolution of gastrointestinal and CFS symptoms supports the theory of a possible, gastrointestinal-associated etiology, potentially arising from alterations to the bowel flora. This is likely not to be the only factor at play in the development of CFS. All 4 of the patients presenting with CFS alone (i.e. no concurrent gastrointestinal symptoms) failed to respond to therapy (Figure 3D), suggesting again a multi-factorial etiology.

Faecal microbiota transplantation (FMT) offers an attractive alternative to bacteriotherapy as it enables the reintroduction of a complete, stable and 'healthy' bowel flora. Similar to bacteriotherapy, FMT involves the infusion (via colonoscopy or

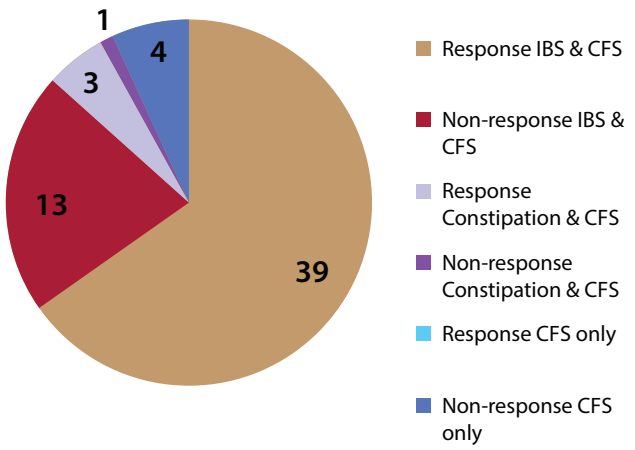


*Figure 3D. Response to bacteriotherapy by disease subgroup. IBS: irritable bowel syndrome, CFS: chronic fatigue syndrome.*

enema) of bacteria. In the case of FMT, however, transplantation of an entire healthy microbiome can be achieved with infusion of mixed and filtered stool from a healthy donor. This 'transplanted' flora can then recolonise the bowel, re-establishing a normal bacterial composition[16]. This therapy has achieved success in inflammatory bowel disease, irritable bowel syndrome, constipation, multiple sclerosis and idiopathic thrombocytopenic purpura, with the use of FMT in other conditions continually expanding[14].

Recent publications suggest treatments like bacteriotherapy and FMT may provide benefit in a number of conditions not previously thought to result from aberrant gastrointestinal functioning. For example, a study in germ-free mice found that mice transplanted with faeces from an obese mouse experienced a 47% increase in body fat, significantly more than was seen in the control mice[17]. Another study of metabolic syndrome found that insulin sensitivity was significantly increased in males infused with stool from lean donors compared to control infusions[18]. Evidence also exists suggesting a link between the gastrointestinal microbiota and neurological disorders such as myoclonic dystonia, Parkinson's disease and autism[19-21].

The success of bacteriotherapy in CFS may provide just one example of the potential involvement of bowel flora imbalances in conditions previously considered unrelated to the gastrointestinal system. While further studies are warranted to evaluate the efficacy and safety of bacteriotherapy and FMT in such conditions, current literature presents a realm of exciting opportunities for the effective treatment of some of the most economically and socially costly diseases plaguing modern society.

*Editor's Note: Findings equate to a 20% follow up rate at 15-20 years.*

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