

Alberta STE Report

Fecal transplantation for the treatment of *Clostridium difficile*-associated disease or ulcerative colitis

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Fecal transplantation for the treatment of *Clostridium difficile*-associated disease or ulcerative colitis

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EXECUTIVE SUMMARY

Objectives

The Alberta Health and Wellness’s Executive Committee accepted the Alberta Health Technology Decision Program’s Advisory Committee’s recommendation to undertake an STE analysis of fecal transplantation. The objectives of this report are:

- to review the prevalence, incidence, risk factors, and consequences of *Clostridium difficile*-associated disease (CDAD) and ulcerative colitis,
- to examine clinical research evidence on the safety and efficacy/effectiveness of fecal transplantation compared to standard care in the prevention and treatment of patients with CDAD or ulcerative colitis, and
- to provide a brief summary of the cost-effectiveness literature on fecal transplantation compared to standard care in the prevention and treatment of patients with CDAD or ulcerative colitis.

Social demographics

***Clostridium difficile*-associated disease**

Health care-associated infections, defined as infections that patients acquire during the course of receiving treatment for other conditions,¹ are an important global public health problem. *Clostridium difficile* (*C. difficile*), a Gram-positive, spore-forming bacterium, is the most important and common nosocomial pathogen of health care-associated diarrhea in hospitalized patients in developed countries and causes millions of human infections worldwide annually. It is the cause of at least 25% of all cases of antibiotic-associated diarrhea and accounts for nearly all cases of pseudomembranous colitis.

According to a national survey conducted by the Canadian Nosocomial Infection Surveillance Program, the overall national incidence of health care-associated CDAD between 1 November 2004 and 30 April 2005 was 4.5 cases per 1000 patient admissions. Twenty-two percent of adult patients with health care-associated CDAD developed complications, and 7.3% of patients had a severe consequence. Nine percent of patients suffered relapse. Two percent of patients were admitted to the intensive care unit for complications related to CDAD, and 1% of patients underwent a colectomy. There were 31 deaths (2.1%) and 53 deaths (3.6%) that were directly and indirectly related to CDAD, respectively, within 30 days of the onset of CDAD. In Alberta, the incidence rate of health care-associated CDAD (2.2 cases per 1000 patient admissions), 30-day mortality rates directly (0.57%) and indirectly (0.57%) related to CDAD, and percentage of patients with severe outcomes (3.3%) were lower than the Canadian average.

The most common risk factor for CDAD is exposure to antibiotics, particularly the use of broad-spectrum antibiotics or concomitant use of multiple antimicrobials and prolonged antimicrobial therapy. Other recognized risk factors for CDAD include advanced age (65 years or older), recent surgery (transplantation, gastrointestinal procedures), immunosuppression, use of proton pump inhibitors, prolonged hospitalization (more than 15 days), malnutrition, nasogastric tube feeding, and the presence of multiple comorbidities.

Standard treatment of CDAD includes discontinuation of the offending/inducing antibiotics, electrolyte normalization, fluid replacement, and *C. difficile* targeted antibiotic therapy with oral

metronidazole or vancomycin. However, recurrent or refractory CDAD occurs in a small portion of patients, and alternative treatments are needed.

Ulcerative colitis

Ulcerative colitis is a chronic and relapsing disease characterized by diffuse mucosal inflammation of the colon. It is a lifelong disease, usually starting in early adulthood in otherwise healthy, active individuals. The disease has a substantial personal burden, which can impact career choices, lead to reduced work hours, affect family planning decisions, and result in disparity and depression. Ulcerative colitis poses unique issues with intimate relationships, contributing to a divorce rate several times higher than the Canadian average.

According to the Crohn's and Colitis Foundation of Canada, approximately 88,500 Canadians are living with ulcerative colitis and more than 4100 new cases are diagnosed every year. There is no gender difference, but there are slightly more cases of ulcerative colitis found in urban than in rural settings.

In our analysis of data from the Discharge Abstract Database, Ambulatory Care Classification System database, and population database from Alberta Health and Wellness for the period between 2002 and 2009, the prevalence and incidence rates of ulcerative colitis were estimated at 56.9 and 41.7 cases per 100,000 population, respectively, in 2003/04, and 75.3 and 36.0 cases per 100,000 population, respectively, in 2008/09. The prevalence and incidence rates varied by age group but were similar among males and females. Prevalence rates increased over the years while the incidence rates slightly decreased. These estimates were likely lower than the actual prevalence and incidence rates of ulcerative colitis because of the exclusion of persons with nonactive or less severe cases who did not use hospital services.

The standard treatment for ulcerative colitis includes medications such as anti-inflammatory 5-aminosalicylate compounds, corticosteroids, and immunomodulatory drugs. Adverse reaction to these drugs occurs in one-quarter to one-third of patients with ulcerative colitis, in whom colectomy may be considered. Emergency surgery is indicated in patients with life-threatening complications, such as perforation, refractory rectal bleeding, and toxic megacolon not responsive to medical treatment. Elective surgery is indicated in patients with dysplasia or cancer, ulcerative colitis refractory to medical treatment, or intolerance to long-term immunosuppression or other medical therapies.

Safety and efficacy/effectiveness

A comprehensive literature search from 2000 onwards located no studies that examined the efficacy/effectiveness of fecal transplantation in the prevention of CDAD or ulcerative colitis. Consequently, this report focuses only on the treatment effects of fecal transplantation.

No systematic reviews or randomized/non-randomized controlled studies were found that examined the safety and efficacy/effectiveness of fecal transplantation for the treatment of CDAD or ulcerative colitis.

No study was found that compared fecal transplantation with other treatments. Furthermore, no study was found that compared different delivery methods for the fecal suspension (i.e., nasogastric tube, retention enemas, or colonoscopy).

Ten case series studies were included: eight studies on CDAD, one on ulcerative colitis, and one on ulcerative colitis complicated by CDAD. Three are full-text articles and the other seven are in abstract form only. Most of these studies reported the experience of a single clinical centre where

fecal transplantation was performed by a single clinician. The number of included patients ranged from 6 to 45 but was less than 20 in most studies. Duration of follow-up was less than 1 year in most studies, with only one study following patients for up to 13 years.

Adverse events associated with the fecal transplantation procedure were not reported in 5 of the 10 studies. Reported adverse events included sore throat, headache, and some gastrointestinal problems. One study reported a death from peritonitis that could be related to the fecal transplantation procedure.

The eight studies on CDAD reported positive results in terms of symptom (diarrhea) improvement or resolution or negative stool tested for *C. difficile* toxins. Sufficient volume of fecal suspension may be required to achieve optimal outcomes.

In the majority of studies, vancomycin or metronidazole was used for up to 2 weeks and was discontinued several hours prior to fecal transplantation. In the absence of a control group, the possible influence of pre-fecal transplantation use of antibiotics on the outcomes could not be determined.

Evidence from one study with six patients demonstrated a promising result of fecal transplantation in patients with ulcerative colitis based on clinical, colonoscopic, and histological examinations.

Cost-effectiveness

Based on the information provided by local clinical experts, total cost for fecal transplantation via rectal retention enema is estimated at CAD 500 to 1500. No information is available regarding the cost of fecal transplantation via other administering methods.

A comprehensive literature search located no cost-effectiveness studies of fecal transplantation used in patients with CDAD or ulcerative colitis.

Conclusions

Management of severe, recurrent, and relapse CDAD, particularly in elderly patients, remains clinically challenging. While the majority of patients respond to standard care, such as discontinuation of inducing antibiotics and use of oral antibiotics against *C. difficile* (metronidazole and vancomycin), a small portion of patients failed to achieve symptom resolution with standard care.

Evidence from 10 case series studies indicated that fecal transplantation appeared to be a promising treatment method for patients with recurrent CDAD, ulcerative colitis, or ulcerative colitis complicated by CDAD. In most cases, symptoms improved immediately after the procedure.

Recent European and American clinical guidelines did not include recommendations on whether fecal transplantation should be used for patients with CDAD or ulcerative colitis.

Results from two ongoing randomized controlled studies comparing fecal transplantation with oral vancomycin in patients with recurrent/refractory CDAD will provide a better understanding about the potential role of fecal transplantation. Future controlled trials are also required to better delineate the role of fecal transplantation in patients with ulcerative colitis.

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LIST OF ABBREVIATIONS

CD – *Clostridium difficile*
CDAD – *Clostridium difficile*-associated disease
ER – emergency room
F – female
FBC – full blood count
FT – fecal transplantation
g – gram
h – hour
HA-CDAD – health care-associated CDAD
HAV – hepatitis A virus
HBV – hepatitis B virus
HCV – hepatitis C virus
HIV – human immunodeficiency virus
HTA – health technology assessment
HTLV – human T cell lymphotropic virus
IBD – inflammatory bowel disease
LFT – liver function test
M – male
mg – milligram
mL – millilitre
N – total number
NA – not available
PBS – phosphate buffered saline
PCR – polymerase chain reaction
QoL – quality of life
SEM – standard error of the mean
UC – ulcerative colitis
wk – week
yr – year

GLOSSARY

Main reference sources: *Mosby's Medical, Nursing, & Allied Health Dictionary* (6th edition, 2005);² Pillai and Nelson 2009;³ Food and Agriculture Organization of the United Nations 2001⁴

***Clostridium difficile*-associated disease (CDAD):** A disease that occurs in a patient with diarrhea who has tested positive for *C. difficile* toxin and/or positive stool culture of *C. difficile*.

***C. difficile* colitis:** Inflammation characterized by a stool test positive for the organism and signs of mucosal inflammation seen on endoscopy.

Colectomy: A surgical procedure to remove the colon.

Fecal transplantation: Also known as fecal bacteriotherapy, fecal transfusion, fecal transplant, or human probiotic infusion, it is a medical treatment for patients with CDAD or ulcerative colitis which involves restoration of colon homeostasis by reintroducing normal bacterial flora from stool obtained from a healthy donor.

Inflammatory bowel disease: A group of inflammatory conditions of the colon and small intestine. The major types of inflammatory bowel diseases are Crohn's disease and ulcerative colitis.

Probiotics: Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Lactic acid bacteria and bifidobacteria are the most common types of microbes used as probiotics; but certain yeasts and bacilli may also be helpful. Probiotics are commonly consumed as part of fermented foods with specially added active live cultures, such as in yogurt or soy yogurt, or as dietary supplements.

Pseudomembranous colitis: The presence of pseudomembranes seen on endoscopy.

Ulcerative colitis: A chronic, episodic, inflammatory disease of the large intestine and rectum, characterized by profuse watery diarrhea containing varying amounts of blood, mucus, and pus.

INTRODUCTION

This rapid assessment report was prepared in response to a request from the Alberta Health Technologies Decision Process, Alberta Health and Wellness, about scientific evidence on the safety and effectiveness of fecal transplantation in the prevention and treatment of *C. difficile*-associated disease (CDAD) and ulcerative colitis.

Objectives

- To review the prevalence, incidence, risk factors, and consequences of CDAD and ulcerative colitis.
- To examine clinical research evidence on the safety and efficacy/effectiveness of fecal transplantation compared to standard care in the prevention and treatment of patients with CDAD or ulcerative colitis.
- To provide a brief summary of literature on the cost-effectiveness of fecal transplantation compared to standard care in the prevention and treatment of patients with CDAD or ulcerative colitis.

In this report, prevention is defined as the use of fecal transplantation in patients who are at high risk but have not yet developed the diseases (CDAD or ulcerative colitis). Treatment is defined as the use of fecal transplantation in patients who developed symptoms and were diagnosed with the diseases (CDAD or ulcerative colitis).

Scope

Social demographics

This section focuses on the prevalence and incidence of CDAD, ulcerative colitis, and ulcerative colitis complicated with CDAD in Alberta, Canada, and internationally, as well as risk factors and consequences of the two diseases.

Safety and efficacy/effectiveness

Patient population

For prevention study: patients who are susceptible to *C. difficile* or ulcerative colitis but have not been diagnosed with the diseases

For treatment study: patients who have already been diagnosed with CDAD or ulcerative colitis, or patients with ulcerative colitis complicated with CDAD

Intervention

Fecal transplantation via retention enema, nasogastric/duodenal tube, or colonoscope

Comparator

- Standard care for CDAD or ulcerative colitis
- Other probiotics
- Different delivery methods for administering fecal transplantation

Outcome measures

For CDAD, any of the following: improvement in symptoms, reduction in mortality related to CDAD, stool testing for *C. difficile*, health-related quality of life, patient acceptance and satisfaction, prevention of recurrence and more severe complications (e.g., toxic megacolon), prevention of surgery (i.e., colectomy).

For ulcerative colitis, any of the following: improvement in symptoms, discontinuation of other medications for ulcerative colitis, health-related quality of life, patient acceptance and satisfaction, increasing remission and maintaining remission, reducing emergency department visits, prevention of relapse, prevention of surgery (colectomy).

Cost-effectiveness analysis

This section will provide a brief summary of the results and conclusions of available cost-effectiveness studies from the literature, if any. No primary cost-effectiveness analysis will be conducted due to time constraints.

A comprehensive literature search (see Appendix A: Methodology/search strategy) located no studies that examined the effects of fecal transplantation in preventing CDAD or ulcerative colitis. Therefore, although the original project scope was to cover both the prevention and treatment aspects, this report is able to provide information only on the treatment aspects of the fecal transplantation procedure. Furthermore, the literature search located no cost-effectiveness studies; thus, no information about cost-effectiveness of fecal transplantation will be provided in this report.

SOCIAL DEMOGRAPHICS

Clostridium difficile-associated disease

Various terms, such as *Clostridium difficile*-associated diarrhea, *Clostridium difficile*-associated disease, *Clostridium difficile* infection, *Clostridium difficile* colitis, or pseudomembranous colitis, have been used in the literature to describe clinical problems associated with *Clostridium difficile*. For the purpose of this report, the term *Clostridium difficile*-associated disease (CDAD) is used to cover a broad spectrum of patient conditions, ranging from mild diarrhea to fulminant colitis, which can lead to death.

Definition

Clostridium difficile, commonly called *C. difficile*, is a Gram-positive, spore-forming, toxin-producing, anaerobic rod bacterium that is transmitted between human beings by the fecal-oral route.⁵ *C. difficile* can exist in a vegetative form, the most common form, or in spore form.^{5,6} While the vegetative form is highly sensitive to oxygen, the spore form is heat stable and able to withstand extreme conditions such as the acidic environment of the human stomach and persist on hospital surfaces after exposure to a variety of commercial disinfectants, including alcohol.⁵

C. difficile was first isolated in 1935 from the stools of healthy newborn infants. In 1978 this pathogen was identified as the major cause of pseudomembranous colitis.⁷ The bacteria produce two types of toxins, enterotoxin (toxin A) and cytotoxin (toxin B), both causing colitis.⁸ Since the early 2000s, a new hypervirulent strain of *C. difficile* called NAP1/BI/027 has been indicated in *C. difficile* outbreaks associated with increased morbidity and mortality.^{9,10} This strain produces increased levels of toxin A and B as well as an additional toxin known as binary toxin, which accounts for its increased toxicity.⁹ Since 2002 an epidemic of CDAD caused by the new strain NAP1/BI/027 has

spread to as many as 30 hospitals in Quebec, with a 30-day mortality rate of 23.0% compared with 7.0% of matched control patients.¹¹

Health care-associated infections, defined as infections that patients acquire during the course of receiving treatment for other conditions,¹ are an important public health problem. *C. difficile* is the most important and common nosocomial pathogen of health care-associated diarrhea in hospitalized patients in developed countries and causes millions of human infections worldwide annually.^{5,12-14} It is the cause of at least 25% of all cases of antibiotic-associated diarrhea that results from an imbalance in the colonic microbiota caused by antibiotic therapy¹⁵ and accounts for nearly all cases of pseudomembranous colitis.¹⁶

Incidence and prevalence

Canada

The Canadian Nosocomial Infection Surveillance Program conducted a national survey of 34 acute-care hospitals across Canada from 1 November 2004 to 30 April 2005. This represents the most comprehensive surveillance of *C. difficile*-associated diarrhea in Canada.¹⁷ The main findings from this survey are summarized in Table 1.

Table 1: Health care-associated CDAD in Canada

	Overall	Highest	Lowest	Alberta
Total cases	1493 (70% ≥ 65 years)	693 (Ontario)	69 (Saskatchewan/Manitoba)	175
Incidence (cases per 1000 patient admissions)	4.5	11.1 (Quebec)	2.2 (Alberta)	2.2
30-day mortality rate (%)	15.9	22.6 (Quebec)	9.1 (Alberta)	9.1
30-day mortality rate directly related to HA-CDAD (%)	2.1	8.0 (Quebec)	0.57 (Alberta)	0.57
30-day mortality rate indirectly related to HA-CDAD (%)	3.6	7.8 (Quebec)	0 (Saskatchewan/Manitoba)	0.57
Severe outcome (%)	7.3	16.7 (Quebec)	2.2 (Atlantic)	3.3

Source: Adapted from Gravel and Miller 2007.¹⁷

As shown in Table 1, 1493 CDAD cases were identified during the 6-month period, with the majority being elderly patients. The overall national incidence of health care-associated CDAD (HA-CDAD) for this 6-month period was 4.5 cases per 1000 patient admissions. The incidence was significantly higher in Quebec than the rest of Canada, and Alberta had the lowest incidence rate. Quebec had the highest 30-day mortality rate, directly or indirectly related to CDAD, and Alberta had lowest 30-day mortality rate directly related to CDAD.

This survey also found that 22% of adult patients with HA-CDAD developed complications, and 7.3% of patients had a severe consequence. Nine percent of patients suffered relapse. Two percent of patients were admitted to the intensive care unit for complications related to CDAD and 1% of patients underwent a colectomy.

This survey found a small decrease in the mean incidence of HA-CDAD since the 1997 survey; however, the number of deaths related to CDAD and severe outcomes increased significantly.

Incidence and prevalence rates of CDAD in Alberta based on the analysis of local administrative data were not possible.

United States

A statistical brief prepared by US Healthcare Cost and Utilization Project¹⁸ reported the following data:

- The number of hospital discharges with CDAD more than doubled from 2001 to 2005, a trend that was considerably steeper than the prior 8-year period (from 1993 to 2001).
- CDAD primarily affects elderly patients; about 49% of CDAD patients were aged 65 to 84 years and 19% were 85 years or older.
- CDAD patients were considerably sicker and CDAD cases were more complex than an average inpatient. Lengths of hospital stay were nearly three times higher than average. The death rate was about 4.5 times higher than average.

Clinical manifestations and consequences

Clinical manifestations of CDAD can range from asymptomatic carrier state, mild and self-limiting diarrhea, to life-threatening pseudomembranous colitis with toxic megacolon.^{8,12,17,19} Mild to moderate CDAD usually presents watery diarrhea accompanied by lower abdominal cramping pain but no systemic symptoms or physical findings. Severe disease is characterized by abdominal pain, profuse diarrhea, and systemic symptoms such as fever, nausea, anorexia, and malaise.²⁰ Fulminant colitis (ileus, toxic megacolon, and perforation) develops in approximately 1% to 3% of patients and is associated with a high mortality rate.²¹

During the past several years, CDAD has become more frequent, more severe, more refractory to standard therapy, and more likely to relapse.^{10,22} This pattern is widely distributed in Canada, the United States, and Europe and is attributed to the new strain of *C. difficile*, NAP1/BI/027.^{9,17} This previously uncommon strain now has become epidemic and has been reported in populations that previously were considered to be at low risk, such as peripartum women and healthy individuals living in the community.⁹

Risk factors

Mature colonic bacterial flora in a healthy adult is generally resistant to *C. difficile* colonization. Any factors associated with the alteration of normal intestinal microflora increases the risk of *C. difficile* colonization after exposure to the bacteria.²³ Disruption of the normal flora with broad-spectrum antimicrobial agents increases susceptibility of the intestinal tract to the overgrowth of *C. difficile*.²⁴

As shown in Table 2, the most common risk factor is exposure to antibiotics, especially those with broad-spectrum activity, or concomitant use of multiple antimicrobials and prolonged antimicrobial therapy.^{14,23,25} Other recognized risk factors for CDAD include advanced age (65 years or older), recent surgery (transplantation, gastrointestinal procedures), use of immunosuppressive drugs or proton pump inhibitors, prolonged hospitalization (more than 15 days), malnutrition, nasogastric tube feeding, and the presence of multiple comorbidities.^{8,12,26-28} However, the host immune response is the major determinant of outcome following exposure to *C. difficile*; for example, the detection of serum antibodies against toxin A and B is protective against disease.⁷

Table 2: Important risk factors for CDAD

Exposure to certain medications

- Antibiotics (clindamycin, penicillins, and cephalosporins are most commonly associated with CDAD)
- Proton pump inhibitors (acid-reducing drugs)
- Valacyclovir (antiviral drug)
- Chemotherapy

Patient characteristics

- Inflammatory bowel disease
- Serious underlying illness/comorbidities
- Gastrointestinal surgery/manipulations
- Advanced age
- Immune-compromising conditions (post transplantation)
- Peripartum
- Hypoalbuminemia
- Low levels of antitoxin A and B antibodies

Environment

- Prolonged stay in healthcare settings

Source: Adapted from Hookman and Barkin 2009⁹ and Lamont 2004.⁷

Diagnosis

The diagnosis of CDAD is based on a combination of clinical findings, laboratory tests for *C. difficile* toxins A or B, and sometimes endoscopy.²⁴ Although not clinically practical because of its slow turnaround time, stool culture is the most sensitive test and is essential for epidemiological studies.²⁹ The enzyme immunoassay for *C. difficile* toxin A and B is now most commonly used because of its ease of processing, lower cost, and quick turnaround time.^{30,31}

Treatment options

Standard treatment of CDAD includes discontinuation of the offending/inducing antibiotics, electrolyte normalization, fluid replacement, and *C. difficile* targeted antibiotic therapy with oral metronidazole or vancomycin.^{5,30,32}

There is an ongoing debate about the choice of the first-line antibiotic.³³ In general, metronidazole is considered the initial treatment of choice for patients with mild infection because of its high efficacy and lower cost.²² Vancomycin is reserved for patients with severe infection because of its more prompt symptom resolution and a significantly lower risk of treatment failure.²²

According to the recent recommendations by the Ontario Provincial Infectious Disease Advisory Committee, vancomycin should also be used in any of these situations: (1) metronidazole is ineffective, (2) the patient is pregnant, (3) the patient is allergic to metronidazole, or (4) true resistance to metronidazole is shown.³⁴

Although the standard treatments are generally effective in achieving clinical improvement, the use of antibiotics (e.g., vancomycin) does not restore intestinal microflora, nor does it reduce the exposure to *C. difficile* in the environment, comorbidities, or other host risk factors.^{16,19}

Other non-antibiotic strategies for the treatment of CDAD include discontinuation of proton pump inhibitors, active and passive immunizations, administration of antitoxins, functional inhibition of toxin activity, use of nonspecific toxin-binding compounds, probiotics, and fecal transplantation.^{20,33}

Standard treatment for life-threatening *C. difficile* colitis is colectomy, which has a high associated mortality rate of up to 80%.¹⁵ The guidelines from the European Society of Clinical Microbiology and Infectious Diseases³⁵ recommended that colectomy be performed in patients with perforation of the colon or systemic inflammation and deteriorating clinical condition such as toxic megacolon and severe ileus not responding to antibiotic therapy.

Recurrent and refractory CDAD

The major problem in treating CDAD is the high recurrence rate.^{30,35} Despite the fact that more than 90% of patients respond to the treatment initially, 15% to 35% of patients will experience a relapse in symptoms after a successful initial therapy, usually in the first few weeks after the treatment is discontinued.^{6,19,20} As many as 26 relapses in a single patient have been reported.³⁶

While some of the recurrent cases might be caused by ongoing exposure to *C. difficile* spores in the environment (i.e., exogenous re-infection), most are due to the bacterial strain that caused the first episode (i.e., relapse), which reflects a lack of effective antibiotic treatment in eliminating the *C. difficile* spores from the gut.¹⁹ Underlying bowel conditions (e.g., inflammatory bowel disease) and other comorbidities also play a role with respect to disease severity and recurrence.¹⁹

Important and consistently reported risk factors for recurrent CDAD include inadequate antitoxin antibody response, persistent disruption of the colonic flora, advanced age, continuation of non-*C. difficile* antimicrobial therapy, prolonged hospital stay, and concomitant receipt of antacid medications.³⁷

Optimal management of multiple relapses remains clinically challenging. Strategies such as additional courses of oral metronidazole or vancomycin, pulsed/tapered antibiotics, the administration of probiotics and intravenous immunoglobulin, toxin binding, and rectal instillates of microbes have been used with varying degrees of success.^{38,39} Fecal transplantation is an option in continued recurrence, although this approach has not been studied in controlled trials.^{22,24,40}

Some patients develop a chronic relapsing pattern of diarrhea after initial improvement with retreatment.³² Reasons for the difficulty in treating recurrent CDAD may include: (1) failure rates during treatment, particularly with metronidazole, have increased in parallel with the emergence of a new strain of *C. difficile* (BI/NAP1/027); (2) successful treatment of the recurrent episode is often followed by another recurrence; and (3) there is little data from randomized controlled trials to support any particular method for the treatment of recurrent CDAD.³⁷

Currently, consensus recommendations for the prevention of recurrent CDAD are unavailable.²⁴

Ulcerative colitis

Definition

Ulcerative colitis, one of the two main forms of inflammatory bowel disease (IBD), is a chronic and relapsing disease characterized by diffuse mucosal inflammation of the colon.⁴¹ It always affects the rectum and may extend proximally in a contiguous pattern to involve the sigmoid colon, the descending colon, or the entire colon.^{42,43}

The cause of ulcerative colitis remains unknown.⁴¹ Both genetic and environmental factors may be involved, but their roles and relative importance in pathogenesis are far from clear.⁴⁴ One hypothesis attributes the etiology and persistence of the chronic inflammatory process to the intestinal flora. A viral, bacterial, or chemical pathogen may trigger an overly aggressive host immune response that is perpetuated by the resident flora long after the initial infection has been resolved. Loss of tolerance

to the normal luminal contents caused by abnormalities in mucosal permeability or a lack of regulatory cells/mediators may induce chronic inflammation in genetically susceptible individuals.⁴⁵ Given the complex composition of the intestinal flora, it is also possible that a persistent infection with a specific pathogen causes chronic, recurrent inflammation associated with ulcerative colitis.^{45,46}

Prevalence and incidence

United States

Ulcerative colitis affects approximately 250,000 to 500,000 persons in the United States, with an annual incidence of 2 to 7 per 100,000 persons.⁴²

Canada

According to the Crohn’s and Colitis Foundation of Canada,⁴⁷ Canada is one of the countries with the highest frequencies of people with ulcerative colitis. An estimated 88,500 Canadians were living with this disease in 2008, and more than 4100 new cases are diagnosed every year. There is no gender difference in ulcerative colitis, but slightly more cases are found in urban than rural settings.

Alberta

In Alberta, an estimated 9484 persons were living with ulcerative colitis in 2008.⁴⁷ According to a Canadian population-based study,⁴⁸ in 2000 the prevalence and incidence rates in Alberta were 185 cases per 100,000 population and 11 cases per 100,000 population, respectively.

An analysis of data obtained from the Discharge Abstract Database, Ambulatory Care Classification System database, and population database from Alberta Health and Wellness was conducted for the period between 2002 and 2009 (Appendix B). The prevalence and incidence rates of ulcerative colitis were estimated at 57 and 42 cases per 100,000 population, respectively, in 2003/04, and 75 and 36 cases per 100,000 population, respectively, in 2008/09. The prevalence and incidence rates varied by age group (Figure 1) but were similar among men and women. The prevalence rates increased over the years while the incidence rates slightly decreased (Figure 2).

Figure 1: Age-specific prevalence and incidence rates of ulcerative colitis in Alberta (2008/09)

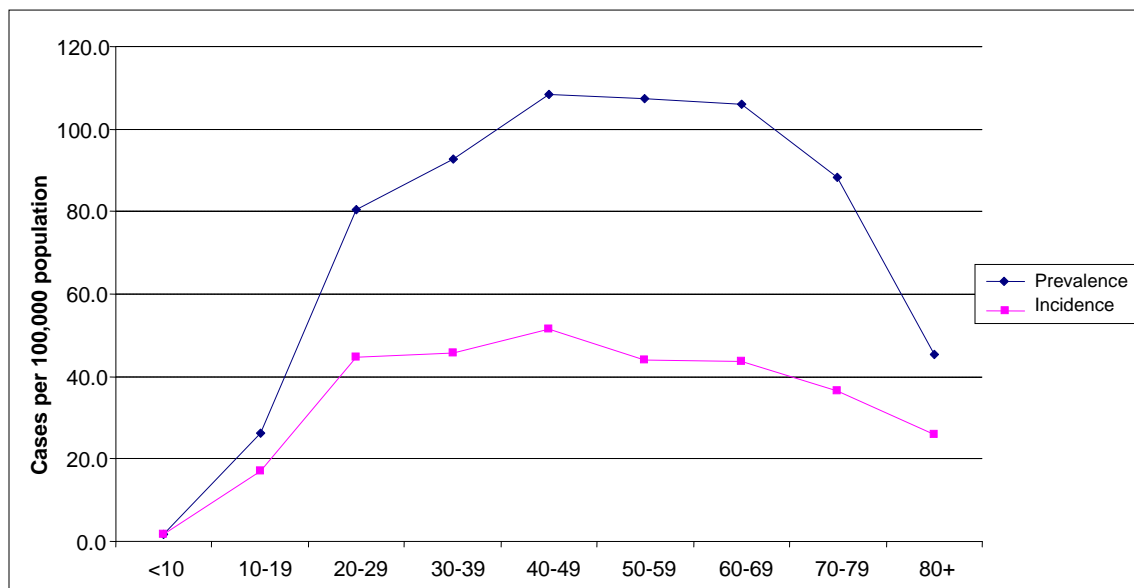
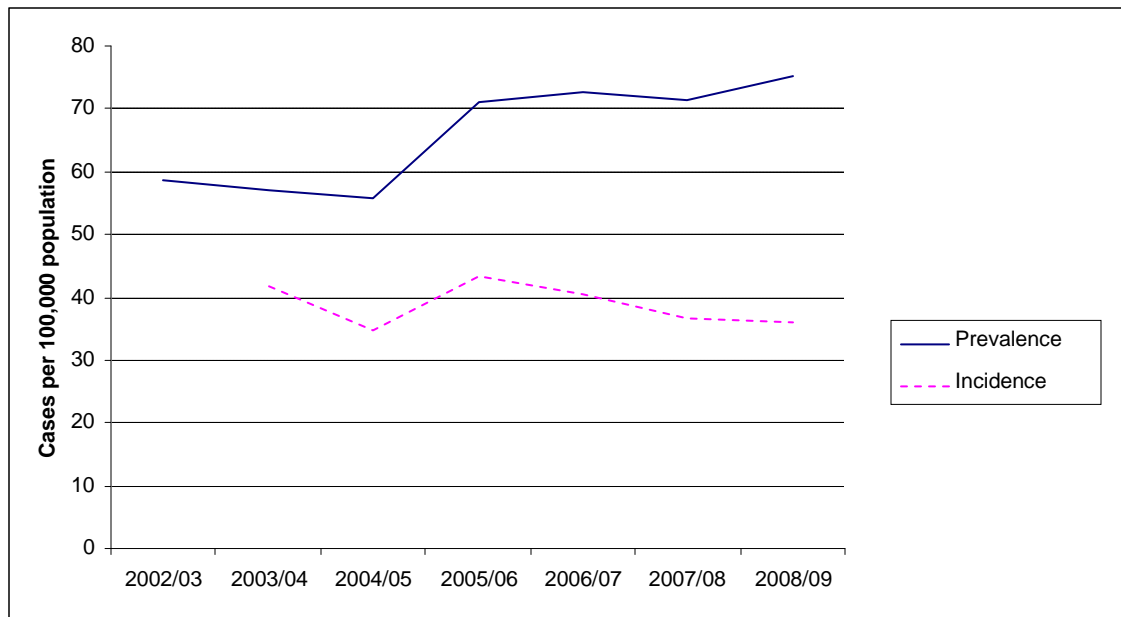


Figure 2: Trends of the prevalence and incidence of ulcerative colitis in Alberta (2002-2009)



The prevalence and incidence of active ulcerative colitis cases estimated in this analysis were likely lower than the prevalence and incidence of all ulcerative colitis cases since the individuals with non-active or less severe ulcerative colitis who did not use hospital in- or out-patient services (for example, who were not treated or who were treated by family physicians) were not included. The databases and case definition used for identifying ulcerative colitis and the time period covered in the Canadian population study⁴⁸ were different from those used in our analysis. These factors may explain the differences in the estimates for the prevalence and incidence rates of ulcerative colitis in Alberta.

Clinical manifestations and consequences

Symptoms of ulcerative colitis include abdominal pain and diarrhea, often accompanied by blood. Other symptoms include fatigue, vomiting, itchiness or irritation around the anus, flatulence, and bloating.⁴¹ Clinical signs of weight loss and anemia also pose significant problems.⁴⁷

In clinical practice, disease severity is usually described as mild (up to four bloody stools daily and no systemic toxicity), moderate (four to six bloody stools daily and minimal toxicity), or severe (more than six bloody stools daily and signs of toxicity, such as fever, tachycardia, anemia, or increased erythrocyte sedimentation rate).⁴⁴ Approximately half of patients with ulcerative colitis have relatively mild symptoms.⁴⁷

Ulcerative colitis is a lifelong disease usually starting in early adulthood in otherwise healthy, active individuals. Individuals with ulcerative colitis suffer a substantial personal burden, which can impact career choices, lead to reduced work hours, affect family planning decisions, and result in disparity and depression.⁴⁷ As well, it poses unique issues with intimate relationships, contributing to a divorce rate several times higher than the Canadian average.⁴⁷

Diagnosis

Clinical history, symptoms, physical examination, and stool examinations for ova parasites, stool culture, and testing for *C. difficile* toxins can help eliminate other causes of chronic diarrhea.⁴²

Colonoscopy or proctosigmoidoscopy and biopsy are the tests of choice to diagnose ulcerative colitis.⁴²

Treatment options

There is currently no medical cure for ulcerative colitis. Medical therapy is directed at control of symptoms or at the underlying inflammatory process. The standard medical therapies for ulcerative colitis involve medications such as anti-inflammatory 5-aminosalicylate compounds, corticosteroids, immunomodulatory drugs,^{43,47} and, more recently, biologics. The treatment goal is to induce and then maintain remission and achieve a normal quality of life.^{41,44,49} Severe adverse effects with the prolonged administration of these drugs limit their use.

Surgical therapy is reserved for patients with medically refractory disease, fulminant disease or its complications, mucosal dysplasia, or malignancy.⁴³ Emergency surgery is indicated in patients with life-threatening complications such as perforation, refractory rectal bleeding, and toxic megacolon not responsive to medical treatment. Elective surgery is indicated in patients with dysplasia or cancer, ulcerative colitis refractory to medical treatment, or intolerance to long-term immunosuppression or other medical therapies.⁴⁹ Surgical therapies are associated with short-term and long-term complications.⁴³

Fecal transplantation may have a role in the treatment of ulcerative colitis because of the possible link between the absence of *C. difficile* and prolonged remission of ulcerative colitis,⁴⁵ or through other as yet unknown mechanisms.

CDAD and ulcerative colitis

Historically, little overlap has been found between CDAD and inflammatory bowel disease (including ulcerative colitis). More recently, *C. difficile* has been identified to exert a significant negative impact on patients with inflammatory bowel disease who are at increased risk for the development of CDAD and have increased rates of hospitalization, surgery, and mortality as a result of this infection.⁵⁰ In the United States, the nationwide rate of CDAD among patients hospitalized for ulcerative colitis reportedly doubled from 1998 to 2004.⁹

The association between the two diseases may be due to a variety of factors, including use of antibiotics for other gastrointestinal pathogens, long-term immunosuppression, and frequent hospitalizations.⁵¹ *C. difficile*, and particularly its toxins, has been implicated as a risk factor for the exacerbation of the inflammatory process in up to 5% of patients with ulcerative colitis or Crohn's disease.⁹ A more severe clinical course may result from *C. difficile* infection superimposed on inflammatory bowel disease, including the precipitation of toxic colitis and toxic megacolon.⁹

Sometimes it is difficult to distinguish the clinical and pathological features of CDAD from those of chronic inflammatory bowel disease.⁵² Prompt diagnosis and treatment are required for patients with severe CDAD, particularly those who have already been diagnosed with ulcerative colitis. Failure to diagnose CDAD can lead to inappropriate treatment with glucocorticoids or immunosuppressive therapy. The prolonged use of steroids may result in the loss of the normal physiological balance among *C. difficile* and other organisms in the intestinal flora.⁵²

TECHNOLOGY – FECAL TRANSPLANTATION

Definition

Fecal transplantation, also known as fecal bacteriotherapy, fecal transfusion, or human probiotic infusion, refers to the process of instilling a liquid suspension of stool from a healthy donor into the patient’s upper gastrointestinal tract through a nasoduodenal catheter or into the colon through a colonoscope or a enema catheter.³²

The use of human fecal flora to treat gastrointestinal disorders is not a novel concept. Fecal transplantation has been used sporadically in one form or another since the mid 1950s, primarily for antibiotic-associated diarrhea and severe *C. difficile*-related diarrhea.¹⁵

Mechanism

Fecal flora is best understood as a complex, living, and interdependent ecosystem.³⁶ Trillions of bacteria, divided into hundreds of different species, inhabit the gastrointestinal tract, which are in intimate relationships with the enteral immunologic system and play a key role in priming and forming the developing immune system and in maintaining the homeostasis of the host.⁴⁴ The vast majority of bacteria are commensal and do not induce a persistent pro-inflammatory reaction.⁴⁴

Protective bacteria suppress growth of *C. difficile* in the colon. The use of broad-spectrum antibiotics can alter the balanced ecology of normal colonic flora, and the consequential overgrowth of pathogenic *C. difficile* strains leads to increased production of toxins that cause diarrhea and other associated symptoms.^{15,36}

The fundamental challenge in treating CDAD is not the presence of the pathogenic organism per se but, rather, the relative paucity of protective microflora. Restoring bacterial homeostasis is believed to resolve infection caused by uncontrolled growth of *C. difficile*.^{36,37} As it is unclear which organism(s) are protective against *C. difficile*, fecal transplantation utilizing the entire human fecal flora as the ultimate therapeutic bacterial mixture may have value in the treatment of CDAD, especially when the disease is refractory to other treatments.¹⁵

The precise mechanisms of fecal transplantation in the treatment of *C. difficile* are unclear but may involve the recolonization of flora with missing components to generate colonization resistance. The other major mechanism could be the direct antagonistic activity of the normal flora to *C. difficile*.¹⁵ Unlike the transient use of antibiotics (e.g., vancomycin) for *C. difficile*, implanted flora provides a prolonged presence of antagonistic activity that may prevent future colonization by *C. difficile*.¹⁵

Fecal transplantation may have several advantages over repeated treatment attempts with antimicrobial drugs. It breaks the cycle of antimicrobial use, which may perpetuate or renew the disruption of the intestinal flora. It also reduces the risk of problems associated with antimicrobial use, such as the emergence of antimicrobial-resistant enteric bacterial strains, allergic reaction, and the high cost of antimicrobes such as vancomycin.^{32,36}

Description of the procedure

Donor screening

Donor screening, including blood tests and stool pathogen examinations, is essential to avoid transmission of diseases from donors to recipients.

Blood tests should include a full blood count, liver function tests, and viral screening for human immunodeficiency virus (type 1 and type 2), hepatitis viruses (A, B, and C), cytomegalovirus,

Epstein-Barr virus, and syphilis. Donor stool examination should include microscopic examination for the presence of protozoa (trophozoites and cysts), helminths and ova, trematodes, and tapeworms.¹⁵

Administration methods

Fecal flora from a healthy donor can be administered via nasogastric/nasoduodenal tube, colonoscope, or rectal retention enema. Compared to fecal transplant via a rectal tube or colonoscope, administration via a nasogastric tube is technically easier to perform and provides more extensive exposure of the gastrointestinal tract to donor flora.^{38,53} It also requires less time for patient preparation and procedure performance, with reduced patient inconvenience and cost.³⁶ A disadvantage of a nasogastric/nasoduodenal tube is that donor feces may be difficult to infuse if patients have signs of diminished passage of fluids through their intestines; these patients should avoid fecal transplantation via the upper gastrointestinal tract.⁵³

Facilities, personnel, and equipment required for performing fecal transplantation differ among the three delivery methods. For example, fecal transplantation via rectal retention enema can be performed at a community setting (such as the patient’s home) by a nurse (Dr. T. Louie, personal communication, October 2010) while fecal transplantation by colonoscopy or nasogastric tube must be done in the hospital by a physician.

Safety concern

A major safety concern with the therapeutic use of donated human feces is the potential for transmission of infectious agents (e.g., viruses, bacteria, or parasites) contained in the donor stool.^{15,36} This risk may be minimized by obtaining feces from donors who have intimate physical contact with the recipient.³⁶

Regulatory status

The researcher found no information in the literature regarding the regulatory status of fecal transplantation.

Cost

The literature search uncovered no information regarding the cost of the fecal transplantation procedure. In Calgary, Alberta, the total cost of the fecal transplantation procedure via rectal retention enema is estimated to be between CAD 500 and 1500 (Dr. T. Louie, personal communication, October 2010). However, currently no information is available about how this procedure is being paid in Alberta. In addition, no information is available about the cost of fecal transplantation via other administering methods (i.e., nasogastric tube or colonoscope).

No formal cost analysis was performed at McMaster University for fecal transplantation procedure (Dr. J. Marshall, personal communication, November 2010).

Local context

In Alberta, one clinical centre in Calgary provides fecal transplantation via rectal retention enema for patients with recurrent CDAD but not for those with ulcerative colitis (Dr. L.A. Dieleman, personal communication, June 2010). Currently, the procedure is offered outside an institutional setting for severe cases referred after six months to two years of recurrent *C. difficile* infection (Dr. T. Louie, personal communication, February 2011).

SAFETY AND EFFICACY/EFFECTIVENESS OF FECAL TRANSPLANTATION

Characteristics of the included studies

Quantity of the identified studies

The literature search (see Appendix A: Methodology/Search Strategy) revealed no systematic review or controlled (randomized or non-randomized) trials that examined the safety and efficacy/effectiveness of fecal transplantation in the treatment of CDAD or ulcerative colitis.

Ten case series studies that met our selection criteria were included. Excluded studies and reasons for exclusion are listed in Table C.1 (see Appendix C: Excluded Studies). The 10 studies reported clinical experience about the safety and effects of fecal transplantation in patients with either CDAD (eight studies^{36,38,54,55,56,58,59,60}), ulcerative colitis (one study⁴⁵), or a combination of CDAD and ulcerative colitis (one study⁵⁷). The eight studies on patients with CDAD were conducted in several countries, including Australia, Canada, the Netherlands, the United Kingdom, and the United States, whereas the two studies on patients with ulcerative colitis or ulcerative colitis plus CDAD were conducted in Australia.

Details regarding the study design, patient characteristics, intervention, and outcomes extracted from each of the 10 studies are presented in Tables D.1 to D.3 (see Appendix D: Evidence Table).

Quality of the included studies

A formal assessment of methodological quality was not performed for the included studies. All studies are case series studies, which are considered the lowest level of evidence for determining the efficacy and effectiveness of a treatment. Of the 10 studies, only three^{36,38,45} were published in full-text articles. The remaining articles were available in abstract form only.

As shown in Table 3, the total number of patients reported in these studies ranged from 6 to 45, with less than 20 in the majority of the studies. The length of follow-up was less than 1 year in most studies. There was a lack of information regarding whether the reported cases were consecutive.

Table 3: Characteristics of the included studies

Study	Patients	Consecutive cases	Follow-up
Aas et al. 2003 ^{36*} United States	N = 18 CDAD	Yes	3 months
Macconnachie et al. 2009 ^{38*} United Kingdom	N = 15 CDAD	NA	Median 4 months (1 to 6 months)
Nieuwdorp et al. 2008 ^{54**} Netherlands	N = 7 CDAD	NA	NA
Louie et al. 2008 ⁵⁸ Canada	N = 45 CDAD	NA	Up to 12 months
Faust et al. 2002 ⁵⁵ Canada	N = 6 CDAD	NA	9 to 50 months
Borody et al. 2003 ⁵⁶ Australia	N = 24 CDAD	NA	1 to 16 months
Wettstein et al. 2007 ⁵⁹ Australia	N = 16 CDAD	NA	1 month

Yoon and Brandt 2008 ⁶⁰ United States	N = 6 CDAD	Yes	NA
Borody et al. 2003 ^{45*} Australia	N = 6 UC	NA	1 to 13 years
Borody et al. 2008 ⁵⁷ Australia	N = 6 CDAD + UC	NA	2 months

*Studies published in full-text articles; **English abstract of an article written in Dutch.

Abbreviations: CDAD: *Clostridium difficile*-associated disease; N: total number; NA: not available; UC: ulcerative colitis.

Safety and effectiveness of fecal transplantation in the treatment of CDAD

Eight studies^{36,38,54-56,58-60} focused on the effects of fecal transplantation in the treatment of patients diagnosed with CDAD.

Patient characteristics

As shown in Table 4, a total of 137 patients were included in the eight studies. The ages of the patients varied considerably across the studies, ranging from 11 to 95 years. While the majority of the patients were elderly individuals, two Australian case series^{56,59} included much younger patients (youngest 11 and 19, respectively). One study⁵⁴ did not provide information on patient sex. The other studies included more female than male patients.

Table 4: Patient characteristics

Study	Age (year)	Gender (M/F)	CDAD
Aas et al. 2003 ³⁶ N = 18	Mean 73 (range 51 to 88)	5/13	Recurrent
Macconnachie et al. 2009 ³⁸ N = 15	Median 81.5 (range 68 to 95)	1/14	Severe, recurrent
Nieuwdorp et al. 2008 ⁵⁴ N = 7	NA	NA	Recurrent
Louie et al. 2008 ⁵⁸ N = 45	Mean 62 (range 30 to 91)	12/33	Recurrent
Faust et al. 2002 ⁵⁵ N = 6	Mean 53 (range 34 to 74)	1/5	Recurrent
Borody et al. 2003 ⁵⁶ N = 24	Range 19 to 59	11/13	Chronic
Wettstein et al. 2007 ⁵⁹ N = 16	Range 11 to 87	5/11	Long-standing
Yoon and Brandt 2008 ⁶⁰ N = 6	Mean 59 (30 to 80)	1/5	Refractory

Abbreviations: CDAD: *Clostridium difficile*-associated disease; F: female; M: male; N: total number; NA: not available

All of the eight studies included patients with recurrent, chronic, or refractory CDAD. Although case definitions for recurrent CDAD are somewhat different among the studies, all the cases were confirmed by positive *C. difficile* toxin, positive stool culture, or colonoscopic findings. Patients included in the two Australian case series^{56,59} appeared to be slightly different from those in the other studies. These patients had chronic diarrhea, abdominal pain/cramping, bloating, flatulence, nausea,

vomiting, and fatigue, and some patients had an associated diagnosis such as irritable bowel syndromes, indicating the presence of underlying gastrointestinal diseases in some patients. While not clearly reported in the majority of the studies, one UK study³⁸ included patients admitted to the hospital, and one US study³⁶ included more outpatients (13/18) than inpatients (5/18). A Canadian case series⁵⁸ reported on 44 of 45 ambulatory patients in whom fecal transplantation was performed at home.

Interventions

Donors/donor screening

As presented in Table D.1 (Appendix D), stool donors included family members (e.g., spouse, brother, son), or healthy related or unrelated individuals. Various blood tests and stool tests summarized in Table 5 were used to screen donors.

Table 5: Summary of donor screening tests

Blood tests	Stool tests
Hepatitis A virus	<i>C. difficile</i> toxin A or B
Hepatitis B virus	Yersinia
Hepatitis C virus	Campylobacter
Human immunodeficiency virus 1 and 2	Shigella
Human T cell lymphotropic virus 1 and 2	Salmonella
Cytomegalovirus	Ova
Epstein-Barr virus	Cysts
Syphilis	Parasites

Method of administration

As indicated in Table D.1 (Appendix D), donor fecal suspensions were infused via nasogastric tubes,^{36,38} colonoscopy,⁶⁰ rectal retention enema,⁵⁸ duodenal catheter or colonoscopy⁵⁴, or a combination of these methods.^{56,59} Only one study⁵⁵ did not report the method for donor feces delivery.

Volume and frequency

Volumes and frequencies of fecal suspension delivery varied significantly across the studies, which may be due to the method used. In two studies,^{36,38} a small amount of 25 to 30 mL fecal suspension was infused through a nasogastric tube, once only. In contrast, a home-based Canadian study⁵⁸ infused much higher volumes (1000 to 1500 mL) of fecal suspension via rectal retention enema, and some patients received two or three infusions. The two Australian case series^{56,59} reported a combination of different methods; most patients received fecal transplantation once daily for 5 to 10 days.

Safety outcomes

As shown in Table C.1 (Appendix C), three studies^{54,55,59} did not report safety outcomes. Of the other five studies, two^{38,60} reported no adverse events associated with fecal transplantation. One study³⁶ reported a death from peritonitis that may be related to the use of the nasogastric tube. Two other studies^{56,58} reported that a small portion of patients experienced some adverse events such as sore throat, headache, and various gastrointestinal problems following fecal transplantation.

Efficacy/effectiveness outcomes

Efficacy/effectiveness outcomes obtained from each study are presented in Appendix C. The main findings are summarized in Table 6.

Table 6: Summary of efficacy and effectiveness outcomes

Study	Diarrhea	Testing for CD toxin	Patient acceptance
Aas et al. 2003 ³⁶ N=18; via nasogastric tube	94% resolved	83% negative	All receptive
Maccconnachie et al. 2009 ³⁸ N=15; via nasogastric tube	73% resolved	NA	Well tolerated
Nieuwdorp et al. 2008 ⁵⁴ N=7; via duodenal catheter or colonoscope	71% resolved	71% negative	NA
Louie et al. 2008 ⁵⁸ N=45; via retention enema	96% resolved	NA	NA
Faust et al. 2002 ⁵⁵ N=6; administration method not reported	100% improved	67% negative	NA
Borody et al. 2003 ³⁶ N=24; via colonoscope/retention enema/nasojejunal tube	46% resolved	83% negative	NA
Wettstein et al. 2007 ⁵⁹ N=16, via colonoscope and retention enema	50% improved, 44% resolved	94% negative	NA
Yoon and Brandt 2008 ⁶⁰ N=6; via colonoscope	100% improved	NA	NA

Abbreviations: CD: *Clostridium difficile*; N: total number; NA: not available

Diarrhea

As shown in Table 6, among the eight studies, diarrhea improved in 46% to 100% of patients and resolved in 44% to 96% of patients after fecal transplantation. Limited data did not demonstrate any difference in outcomes among different administration methods.

Two studies^{38,54} reported that some patients experienced a relapse after receiving the first infusion of an insufficient amount of feces, but the diarrhea resolved after a second infusion with the correct amount of fecal suspension, which may suggest the importance of delivering a sufficient amount of fecal flora.

Two full-text studies^{36,38} used similar fecal transplantation protocols (donor screening, fecal suspension preparation, administration method). Both studies reported a case in which a patient experienced a relapse after fecal transplantation; however, after receiving an additional 10-day antibiotic treatment with vancomycin or metronidazole, the patient was diarrhea free. In such cases, it is assumed that fecal transplant replaces sufficient gut flora to allow effective antibiotic treatment.³⁸ This treatment sequence may have important clinical implications.

Another patient relapsed after receiving broad-spectrum antibiotics,³⁸ highlighting the need to monitor the use of broad-spectrum antibiotics in such patients.

There are several limitations associated with these studies. First, most of these studies are a retrospective examination of an uncontrolled series of cases. Second, in all but one study,⁶⁰ antibiotics such as vancomycin or metronidazole were used prior to fecal transplantation to reduce the infectious burden. These patients had failed previous courses of vancomycin, and it is unlikely that pre-treatment with vancomycin influenced the results. However, in the absence of a control group it is not possible to determine whether the observed outcomes are the results of the pre-transplantation antibiotic treatment or the results of fecal transplantation.

Test for *C. difficile* toxin

Five studies^{36,54-56,59} reported test results for *C. difficile* toxin after the fecal transplantation procedure. As shown in Table 6, while tests were negative in the majority of patients, this result is not always consistent with the improvement or resolution of diarrhea.

Patient acceptance and satisfaction

Only two full-text studies^{36,38} reported this outcome. Both studies reported a high level of patient acceptance; one highly satisfied patient felt compelled to publicize the treatment in the national press.³⁸ An informal generic patient survey conducted by the Alberta College of Physicians and Surgeons indicated high patient satisfaction with services provided by specialists in fecal transplantation (Dr. T. Louie, personal communication, February 2011).

None of these studies provided information about physician acceptance of doing this procedure or donors' willingness to provide fecal samples.

Given that patients with recurrent CDAD are difficult to treat, if fecal transplant is performed according to a strict protocol by an expert in the field, both doctor and patient acceptance are expected to be high. This procedure will never be performed on a large scale unless genetically engineered cocktails of the same transplant content can be produced (Dr. S. Veldhuyzen van Zanten, personal communication, February 2011).

Other outcomes

None of the eight studies reported on quality of life measures or colonoscopic/histological changes before and after fecal transplantation.

Safety and effectiveness of fecal transplantation in the treatment of ulcerative colitis

The only study in this category⁴⁵ reported outcomes on six patients with long-standing (defined as 5 years or longer) ulcerative colitis; in all of these patients the *C. difficile* test was negative.

In this study, all but one stool donor were healthy individuals who were related to the patients (Table D. 2 in Appendix D). Various blood and stool tests were used for donor screening. Blood tests included a full blood count, liver function tests, and tests for hepatitis A, B, C; cytomegalovirus; Epstein-Barr virus; and syphilis. Stools were tested for *C. difficile* and, using microscopy, the presence of protozoa such as trophozoites and cysts, helminths and ova, trematodes, and tapeworms.

For all six patients, donor fecal suspension was infused via rectal retention enema, once daily for 5 days consecutively.

Safety outcome

No information was available from this study about whether there were adverse events associated with the fecal transplantation procedure.

Efficacy/effectiveness outcomes

Improvement of symptoms

As shown in Table D.2 in Appendix D, immediate improvement in the symptom of diarrhea occurred in some patients within one week following fecal transplantation, and complete resolution of diarrhea was achieved in all six patients by 4 months after fecal transplantation. Other symptoms such as abdominal pain, rectal bleeding, or fatigue improved in some or all patients. At 4 months post-fecal transplantation, all medications for the treatment of ulcerative colitis were discontinued in all patients. During an average of 5 years' (range 1 to 13 years) follow-up, no clinical symptoms and signs occurred in any of the six patients who continued to be off medications for ulcerative colitis.

Colonoscopic/histologic changes

Colonoscopic and histologic examinations indicated that, at 1 to 13 years post-fecal transplantation and without any medications for ulcerative colitis, no colonoscopic or histologic evidence of ulcerative colitis was found in any of the six patients.

Safety and effectiveness of fecal transplantation in the treatment of ulcerative colitis complicated by CDAD

Only one abstract⁵⁷ reported the results of fecal transplantation on patients with inflammatory bowel disease complicated with CDAD (Table D.3 in Appendix D). Of the six patients reported in this abstract, four had CDAD and ulcerative colitis and two patients had CDAD and Crohn's disease. This abstract provided no information about the donor, donor screening, and volume/frequency of feces infusion. Donor fecal suspension was infused repeatedly via retention enema. No information regarding adverse events associated with the procedure was included. At 8 weeks following fecal transplantation, diarrhea was improved, and testing for *C. difficile* was negative in all patients.

Ongoing research

Two proposed randomized controlled trials (RCTs), one led by the investigators in the Netherlands⁶¹ and the other by investigators in Canada,⁶² were designed to compare fecal transplantation with vancomycin in the treatment of recurrent *C. difficile* infection. Details of the two proposed RCTs are summarized in Table 7.

Table 7: Protocols for the ongoing RCTs

	RCT in the Netherlands⁶¹	RCT in Canada⁶²
Objectives	To investigate whether treatment of recurrent CDAD with FT is more effective than conventional antibiotic therapy To evaluate the cost-effectiveness and cost-utility of FT compared to conventional antibiotic regimens To explore the psychological impact on patients and patient acceptance of FT	To compare fecal transplantation with a 6-week taper of oral vancomycin
Study design	Multicentre RCT	Single centre, non-blinded RCT, crossover if a relapse of symptom occurs
Patient selection	N = 40 patients per treatment arm Inclusion: adult patients (≥ 18 years) with a clinically and microbiologically proven relapse of CDAD after at least one course of adequate antibiotic therapy Exclusion: patients with prolonged compromised immunity	N = 146 Inclusion: adult patients (≥ 18 years) with laboratory or pathogen-confirmed diagnosis of recurrent CDAD with symptoms within the previous 60 days Exclusion: patients with conditions such as neutropenia, graft versus host disease, or severe immunocompromise, in whom enemas are contraindicated; more than one episode of CDAD that has been severe or rapid in onset
Intervention	Bowel lavage combined with FT via nasoduodenal tube	2 weeks of oral vancomycin pre-treatment followed by FT via rectal enema (50 g stool blended in 500 mL of normal saline)
Comparator	Vancomycin only	2 weeks of oral vancomycin pre-treatment followed by 6-week taper of oral vancomycin
Follow-up	70 days (10 weeks)	120 days
Outcome measures	Primary: response to treatment at 70 days after initiation of therapy Secondary: response at 35 days (5 weeks) and time without diarrhea during a follow-up period of 70 days, costs, and quality-adjusted life-years Cost-effectiveness and cost-utility analysis: FT against antibiotic therapy as its best alternative; analysis will be performed from a societal perspective Psychological evaluation: patient acceptance and coping	Primary: recurrence of toxin-confirmed CDAD within 120 days of starting the intervention Secondary: early recurrence of symptoms within 14 days, relapse within 120 days, attributable mortality, hospitalization, and serious adverse events
Study period	April 2008 to February 2012	October 2010 to December 2013

Abbreviations: CDAD: *Clostridium difficile*-associated disease; FT: fecal transplantation; RCT: randomized controlled trial

Expert opinion

According to the opinions obtained from a gastroenterologist from the University of Alberta (Dr. L.A. Dieleman), fecal transplantation is considered experimental and is not provided at the University of Alberta. The subgroup of patients with ulcerative colitis that would benefit the most from fecal transplantation still needs to be determined. Patients with the following characteristics could be considered for fecal transplantation: (1) frequent relapsing ulcerative colitis, (2) steroid dependence, or (3) need for azathioprine and/or even biologics, such as anti-tumour necrosis factor infusions.

Clinical practice guidelines

For CDAD

In the Best Practice Guidance entitled *Clostridium difficile infection: How to deal with the problem*, prepared by the Department of Health and Health Protection Agency, England, in 2008,⁶³ donor fecal transplantation is recommended for consideration as a last-resort treatment for recurrent *C. difficile* infection.

The 2009 European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI)³⁵ and the Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)²⁹ provided no recommendations on the use of fecal transplantation in the treatment of CDAD. Further discussions are under way within the Infectious Diseases Society of America/American Gastroenterology Association in hopes of developing a consensus document (Dr. T. Louie, personal communication, February 2011).

No Canadian clinical practice guidelines were found that provide information about the use of fecal transplantation for the prevention or treatment of CDAD.

For ulcerative colitis

The researcher reviewed number of relevant Canadian and American association/society guidelines were reviewed but found no recommendations on the use of fecal transplantation for the prevention or treatment of ulcerative colitis.

Discussion

Limitations of the review

The current review has several limitations. First, only studies published in the English language were included in this review, which might have introduced publication bias. Second, to compensate for the paucity of primary studies in this area, studies published in abstract forms were also included. Insufficient details provided in these abstracts in terms of patient characteristics, fecal transplantation procedures (e.g., donor/donor screening, fecal suspension preparation, and volume/frequency of feces infusion), and outcome measures makes it difficult to compare results across studies. Third, no formal quality assessment of the included studies was conducted.

Summary of findings

Researchers found no systematic reviews (according to Cook's criteria⁶⁴) or randomized/non-randomized controlled studies that examined the safety and efficacy/effectiveness of fecal transplantation for the prevention or treatment of patients with CDAD or ulcerative colitis.

The literature search uncovered no studies that compared fecal transplantation with other treatments. Furthermore, no study was found that compared different administration methods of the fecal flora (i.e., nasogastric tube, retention enemas, or colonoscopy).

Ten case series studies were included; three were full-text articles while seven were presented in abstract form only. Most of these studies reported the experience of a single clinical centre where fecal transplantation was performed by a single clinician. The total number of included patients ranged from 6 to 45, but was less than 20 in most studies. The duration of follow-up was less than one year in most studies, with one study following patients for up to 13 years.

Adverse events associated with the fecal transplantation procedure were reported in only five of the 10 studies. While, in general, reported adverse events were not severe (such as sore throat, headache, and gastrointestinal problems), one study reported a death from peritonitis that was possibly linked to fecal transplantation via a nasogastric tube.

In terms of treatment effects, all studies reported promising results. Symptoms, most frequently diarrhea, usually improved immediately following the fecal transplantation procedure. However, the improvement or resolution of diarrhea was not always consistent with negative testing for CD toxins.

Factors that may have impacted outcomes

Patient characteristics

The majority of patients included in these studies were older people and females with recurrent CDAD. One study⁴⁵ that included six younger patients with ulcerative colitis also showed promising results.

Method of administration

In most studies, the same method of administration was used in all patients. In studies where different methods were used alone or in combination, outcomes were not reported separately. No study compared the results of different methods of administration. Furthermore, different methods of administration were also linked to different volumes and frequencies of feces infusion; for example, much smaller amounts of fecal suspension were infused through a nasogastric tube than via rectal retention enema. Therefore, with currently available evidence, it is not possible to determine either the superiority of one method of fecal transplantation over another or whether there is a dose-related response.

Volume and frequency

Findings from several studies suggested that a sufficient amount of fecal suspension may be essential to achieve optimal outcomes. Two studies^{38,54} reported that patients failed the first infusion because of an insufficient amount of fecal suspension but achieved symptom resolution after the second infusion with a higher volume of fecal flora. A Canadian study⁵⁸ reported a high success rate following infusion of a 1000 to 1500 mL fecal suspension. However, without a control group and with the evidence from such a small number of patients, no conclusion could be drawn about the optimal volume or frequency of fecal infusion.

Pre-transplantation use of vancomycin and metronidazole

When assessing effectiveness of fecal transplantation, one needs to take into account the pre-transplantation use of antibiotics against *C. difficile* to differentiate the effect of antibiotic medications from the effect of fecal transplantation.¹⁵

In the majority of studies, vancomycin or metronidazole was used for up to 2 weeks prior to fecal transplantation and was usually discontinued several hours before the procedure, which raises a question about the potential impact of pre-transplantation antibiotic therapy on the reported outcomes. It was generally thought that this was unlikely to influence the results because these patients have failed previous courses of vancomycin/metronidazole. However, in the absence of a control group, the possible impact of pre-fecal transplantation use of antibiotics on the outcomes could not be determined.

Research gaps

Although fecal transplantation has been performed since the 1950s, only a small number of cases from several clinical centres around the world were reported in the literature. Results from these small case series studies appeared to be promising. However, in the absence of a control group, the role of fecal transplantation in the prevention and treatment of CDAD and ulcerative colitis remains to be further clarified.

Larger scale research, particularly Alberta-centred research, is needed to bridge the evidence gaps. Longitudinal studies are also needed for economic evaluation (Dr. T. Louie, personal communication, October 2010).

Studies that provide details on the precise techniques used to prepare and deliver fecal suspensions are needed to determine the most appropriate method of administration and the amount, concentration, and frequency of fecal infusions to achieve optimal outcomes.

Studies that compare fecal transplantation with use of vancomycin, metronidazole, or both are required to differentiate the effects of fecal transplantation from the effects of antibiotics in the treatment of CDAD. The two proposed randomized clinical trials might help researchers and clinicians to better delineate the role of fecal transplantation.

Subgroup analysis may be helpful in identifying patient groups (in terms of age, gender, comorbidities, etc.) who would benefit most from fecal transplantation.

There is also a lack of literature documenting the methods used to monitor long-term follow-up, including regular stool tests for *C. difficile* and colonoscopy and biopsies for histological examination. No feasible methods are currently available for quantitative analysis of fecal composition prior to and following treatment. However, a clinic in Calgary follows patients with quantitative profiles of the microbiome (Dr. T. Louie, personal communication, February 2011).

The most appropriate protocol for the fecal transplantation procedure remains a clinical issue. The lack of definition of “normal gut microflora” makes it difficult to develop a standard fecal transplantation formula that can be administered safely. Even if the presence of stool pathogens in the donor feces is ruled out, there remain a host of potential pathogens present, most of which are uncultivable. There is a clear need for more research about the normal or protective human microbiome before a standard fecal transplantation can be safely administered (Dr. L.A. Dieleman, personal communication, November 2010).

CONCLUSIONS

Management of severe, recurrent, and relapse CDAD, particularly in elderly patients, remains clinically challenging. While the majority of patients respond to standard care, including discontinuation of inducing antibiotics and use of antibiotics against *C. difficile* (vancomycin and metronidazole), a small portion of patients fail to achieve disease resolution with standard care.

Transplantation of fecal suspension obtained from healthy donors may restore normal flora, breaking the cycle of recurrent CDAD, usually after treatment with pulsed/tapered vancomycin therapy has failed.

Based on the limited evidence of 10 case series studies, fecal transplantation appears to be a safe procedure. In most cases, symptoms improved immediately after fecal transplantation and patients stayed diarrhea-free for several months or even years, indicating that fecal transplantation could be an effective alternative in the treatment of patients with recurrent CDAD, ulcerative colitis, or CDAD superimposed on ulcerative colitis.

Two ongoing RCTs that compare fecal transplantation with oral vancomycin in patients with recurrent CDAD may provide a better understanding of the potential role of fecal transplantation in the management of patients with recurrent/refractory CDAD. Future controlled trials are also required to better delineate the role of fecal transplantation in patients with ulcerative colitis.

The status of fecal transplantation as an experimental or accepted procedure for patients with recurrent CDAD remains to be determined.

APPENDIX A: METHODOLOGY

Search strategy

The IHE Information Specialist conducted a literature search in February 2010 to retrieve articles published between January 2000 and February 2010. The searches were further limited to English language articles and human studies where possible. As shown in Table A.1, three databases, including Biological Abstracts, BIOSIS, and Web of Science, were searched for conference abstracts. Reference lists of relevant articles were also checked.

Table A.1: Search strategy

Database	Edition or date searched	Search Terms ††
Core Databases		
The Cochrane Library http://www.thecochranelibrary.com	1 Feb 2010	<ol style="list-style-type: none"> 1. (ulcerative colitis or pseudomembranous colitis or clostridium difficile* or c-difficile*)Title/Abstract/Keywords 2. (bowel or feces or faeces or fecal or faecal or stool) Title/Abstract/Keywords) 3. (administration or bacteriotherapy or donat* or donor* or enema* or implant* or infusion* or transfusion* or transplant*)Title/Abstract/Keywords) 4. 1 and 2 and 3 5. (human probiotic infusion)Title/Abstract/Keywords 6. 4 or 5 7. limit 6 to yr="2000-2010" 8 results (Cochrane Reviews) 1 (Other reviews) 89 results (Central) 2 results (HTA)
MEDLINE (OVID)	30 Jan 2010	<ol style="list-style-type: none"> 1. Clostridium Infections/ or Clostridium difficile/ 2. Colitis, Ulcerative/ or enterocolitis, pseudomembranous/ 3. (clostridium difficile or c-difficile or ulcerative colitis or pseudomembranous colitis).tw. 4. 1 or 2 or 3 5. limit 4 to yr="2000-Current" 6. Feces/ 7. Enema/ or administration, rectal/ or intubation, gastrointestinal/ 8. 6 and 7 9. ((feces or faeces or fecal or faecal or stool or bowel or colon flora) adj5 (administration or bacteriotherapy or colonization or donat* or donor* or enema* or implant* or infusion* or nasogastric tube or transfusion* or transplant*)).tw. 10. 8 or 9 11. 5 and 10 12. human probiotic infusion*.tw. 13. 5 and 12 14. 11 or 13 15. limit 14 to animals 16. limit 14 to (animals and humans) 17. 15 not 16

		18. 14 not 17 59 results
Cochrane Central Register of Controlled Trials (OVID) NHSEED (OVID) HTA Database (OVID)	1 st Quarter 2010 1 st Quarter 2010 1 st Quarter 2010	1. Clostridium Infections/ or Clostridium difficile/ 2. Colitis, Ulcerative/ or enterocolitis, pseudomembranous/ 3. (clostridium difficile or c-difficile or ulcerative colitis or pseudomembranous colitis).tw,kw,hw. 4. 1 or 2 or 3 5. limit 4 to yr="2000 -Current" 6. Feces/ 7. Enema/ or administration, rectal/ or intubation, gastrointestinal/ 8. 6 and 7 9. ((feces or faeces or fecal or faecal or stool or bowel or colon flora) adj5 (administration or bacteriotherapy or colonization or donat* or donor* or enema* or implant* or infusion* or nasogastric tube or transfusion* or transplant*).tw,kw,hw. 10. 8 or 9 11. 5 and 10 12. human probiotic infusion*.tw,kw,hw. 13. 5 and 12 14. 11 or 13 15. limit 14 to animals 16. limit 14 to (animals and humans) 17. 15 not 16 18. 14 not 17 7 results (Cochrane CENTRAL) 0 results (NHSEED) 1 results (HTA)
Cochrane Database of Systematic Reviews (OVID) DARE Database of Abstracts of Reviews of Effects (OVID)	4 th Quarter 2009 1 st Quarter 2010	1. (clostridium difficile or c-difficile or ulcerative colitis or pseudomembranous colitis).tw,kw. 2. ((feces or faeces or fecal or faecal or stool or bowel or colon flora) adj5 (administration or bacteriotherapy or colonization or donat* or donor* or enema* or implant* or infusion* or nasogastric tube or transfusion* or transplant*).tw,kw. 3. human probiotic infusion*.tw,kw. 4. 2 or 3 5. 1 and 4 4 results (Cochrane Database of Systematic Reviews) 1 results (DARE)
Biological Abstracts (OVID to 2005)	1 Feb 2010	1. (clostridium difficile or c-difficile or ulcerative colitis or pseudomembranous colitis).tw,hw,mc. 2. ((feces or faeces or fecal or faecal or stool or bowel or colon flora) adj5 (administration or bacteriotherapy or colonization or donat* or donor* or enema* or implant* or infusion* or nasogastric tube or transfusion* or transplant*).tw,hw,mc. 3. human probiotic infusion*.tw,hw,mc. 4. 2 or 3 5. 1 and 4 6. limit 5 to yr= "2000-2005" 40 results

PubMed	30 Jan 2010	<ol style="list-style-type: none"> 1. Clostridium Infections[MeSH] or Clostridium difficile[MeSH] 2. Colitis, Ulcerative[MeSH] or enterocolitis, pseudomembranous[MeSH] 3. clostridium difficile[tiab] or c-difficile[tiab] or ulcerative colitis[tiab] or pseudomembranous colitis[tiab] 4. 1 or 2 or 3 5. limit 4 to yr="2009 -Current" 6. Feces[MeSH] 7. Enema[MeSH] or administration, rectal[MeSH] or intubation, gastrointestinal[MeSH] 8. 6 and 7 9. (feces[tiab] or faeces[tiab] or fecal[tiab] or faecal[tiab] or stool[tiab] or bowel[tiab] or colon flora[tiab]) and (administration[tiab] or bacteriotherapy[tiab] or colonization[tiab] or donat*[tiab] or donor*[tiab] or enema*[tiab] or implant*[tiab] or infusion*[tiab] or nasogastric tube*[tiab] or transfusion*[tiab] or transplant*[tiab]) 10. 8 or 9 11. 5 and 10 12. human probiotic infusion*[tiab] 13. 5 and 12 14. 11 or 13 15. limit 14 to animals 16. limit 14 to (animals and humans) 17. 15 not 16 18. 14 not 17 116 results
EMBASE (OVID)	30 Jan 2010	<ol style="list-style-type: none"> 1. clostridium difficile/ or clostridium difficile infection/ 2. pseudomembranous colitis/ 3. ulcerative colitis/ or colitis/ or enteritis/ 4. (ulcerative colitis or pseudomembranous colitis).tw. 5. (clostridium difficile* or c-difficile*).tw. 6. 1 or 2 or 3 or 4 or 5 7. limit 6 to yr="2000 -Current" 8. feces/ or feces microflora/ or colon flora/ 9. ((bowel or colon flora or feces or faeces or fecal or faecal or stool) adj5 (administration or bacteriotherapy or colonization or donat* or donor* or enema* or implant* or infusion* or nasogastric tube or transfusion* or transplant*)).tw. 10. bacterial colonization/ or enema/ 11. nasogastric tube/ 12. rectal drug administration/ 13. 10 or 11 or 12 14. 8 and 13 15. 9 or 14 16. 7 and 15 17. human probiotic infusion*.tw. 18. fecal bacteriotherapy.sh. 19. 17 or 18 20. 7 and 19 21. 16 or 20 22. limit 21 to animal studies

		23. 21 not 22 157 results
CINAHL (EBSCO)	31 Jan 2010	1. MH(clostridium difficile or clostridium infections or enterocolitis, pseudomembranous or colitis, ulcerative or colitis) 2. TI (ulcerative colitis or pseudomembranous colitis or clostridium difficile* or c-difficile*) or AB (ulcerative colitis or pseudomembranous colitis or clostridium difficile* or c-difficile*) 3. 1 or 2 4. TI (bowel or feces or faeces or fecal or faecal or stool) or AB (bowel or feces or faeces or fecal or faecal or stool) 5. TI (administration or bacteriotherapy or donat* or donor* or enema* or implant* or infusion* or transfusion* or transplant*) or AB (administration or bacteriotherapy or donat* or donor* or enema* or implant* or infusion* or transfusion* or transplant*) 6. 3 and 4 and 5 7. TI (human probiotic infusion) or AB (human probiotic infusion) 8. 6 or 7 9. limit 8 to yr="2000-2010" 61 results
BIOSIS Previews (ISI) Web of Science (ISI)	30 Jan 2010	1. TS=(clostridium difficile or clostridium infections or enterocolitis, pseudomembranous or colitis, ulcerative or colitis) or TI=(ulcerative colitis or pseudomembranous colitis or clostridium difficile* or c-difficile*) 2. TS=(bowel or feces or faeces or fecal or faecal or stool) or TI=(bowel or feces or faeces or fecal or faecal or stool) 3. TS= (administration or bacteriotherapy or donat* or donor* or enema* or implant* or infusion* or transfusion* or transplant*) or TI=(administration or bacteriotherapy or donat* or donor* or enema* or implant* or infusion* or transfusion* or transplant*) 4. 1 and 2 and 3 5. TS=(human probiotic infusion) or TI=(human probiotic infusion) 6. 4 or 5 7. limit 6 to yr="2000-2010" 51 results (BIOSIS Previews) 95 results (Web of Science)
HTA Agencies		
AETMIS http://www.aetmis.gouv.qc.ca/site/en_publications.phtml	8 Feb 2010	Browsed complete list of publications.
CADTH http://www.cadth.ca/index.php/en/hta/reports-publications/search	8 Feb 2010	Searched: fecal; faecal; feces; faeces; stool; bacteriotherapy; "bacterial therapy"; probiotic; probiotics
ICES http://www.ices.on.ca	8 Feb 2010	Browsed list of publications
Health Technology Assessment McGill http://www.mcgill.ca/tau/	8 Feb 2010	Browsed list of reports 1 result http://www.mcgill.ca/files/tau/PROBIOTICS_Report_5Final.pdf
Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas_mn.html	8 Feb 2010	Browsed list of HTAs

ASERNIPS http://www.surgeons.org/racs/research-and-audit/asernip-s/asernip-s-publications	8 Feb 2010	Browsed publications
MSAC http://www.msac.gov.au/	8 Feb 2010	Browsed assessments
Health Evidence Bulletins Wales http://hebw.cf.ac.uk	8 Feb 2010	Browsed publications
NHS Evidence http://www.evidence.nhs.uk	8 Feb 2010	Searched: “fecal transplant”; “fecal transplantation”; “faecal transplant”; “faecal transplantation”; bacteriotherapy; “bacterial therapy”; “probiotic infusion” 1 result http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1232006607827
National Horizon Scanning Centre http://www.haps.bham.ac.uk/publichealth/horizon/topic.shtml	8 Feb 2010	Searched: fecal; faecal; feces; faeces; stool; bacteriotherapy; “bacterial therapy”; probiotic; probiotics
National Coordinating Centre for Health Technology Assessment http://www.hta.ac.uk	8 Feb 2010	Searched and browsed by disease group
CCE http://www.southernhealth.org.au/page/Health_Professionals/CCE/Evidence_reviews/	8 Feb 2010	Browsed evidence reviews
Euroscan http://www.euroscan.org.uk	8 Feb 2010	Searched: fecal; faecal; stool; bacteriotherapy; “bacterial therapy”; probiotics; probiotic
ECRI HTAIS https://www.ccri.org	8 Feb 2010	Searched: fecal; faecal; feces; faeces; stool; bacteriotherapy; “bacterial therapy”; probiotic; probiotics
California Health Benefits Review Program http://www.chbrp.org	8 Feb 2010	Browsed publications
California Technology Assessment Forum http://www.ctaf.org	8 Feb 2010	Browsed publications
AHRQ http://healthit.ahrq.gov	8 Feb 2010	Browsed publications
VA Technology Assessment Program http://www.va.gov/VATAP/P_hase2pubspage.asp	8 Feb 2010	Browsed publications
Blue Cross Blue Shield http://www.bcbs.com/blueresources/tec/tec-assessments.html	8 Feb 2010	Browsed publications
Guidelines		
Towards Optimized Practice - Clinical Practice Guidelines http://www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines.html	8 Feb 2010	Browsed guidelines
CMA Infobase http://www.cma.ca	8 Feb 2010	Browsed specialties

National Guideline Clearing House http://www.guideline.gov	8 Feb 2010	Searched: fecal; faecal; feces; faeces; stool; bacteriotherapy; “bacterial therapy”; probiotic; probiotics ulcerative colitis, clostridium difficile, c-difficile, pseudomembranous colitis
New Zealand Guidelines Group http://www.nzgg.org.nz	8 Feb 2010	Browsed publications
Guidelines Advisory Committee http://www.gacguidelines.ca	8 Feb 2010	Browsed topics
BC Guidelines and Protocol Advisory http://www.bcguidelines.ca/gpac	8 Feb 2010	Browsed topics
Clinical Trials		
Clinical trials.gov http://www.clinicaltrials.gov	8 Feb 2010	Searched: “fecal transplant” OR “fecal bacteriotherapy” OR fecal bacterial therapy OR probiotic* OR “human probiotic infusion”
CCT Current Controlled Trials http://www.controlled-trials.com	8 Feb 2010	“fecal transplant” OR “fecal bacteriotherapy” OR fecal bacterial therapy OR probiotic* OR “human probiotic infusion” 1 result http://www.controlled-trials.com/mrct/trial/384783/bacteriotherapy
Regulatory Agencies		
Alberta Health and Wellness http://www.health.alberta.ca	8 Feb 2010	Searched: “fecal transplant” OR “fecal bacteriotherapy” OR “fecal bacterial therapy” OR probiotic* OR “human probiotic infusion”
Health Canada http://www.hc-sc.gc.ca	8 Feb 2010	Searched: “fecal transplant” OR “fecal bacteriotherapy” OR “fecal bacterial therapy” OR probiotic* OR “human probiotic infusion” 1 result http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/mono_probioti-eng.pdf
US Food and Drug Administration http://www.fda.gov	8 Feb 2010	Searched: “fecal transplant” OR “fecal bacteriotherapy” OR “fecal bacterial therapy” OR probiotic* OR “human probiotic infusion”
Search Engines and Websites		
Google	8 Feb 2010	Searched: “fecal transplant” OR “fecal bacteriotherapy” OR “human probiotic infusion”
Canadian Association of Gastroenterology http://www.cag-acg.org	8 Feb 2010	Browsed research pages
Crohn’s and Colitis Foundation of Canada http://www.cffc.ca/English/index.html	8 Feb 2010	Browsed pages
American College of Gastroenterology http://www.acg.gi.org	8 Feb 2010	Searched: bacteriotherapy; fecal transplant; faecal; fecal probiotics
World Gastroenterology Organisation http://www.worldgastroenterology.org	8 Feb 2010	Searched: bacteriotherapy; fecal; faecal

Study selection

One researcher (BG) reviewed titles and abstracts identified from the literature search and retrieved full-text articles that appeared to be relevant. Articles that contained information related to cost or cost-effectiveness of the procedure were forwarded to and reviewed by a health economist. Key studies for the safety and efficacy/effectiveness of fecal transplantation were selected according to the following predefined inclusion and exclusion criteria.

Inclusion criteria

Studies were included if they met all of the following criteria:

Study type: systematic reviews, randomized or non-randomized controlled trials, case series studies.

Note: An article was deemed to be a systematic review if it met all of the following criteria as defined by Cook et al. 1997:⁶⁴

- focused clinical question;
- explicit search strategy;
- use of explicit, reproducible, and uniformly applied criteria for article selection;
- critical appraisal of the included studies; and
- qualitative or quantitative data synthesis.

Population: patients with *Clostridium difficile*-associated disease (or other terms such as *C. difficile*-associated diarrhea, *C. difficile* infection, pseudomembranous colitis), and/or ulcerative colitis.

Intervention: fecal transplantation (or other terms such as fecal bacteriotherapy, fecal transfusion, fecal transplant, stool transplant, or human probiotic infusion).

Comparator: standard care for CDAD or ulcerative colitis, other probiotics, or comparisons among different methods for administering fecal transplantation.

Outcome measures: studies included at least one of the following.

For CDAD: improvement in symptoms (mainly diarrhea), reduction in mortality related to CDAD, stool testing for *C. difficile* and its toxins, health-related quality of life, patient acceptance and satisfaction, prevention of recurrence or more severe complications (e.g., toxic megacolon), or prevention of more aggressive therapies (e.g., colectomy).

For ulcerative colitis: improvement in symptoms, discontinuation of other medications for ulcerative colitis, health-related quality of life, patient acceptance and satisfaction, inducing and maintaining remission, prevention of relapse, prevention of more aggressive therapy (e.g., use of steroid or immunosuppressive drugs, or colectomy), reduction in emergency department visits.

Clinical practice guidelines on the use of fecal transplantation for the prevention and treatment of CDAD or ulcerative colitis and documents on the regulatory status of fecal transplantation were also included in the report.

Exclusion criteria

Studies were excluded if they met any of the following criteria:

Study type: case report, letters, news, comments, editorials.

Population: patients with other gastrointestinal diseases such as Crohn's disease or irritable bowel syndrome.

Intervention: use of antibiotics or other probiotics as the main interventions.

Data extraction

Data from each of the included key studies were extracted by one researcher (BG) according to a pre-developed data extraction form and were cross-checked for consistency and accuracy by a second person (CH).

Studies: author, year of publication, country where the study is conducted, study design, study objective.

Patient: total number, age, gender (male/female), condition, case definition, baseline *C. difficile* test, clinical setting.

Intervention: donors, donor screening tests, fecal suspension preparation, method of administration, volume and frequency of feces infusion, length of follow-up, and co-intervention(s).

Outcomes:

Safety: any adverse events associated with the use of fecal transplantation.

Clinical efficacy/effectiveness: improvement in symptoms (e.g. diarrhea), testing for *C. difficile* and its toxin, colonoscopic and histological changes, health-related quality of life, patient acceptance, prevention of more aggressive therapies, or reduction of emergency department visits.

Quality assessment

No formal quality assessment was conducted for the included case series studies. Important methodological issues were identified and discussed.

Data synthesis

Data extracted from each study were synthesized qualitatively. No attempt was made to conduct a meta-analysis due to the nature of case series studies.

APPENDIX B: PREVALENCE AND INCIDENCE OF ULCERATIVE COLITIS IN ALBERTA

Methods

We estimated the total and the age- and sex-specific prevalence and incidence of ulcerative colitis (UC) in Alberta by years from fiscal year 2002/2003 to fiscal year 2008/2009 using the Discharged Abstract Database (DAD), Ambulatory Care Classification System database (ACCS), and population database from Alberta Health and Wellness (AHW). The yearly prevalence (incidence) was estimated per 100,000 population and equal to the number of active UC cases (new active UC cases) in a given year divided by population (population at risk) in that year. The number of active UC cases in a given year was the number of unique patients with an UC diagnosis who used health services included in either DAD or ACCS or both databases in that year. The number of new active UC cases in a given year was the number of unique patients with an UC diagnosis who used health services included in either DAD or ACCS or both databases in that year and never included in any of the previous years. The population at risk was the population excluding those who have already been diagnosed with the disease.

This study excluded people with UC who were not included in the DAD and ACCS databases.

Results

Table B.1 shows prevalence and Table B.2 shows incidence of UC by sex, age, and year in Alberta. In 2008/09, prevalence and incidence of UC was estimated at 75.3 and 36.0 cases per 100,000 population, respectively. The prevalence and incidence varied by age group but were similar between men and women. Adult people aged 25 to 79 years had a higher prevalence and incidence than other age groups.

Regarding the time trend, the prevalence increased over the years from 58.5 cases per 100,000 in 2002/03 to 75.3 cases per 100,000 in 2008/09.

It is difficult to compare the incidence between the years in this study since the new cases meant new compared to the previous years, so the more recent years will show lower and more accurate incidences.

The prevalence and incidence of active UC cases estimated in this study were likely lower than the prevalence and incidence of all UC cases since the non-active or less severe cases who did not use any hospital in- or out-patient services (for example, who were not treated or who were treated by family physicians) were not included.

Table B.1: Ulcerative colitis prevalence by age, sex, and year

Age	# of UC patients			Population			Prevalence per 100,000 pop		
	F	M	Total	F	M	Total	F	M	Total
2002/03									
0 to 4	2	3	5	82,586	86,028	168,614	2.4	3.5	3.0
5 to 9	9	10	19	103,165	109,189	212,354	8.7	9.2	8.9
10 to 14	8	14	22	113,251	118,997	232,248	7.1	11.8	9.5
15 to 19	34	42	76	114,434	120,139	234,573	29.7	35.0	32.4
20 to 24	71	74	145	119,053	122,584	241,637	59.6	60.4	60.0
25 to 29	93	76	169	116,777	118,735	235,512	79.6	64.0	71.8
30 to 34	90	93	183	117,649	119,821	237,470	76.5	77.6	77.1
35 to 39	112	102	214	122,922	123,016	245,938	91.1	82.9	87.0
40 to 44	109	101	210	140,833	141,030	281,863	77.4	71.6	74.5
45 to 49	88	102	190	130,736	135,597	266,333	67.3	75.2	71.3
50 to 54	79	81	160	104,256	108,760	213,016	75.8	74.5	75.1
55 to 59	45	90	135	83,594	85,661	169,255	53.8	105.1	79.8
60 to 64	54	66	120	60,936	61,793	122,729	88.6	106.8	97.8
65 to 69	33	46	79	50,226	49,077	99,303	65.7	93.7	79.6
70 to 74	19	35	54	45,184	42,801	87,985	42.1	81.8	61.4
75 to 79	28	30	58	38,141	31,739	69,880	73.4	94.5	83.0
80 to 84	10	12	22	30,427	20,450	50,877	32.9	58.7	43.2
85 and over	14	5	19	31,083	15,167	46,250	45.0	33.0	41.1
Missing				109	440	549	0.0	0.0	0.0
Total	898	982	1880	1,605,362	1,611,024	3,216,386	55.9	61.0	58.5

Table B.1: Ulcerative colitis prevalence by age, sex, and year (cont'd)

Age	# of UC patients			Population			Prevalence per 100,000 pop		
	F	M	Total	F	M	Total	F	M	Total
2003/04									
0 to 4	3	2	5	83,251	87,115	170,366	3.6	2.3	2.9
5 to 9	7	8	15	102,534	107,947	210,481	6.8	7.4	7.1
10 to 14	10	11	21	112,111	118,340	230,451	8.9	9.3	9.1
15 to 19	41	26	67	115,892	121,615	237,507	35.4	21.4	28.2
20 to 24	56	64	120	121,318	124,727	246,045	46.2	51.3	48.8
25 to 29	101	87	188	119,350	121,109	240,459	84.6	71.8	78.2
30 to 34	96	83	179	117,827	120,909	238,736	81.5	68.6	75.0
35 to 39	100	82	182	120,542	121,032	241,574	83.0	67.8	75.3
40 to 44	125	116	241	140,639	140,144	280,783	88.9	82.8	85.8
45 to 49	110	115	225	134,171	138,619	272,790	82.0	83.0	82.5
50 to 54	79	78	157	109,563	114,168	223,731	72.1	68.3	70.2
55 to 59	51	81	132	88,463	90,884	179,347	57.7	89.1	73.6
60 to 64	40	62	102	63,651	64,676	128,327	62.8	95.9	79.5
65 to 69	36	44	80	51,078	50,022	101,100	70.5	88.0	79.1
70 to 74	31	31	62	45,651	43,350	89,001	67.9	71.5	69.7
75 to 79	23	25	48	39,019	32,936	71,955	58.9	75.9	66.7
80 to 84	12	13	25	31,450	21,386	52,836	38.2	60.8	47.3
85 and over	5	2	7	32,285	15,830	48,115	15.5	12.6	14.5
Missing				86	362	448	0.0	0.0	0.0
Total	926	930	1856	1,628,881	1,635,171	3,264,052	56.8	56.9	56.9

Table B.1: Ulcerative colitis prevalence by age, sex, and year (cont'd)

Age	# of UC patients			Population			Prevalence per 100,000 pop		
	F	M	Total	F	M	Total	F	M	Total
2004/05									
0 to 4	2	3	5	84,787	88,909	173,696	2.4	3.4	2.9
5 to 9	4	5	9	101,176	106,459	207,635	4.0	4.7	4.3
10 to 14	17	11	28	111,295	117,249	228,544	15.3	9.4	12.3
15 to 19	41	30	71	116,630	122,440	239,070	35.2	24.5	29.7
20 to 24	82	80	162	122,997	126,048	249,045	66.7	63.5	65.0
25 to 29	92	76	168	121,310	122,630	243,940	75.8	62.0	68.9
30 to 34	100	88	188	118,294	120,669	238,963	84.5	72.9	78.7
35 to 39	77	95	172	120,491	121,078	241,569	63.9	78.5	71.2
40 to 44	114	93	207	137,696	136,791	274,487	82.8	68.0	75.4
45 to 49	107	120	227	136,899	140,489	277,388	78.2	85.4	81.8
50 to 54	72	74	146	115,464	119,913	235,377	62.4	61.7	62.0
55 to 59	67	82	149	93,178	95,747	188,925	71.9	85.6	78.9
60 to 64	39	58	97	66,098	67,136	133,234	59.0	86.4	72.8
65 to 69	32	40	72	52,368	51,503	103,871	61.1	77.7	69.3
70 to 74	24	36	60	45,864	43,369	89,233	52.3	83.0	67.2
75 to 79	25	22	47	39,924	34,362	74,286	62.6	64.0	63.3
80 to 84	11	12	23	31,749	22,125	53,874	34.6	54.2	42.7
85 and over	6	6	12	34,163	16,815	50,978	17.6	35.7	23.5
Missing				61	297	358	0.0	0.0	0.0
Total	912	931	1843	1,650,444	1,654,029	3,304,473	55.3	56.3	55.8

Table B.1: Ulcerative colitis prevalence by age, sex, and year (cont'd)

Age	# of UC patients			Population			Prevalence per 100,000 pop		
	F	M	Total	F	M	Total	F	M	Total
	2005/06								
0 to 4	1	1	2	87,910	91,887	179,797	1.1	1.1	1.1
5 to 9	4	3	7	101,511	106,776	208,287	3.9	2.8	3.4
10 to 14	17	12	29	110,551	116,968	227,519	15.4	10.3	12.7
15 to 19	40	50	90	117,763	123,455	241,218	34.0	40.5	37.3
20 to 24	78	66	144	125,455	128,138	253,593	62.2	51.5	56.8
25 to 29	105	104	209	125,546	125,413	250,959	83.6	82.9	83.3
30 to 34	118	100	218	120,973	122,381	243,354	97.5	81.7	89.6
35 to 39	106	122	228	122,424	123,646	246,070	86.6	98.7	92.7
40 to 44	149	131	280	134,819	134,174	268,993	110.5	97.6	104.1
45 to 49	152	137	289	139,833	141,820	281,653	108.7	96.6	102.6
50 to 54	122	145	267	121,507	126,436	247,943	100.4	114.7	107.7
55 to 59	92	118	210	96,588	99,364	195,952	95.2	118.8	107.2
60 to 64	53	85	138	70,994	71,909	142,903	74.7	118.2	96.6
65 to 69	50	62	112	54,273	53,188	107,461	92.1	116.6	104.2
70 to 74	33	49	82	46,356	43,727	90,083	71.2	112.1	91.0
75 to 79	28	27	55	40,796	35,703	76,499	68.6	75.6	71.9
80 to 84	15	11	26	32,047	22,850	54,897	46.8	48.1	47.4
85 and over	5	3	8	36,023	18,005	54,028	13.9	16.7	14.8
Missing				46	251	297	0.0	0.0	0.0
Total	1168	1226	2394	1,685,415	1,686,091	3,371,506	69.3	72.7	71.0

Table B.1: Ulcerative colitis prevalence by age, sex, and year (cont'd)

Age	# of UC patients			Population			Prevalence per 100,000 pop		
	F	M	Total	F	M	Total	F	M	Total
	2006/07								
0 to 4	2	1	3	93,441	97,417	190,858	2.1	1.0	1.6
5 to 9	3	2	5	104,105	109,389	213,494	2.9	1.8	2.3
10 to 14	16	19	35	110,432	117,250	227,682	14.5	16.2	15.4
15 to 19	42	43	85	119,973	125,387	245,360	35.0	34.3	34.6
20 to 24	98	85	183	128,633	132,236	260,869	76.2	64.3	70.2
25 to 29	106	119	225	133,654	132,204	265,858	79.3	90.0	84.6
30 to 34	131	114	245	126,211	127,783	253,994	103.8	89.2	96.5
35 to 39	112	107	219	126,355	128,504	254,859	88.6	83.3	85.9
40 to 44	135	122	257	132,858	133,626	266,484	101.6	91.3	96.4
45 to 49	161	156	317	143,265	144,709	287,974	112.4	107.8	110.1
50 to 54	125	159	284	127,725	132,476	260,201	97.9	120.0	109.1
55 to 59	91	114	205	99,643	102,912	202,555	91.3	110.8	101.2
60 to 64	64	93	157	77,248	78,144	155,392	82.9	119.0	101.0
65 to 69	54	61	115	56,750	55,921	112,671	95.2	109.1	102.1
70 to 74	37	67	104	46,932	44,382	91,314	78.8	151.0	113.9
75 to 79	25	28	53	41,520	36,673	78,193	60.2	76.4	67.8
80 to 84	19	12	31	32,641	23,872	56,513	58.2	50.3	54.9
85 and over	5	6	11	38,188	19,193	57,381	13.1	31.3	19.2
Missing				32	193	225	0.0	0.0	0.0
Total	1226	1308	2534	1,739,606	1,742,271	3,481,877	70.5	75.1	72.8

Table B.1: Ulcerative colitis prevalence by age, sex, and year (cont'd)

Age	# of UC patients			Population			Prevalence per 100,000 pop		
	F	M	Total	F	M	Total	F	M	Total
	2007/08								
0 to 4	5	1	6	98,068	102,292	200,360	5.1	1.0	3.0
5 to 9	2	2	4	106,258	111,463	217,721	1.9	1.8	1.8
10 to 14	12	13	25	110,705	117,589	228,294	10.8	11.1	11.0
15 to 19	48	45	93	120,253	126,244	246,497	39.9	35.6	37.7
20 to 24	89	102	191	131,363	133,803	265,166	67.8	76.2	72.0
25 to 29	115	121	236	141,521	140,580	282,101	81.3	86.1	83.7
30 to 34	144	108	252	131,636	133,388	265,024	109.4	81.0	95.1
35 to 39	131	130	261	129,325	132,781	262,106	101.3	97.9	99.6
40 to 44	156	116	272	131,183	132,957	264,140	118.9	87.2	103.0
45 to 49	131	131	262	145,640	147,022	292,662	89.9	89.1	89.5
50 to 54	142	139	281	132,744	137,853	270,597	107.0	100.8	103.8
55 to 59	96	115	211	104,129	108,160	212,289	92.2	106.3	99.4
60 to 64	82	99	181	82,209	82,992	165,201	99.7	119.3	109.6
65 to 69	51	61	112	59,248	58,690	117,938	86.1	103.9	95.0
70 to 74	42	38	80	48,042	45,130	93,172	87.4	84.2	85.9
75 to 79	25	26	51	41,848	37,259	79,107	59.7	69.8	64.5
80 to 84	22	12	34	33,327	25,023	58,350	66.0	48.0	58.3
85 and over	3	3	6	39,699	20,127	59,826	7.6	14.9	10.0
Missing				29	167	196	0.0	0.0	0.0
Total	1296	1262	2558	1,787,227	1,793,520	3,580,747	72.5	70.4	71.4

Table B.1: Ulcerative colitis prevalence by age, sex, and year (cont'd)

Age	# of UC patients			Population			Prevalence per 100,000 pop		
	F	M	Total	F	M	Total	F	M	Total
2008/09									
0 to 4	1	3	4	102,476	107,395	209,871	1.0	2.8	1.9
5 to 9	1	3	4	108,420	113,498	221,918	0.9	2.6	1.8
10 to 14	12	17	29	110,978	117,430	228,408	10.8	14.5	12.7
15 to 19	50	46	96	119,962	126,531	246,493	41.7	36.4	38.9
20 to 24	96	105	201	134,519	135,334	269,853	71.4	77.6	74.5
25 to 29	126	129	255	148,950	147,004	295,954	84.6	87.8	86.2
30 to 34	123	123	246	138,135	139,483	277,618	89.0	88.2	88.6
35 to 39	135	126	261	131,970	137,154	269,124	102.3	91.9	97.0
40 to 44	159	131	290	130,674	133,798	264,472	121.7	97.9	109.7
45 to 49	169	148	317	146,938	148,242	295,180	115.0	99.8	107.4
50 to 54	147	162	309	136,792	142,078	278,870	107.5	114.0	110.8
55 to 59	98	132	230	109,604	114,156	223,760	89.4	115.6	102.8
60 to 64	84	95	179	86,843	88,201	175,044	96.7	107.7	102.3
65 to 69	60	77	137	62,061	61,375	123,436	96.7	125.5	111.0
70 to 74	44	47	91	48,961	46,327	95,288	89.9	101.5	95.5
75 to 79	22	42	64	42,280	37,907	80,187	52.0	110.8	79.8
80 to 84	19	18	37	34,197	26,235	60,432	55.6	68.6	61.2
85 and over	15	4	19	41,376	21,262	62,638	36.3	18.8	30.3
Missing				21	137	158	0.0	0.0	0.0
Total	1361	1408	2769	1,835,157	1,843,547	3,678,704	74.2	76.4	75.3

Table B.2: Ulcerative colitis incidence by age, sex, and year

Age	New cases of UC			Population at risk			Incidence per 100,000 pop.		
	F	M	Total	F	M	Total	F	M	Total
2003/04									
0 to 4	3	2	5	83,251	87,115	170,366	3.6	2.3	2.9
5 to 9	4	6	10	102,531	107,945	210,476	3.9	5.6	4.8
10 to 14	10	8	18	112,111	118,337	230,448	8.9	6.8	7.8
15 to 19	30	18	48	115,881	121,607	237,488	25.9	14.8	20.2
20 to 24	39	49	88	121,301	124,712	246,013	32.2	39.3	35.8
25 to 29	71	66	137	119,320	121,088	240,408	59.5	54.5	57.0
30 to 34	73	58	131	117,804	120,884	238,688	62.0	48.0	54.9
35 to 39	64	55	119	120,506	121,005	241,511	53.1	45.5	49.3
40 to 44	102	83	185	140,616	140,111	280,727	72.5	59.2	65.9
45 to 49	86	84	170	134,147	138,588	272,735	64.1	60.6	62.3
50 to 54	59	50	109	109,543	114,140	223,683	53.9	43.8	48.7
55 to 59	38	59	97	88,450	90,862	179,312	43.0	64.9	54.1
60 to 64	25	42	67	63,636	64,656	128,292	39.3	65.0	52.2
65 to 69	29	33	62	51,071	50,011	101,082	56.8	66.0	61.3
70 to 74	26	25	51	45,646	43,344	88,990	57.0	57.7	57.3
75 to 79	16	19	35	39,012	32,930	71,942	41.0	57.7	48.7
80 to 84	12	12	24	31,450	21,385	52,835	38.2	56.1	45.4
85 and over	4	2	6	32,284	15,830	48,114	12.4	12.6	12.5
Missing				86	362	448	0.0	0.0	0.0
Total	691	671	1362	1,628,646	1,634,912	3,263,558	42.4	41.0	41.7

Table B.2: Ulcerative colitis incidence by age, sex, and year (cont'd)

Age	New cases of UC			Population at risk			Incidence per 100,000 pop.		
	F	M	Total	F	M	Total	F	M	Total
2004/05									
0 to 4	2	3	5	84,787	88,909	173,696	2.4	3.4	2.9
5 to 9	1	3	4	101,173	106,457	207,630	1.0	2.8	1.9
10 to 14	12	8	20	111,290	117,246	228,536	10.8	6.8	8.8
15 to 19	29	20	49	116,618	122,430	239,048	24.9	16.3	20.5
20 to 24	54	60	114	122,969	126,028	248,997	43.9	47.6	45.8
25 to 29	58	46	104	121,276	122,600	243,876	47.8	37.5	42.6
30 to 34	63	56	119	118,257	120,637	238,894	53.3	46.4	49.8
35 to 39	49	59	108	120,463	121,042	241,505	40.7	48.7	44.7
40 to 44	70	64	134	137,652	136,762	274,414	50.9	46.8	48.8
45 to 49	67	76	143	136,859	140,445	277,304	49.0	54.1	51.6
50 to 54	40	35	75	115,432	119,874	235,306	34.7	29.2	31.9
55 to 59	43	42	85	93,154	95,707	188,861	46.2	43.9	45.0
60 to 64	23	32	55	66,082	67,110	133,192	34.8	47.7	41.3
65 to 69	18	23	41	52,354	51,486	103,840	34.4	44.7	39.5
70 to 74	14	24	38	45,854	43,357	89,211	30.5	55.4	42.6
75 to 79	18	16	34	39,917	34,356	74,273	45.1	46.6	45.8
80 to 84	6	7	13	31,744	22,120	53,864	18.9	31.6	24.1
85 and over	6	4	10	34,163	16,813	50,976	17.6	23.8	19.6
Missing				61	297	358	0.0	0.0	0.0
Total	573	578	1151	1,650,105	1,653,676	3,303,781	34.7	35.0	34.8

Table B.2: Ulcerative colitis incidence by age, sex, and year (cont'd)

Age	New cases of UC			Population at risk			Incidence per 100,000 pop.		
	F	M	Total	F	M	Total	F	M	Total
	2005/06								
0 to 4	0	1	1	87,909	91,887	179,796	0.0	1.1	0.6
5 to 9	1	2	3	101,508	106,775	208,283	1.0	1.9	1.4
10 to 14	9	8	17	110,543	116,964	227,507	8.1	6.8	7.5
15 to 19	25	36	61	117,748	123,441	241,189	21.2	29.2	25.3
20 to 24	57	49	106	125,434	128,121	253,555	45.4	38.2	41.8
25 to 29	62	74	136	125,503	125,383	250,886	49.4	59.0	54.2
30 to 34	66	67	133	120,921	122,348	243,269	54.6	54.8	54.7
35 to 39	64	81	145	122,382	123,605	245,987	52.3	65.5	58.9
40 to 44	90	73	163	134,760	134,116	268,876	66.8	54.4	60.6
45 to 49	97	75	172	139,778	141,758	281,536	69.4	52.9	61.1
50 to 54	77	83	160	121,462	126,374	247,836	63.4	65.7	64.6
55 to 59	50	71	121	96,546	99,317	195,863	51.8	71.5	61.8
60 to 64	33	47	80	70,974	71,871	142,845	46.5	65.4	56.0
65 to 69	31	30	61	54,254	53,156	107,410	57.1	56.4	56.8
70 to 74	22	28	50	46,345	43,706	90,051	47.5	64.1	55.5
75 to 79	18	16	34	40,786	35,692	76,478	44.1	44.8	44.5
80 to 84	13	4	17	32,045	22,843	54,888	40.6	17.5	31.0
85 and over	4	2	6	36,022	18,004	54,026	11.1	11.1	11.1
Missing				46	251	297	0.0	0.0	0.0
Total	719	747	1466	1,684,966	1,685,612	3,370,578	42.7	44.3	43.5

Table B.2: Ulcerative colitis incidence by age, sex, and year (cont'd)

Age	New cases of UC			Population at risk			Incidence per 100,000 pop.		
	F	M	Total	F	M	Total	F	M	Total
2006/07									
0 to 4	2	1	3	93,441	97,417	190,858	2.1	1.0	1.6
5 to 9	2	1	3	104,104	109,388	213,492	1.9	0.9	1.4
10 to 14	9	13	22	110,425	117,244	227,669	8.2	11.1	9.7
15 to 19	22	26	48	119,953	125,370	245,323	18.3	20.7	19.6
20 to 24	58	55	113	128,593	132,206	260,799	45.1	41.6	43.3
25 to 29	64	70	134	133,612	132,155	265,767	47.9	53.0	50.4
30 to 34	60	61	121	126,140	127,730	253,870	47.6	47.8	47.7
35 to 39	59	58	117	126,302	128,455	254,757	46.7	45.2	45.9
40 to 44	75	70	145	132,798	133,574	266,372	56.5	52.4	54.4
45 to 49	92	94	186	143,196	144,647	287,843	64.2	65.0	64.6
50 to 54	69	87	156	127,669	132,404	260,073	54.0	65.7	60.0
55 to 59	43	52	95	99,595	102,850	202,445	43.2	50.6	46.9
60 to 64	39	53	92	77,223	78,104	155,327	50.5	67.9	59.2
65 to 69	26	31	57	56,722	55,891	112,613	45.8	55.5	50.6
70 to 74	23	38	61	46,918	44,353	91,271	49.0	85.7	66.8
75 to 79	13	17	30	41,508	36,662	78,170	31.3	46.4	38.4
80 to 84	12	7	19	32,634	23,867	56,501	36.8	29.3	33.6
85 and over	5	4	9	38,188	19,191	57,379	13.1	20.8	15.7
Missing				32	193	225	0.0	0.0	0.0
Total	673	738	1411	1,739,053	1,741,701	3,480,754	38.7	42.4	40.5

Table B.2: Ulcerative colitis incidence by age, sex, and year (cont'd)

Age	New cases of UC			Population at risk			Incidence per 100,000 pop.		
	F	M	Total	F	M	Total	F	M	Total
2007/08									
0 to 4	4	1	5	98,067	102,292	200,359	4.1	1.0	2.5
5 to 9	2	2	4	106,258	111,463	217,721	1.9	1.8	1.8
10 to 14	8	6	14	110,701	117,582	228,283	7.2	5.1	6.1
15 to 19	26	26	52	120,231	126,225	246,456	21.6	20.6	21.1
20 to 24	51	66	117	131,325	133,767	265,092	38.8	49.3	44.1
25 to 29	60	65	125	141,466	140,524	281,990	42.4	46.3	44.3
30 to 34	64	60	124	131,556	133,340	264,896	48.6	45.0	46.8
35 to 39	68	67	135	129,262	132,718	261,980	52.6	50.5	51.5
40 to 44	82	63	145	131,109	132,904	264,013	62.5	47.4	54.9
45 to 49	65	62	127	145,574	146,953	292,527	44.7	42.2	43.4
50 to 54	65	66	131	132,667	137,780	270,447	49.0	47.9	48.4
55 to 59	46	59	105	104,079	108,104	212,183	44.2	54.6	49.5
60 to 64	45	47	92	82,172	82,940	165,112	54.8	56.7	55.7
65 to 69	28	24	52	59,225	58,653	117,878	47.3	40.9	44.1
70 to 74	28	14	42	48,028	45,106	93,134	58.3	31.0	45.1
75 to 79	14	13	27	41,837	37,246	79,083	33.5	34.9	34.1
80 to 84	12	5	17	33,317	25,016	58,333	36.0	20.0	29.1
85 and over	3	2	5	39,699	20,126	59,825	7.6	9.9	8.4
Missing				29	167	196	0.0	0.0	0.0
Total	671	648	1319	1,786,602	1,792,906	3,579,508	37.6	36.1	36.8

Table B.2: Ulcerative colitis incidence by age, sex, and year (cont'd)

Age	New cases of UC			Population at risk			Incidence per 100,000 pop.		
	F	M	Total	F	M	Total	F	M	Total
2008/09									
0 to 4	0	3	3	102,475	107,395	209,870	0.0	2.8	1.4
5 to 9	1	3	4	108,420	113,498	221,918	0.9	2.6	1.8
10 to 14	9	12	21	110,975	117,425	228,400	8.1	10.2	9.2
15 to 19	34	26	60	119,946	126,511	246,457	28.3	20.6	24.3
20 to 24	53	57	110	134,476	135,286	269,762	39.4	42.1	40.8
25 to 29	70	73	143	148,894	146,948	295,842	47.0	49.7	48.3
30 to 34	56	68	124	138,068	139,428	277,496	40.6	48.8	44.7
35 to 39	60	66	126	131,895	137,094	268,989	45.5	48.1	46.8
40 to 44	69	65	134	130,584	133,732	264,316	52.8	48.6	50.7
45 to 49	83	70	153	146,852	148,164	295,016	56.5	47.2	51.9
50 to 54	66	67	133	136,711	141,983	278,694	48.3	47.2	47.7
55 to 59	40	48	88	109,546	114,072	223,618	36.5	42.1	39.4
60 to 64	35	31	66	86,794	88,137	174,931	40.3	35.2	37.7
65 to 69	28	36	64	62,029	61,334	123,363	45.1	58.7	51.9
70 to 74	19	15	34	48,936	46,295	95,231	38.8	32.4	35.7
75 to 79	12	18	30	42,270	37,883	80,153	28.4	47.5	37.4
80 to 84	8	11	19	34,186	26,228	60,414	23.4	41.9	31.4
85 and over	9	4	13	41,370	21,262	62,632	21.8	18.8	20.8
Missing				21	137	158	0.0	0.0	0.0
Total	652	673	1325	1,834,448	1,842,812	3,677,260	35.5	36.5	36.0

APPENDIX C: EXCLUDED STUDIES

Table C.1: Excluded studies and reason for exclusion

Excluded study	Reason for exclusion
Hellemans et al. Fecal transplantation for recurrent <i>Clostridium difficile</i> colitis, an underused treatment modality. <i>Acta Gastro-Enterologica Belgica</i> 2009;72(2):269-70	Case report (letter)
Khoruts et al. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent <i>Clostridium difficile</i> -associated diarrhea. <i>Journal of Clinical Gastroenterology</i> 2010;44(5):354-60	Case report
Persky et al. Treatment of recurrent <i>Clostridium difficile</i> -associated diarrhea by administration of donated stool directly through a colonoscope. <i>American Journal of Gastroenterology</i> 2000;95(11):3283-85	Case report
Rubin et al. Stool transplantation for older patients with <i>Clostridium difficile</i> infection. <i>JAGS</i> 2009;57(12):2386-87	Letter
Wang et al. Ulcerative colitis complicating pseudomembranous colitis of the right colon. <i>Journal of Gastroenterology</i> 2005;37(4):309-12	Case report
You and Franzos. Successful treatment of fulminant <i>Clostridium difficile</i> infection with fecal bacteriotherapy. <i>Annals of Internal Medicine</i> 2008;148(8):632-33	Case report

APPENDIX D: EVIDENCE TABLES

Abbreviations for Appendix D

CD – *Clostridium difficile*

CDAD – *Clostridium difficile*-associated disease

ER – emergency room

F – female

FBC – full blood count

FT – fecal transplantation

g – gram

h – hour

HAV – hepatitis A virus

HBV – hepatitis B virus

HCV – hepatitis C virus

HIV – human immunodeficiency virus

HTLV – Human T cell lymphotropic virus

IBD – inflammatory bowel disease

LFT – liver function test

M – male

mg – milligram

mL – millilitre

NA – not available

PBS – phosphate buffered saline

PCR – polymerase chain reaction

QoL – quality of life

SEM – standard error of the mean

UC – ulcerative colitis

wk – week

yr – year

Table D.1: Safety and effectiveness of fecal transplantation for the treatment of CDAD

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Aas et al. 2003³⁶ United States Study design: single centre, retrospective case series study (1994-2002) Objective: to report the results obtained in a study of patients with relapsing CDAD treated with nasogastrically administered stool in a single institution during a 9-year period</p>	<p>Total number: 18 Consecutive cases: yes Age (mean ± SEM, yr): 73 ± 9 (range 51 to 88) Gender (M/F): 5/13 Condition: recurrent CDAD Case definition: lab confirmed diagnosis of CDAD (≥ 2 stool test results positive for CD toxin) and ≥ 2 lab-confirmed relapses of CDAD after receipt of initial specific antimicrobial treatment Clinical setting: 5 in hospital, 13 outpatient gastroenterology clinic</p>	<p>Donor: family members (15), healthy clinic staff volunteer (3) Donor screening: Blood tests: HAV, HBV, HCV, HIV-I, HIV-II, syphilis Stool tests: stool culture for enteric bacterial pathogens; microscopy for presence of ova and parasites Fecal suspension preparation: 30 g fresh donor stool blended in 50-70 mL saline and filtered Method of administration: nasogastric tube Volume/frequency: 25 mL fecal suspension, once Length of follow-up: 90 days Treatments prior to FT: Antibiotics for C. difficile: oral vancomycin (250 mg, q8h) starting 4 days before FT until the evening before FT, which reduced or eliminated diarrhea in most cases Other: proton pump inhibitor omeprazole 20 mg, once in the evening before and the morning of FT</p>	<p>Adverse events: Two deaths: one died after the development of peritonitis (the possibility that use of the nasogastric tube contributed to the peritonitis could not be excluded), and the other died as a result of pneumonia Effectiveness: Diarrhea: of 16 surviving patients, 15 (94%) were diarrhea free during 90-day follow-up; the other one relapsed 17 days post-FT and received an additional 10-day oral vancomycin. This patient was diarrhea free with negative results for CD toxin test at 6 months. Testing for C. difficile post-FT: negative in 15/18 patients Colonoscopy and histology: NA QoL: NA Patient acceptance: patients were uniformly receptive to the prospect of stool transplantation; none raised objections to the proposed fecal transplantation procedure on the basis that it lacked aesthetic appeal</p>	<p>Fecal transplantation has the potential of providing patients and clinicians with an effective, low-risk, and inexpensive alternative to conventional antimicrobial treatment regimens. Additional studies will be needed before the results can be generalized for broader clinical use.</p>

Table D.1: Safety and effectiveness of fecal transplantation for the treatment of CDAD (cont'd)

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Macconnachie et al. 2009³⁸ United Kingdom Study design: single centre, retrospective case series study (2003-2008) Objective: to present clinical experience with severe recurrent CDAD in the Glasgow Infection Unit</p>	<p>Total number: 15 Consecutive cases: NA Age (yr): median 81.5 (range 68 to 95) Gender (M/F): 1/14 Condition: severe, recurrent CDAD; median 4 (3 to 7) episodes Case definition: recurrence of loose stool following successful antibiotic treatment in a patient recently treated for toxin positive CDAD Clinical setting: 11 inpatients, four readmitted following recent discharge</p>	<p>Donor: healthy related volunteers Donor screening: blood-borne viruses, syphilis, enteropathogens Fecal suspension preparation: 30 g fresh donor stool blended in 150 mL saline and filtered Method of administration: nasogastric tube Volume/frequency: 30 mL fecal suspension, once Length of follow-up: median 16 wks (range 4 to 24 wks) Treatments prior to FT: Antibiotics for C. difficile: oral vancomycin (125 mg, 4 times daily), 4 to 51 days; discontinued 12 hours before FT Other: proton pump inhibitor omeprazole 20 mg to produce a favourable gastric pH</p>	<p>Adverse events: No adverse events were noted in any patient; one patient had upper gastrointestinal hemorrhage, perhaps caused by aspirin and nonsteroid anti-inflammatory drugs rather than the fecal transplantation procedure itself. Effectiveness: Diarrhea: resolved in 11/15 patients (73%). Of the remaining 4 patients, 2 did not respond to FT, they received an additional 10-day oral metronidazole and were diarrhea free at 8 and 24 months' follow-up, respectively. A third patient relapses 29 days after FT, having received broad-spectrum antibiotics. The fourth relapsed after the first FT because of inadequate initial donor stool volume and was diarrhea free 12 wks after receiving a second FT. Testing for C. difficile post-FT: conducted for some patients but results not presented Colonoscopy and histology: NA QoL: NA Patient acceptance: fecal transplantation via nasogastric tube was well tolerated. There was a high level of patient acceptance with one highly satisfied patient feeling compelled to publicize the treatment in the national press.</p>	<p>Fecal transplantation is a safe and effective treatment for recurrent CDAD. Fecal transplantation via a nasogastric tube could be considered in patients with refractory relapsing CDAD. An appropriately controlled clinical study would better delineate its role in the management of this difficult and debilitating condition.</p>

Table D.1: Safety and effectiveness of fecal transplantation for the treatment of CDAD (cont'd)

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Nieuwdorp et al. 2008⁵⁴ (English abstract of an article in Dutch) Netherlands Study design: single centre case series study Objective: to study the effect of treating recurrent CDAD with a suspension of donor feces</p>	<p>Total number: 7 Consecutive cases: NA Age (yr): NA Gender (M/F): NA Condition: recurrent CDAD, two with hypervirulent CD-strain PCR ribotype 027, toxinotype III Case definition: ≥ 2 recurrences of CDAD, including ≥ 1 recurrence treated with a vancomycin tapering regimen Clinical setting: NA</p>	<p>Donor: relatives or volunteers Donor screening: Blood tests: HIV, HBV, HCV, acute infection with cytomegalovirus or Epstein-Barr virus Stool tests: <i>C. difficile</i>, <i>yersinia</i>, campylobacter, shigella, salmonella, and parasites Fecal suspension preparation: 150 g donor feces dissolved in 300-400 mL saline Method of administration: duodenal catheter or colonoscopy Volume/frequency: 300-400 mL fecal suspension infused, once; repeated in 2 patients Length of follow-up: NA Treatments prior to FT: Antibiotics for C. difficile: 4-day vancomycin 500 mg, 4 times daily; followed by colon lavage Other: NA</p>	<p>Adverse events: NA Effectiveness: Diarrhea: defecation frequency returned to normal immediately in 5/7 patients; the other two responded after a repeated infusion from a different donor Testing for C. difficile post-FT: negative in five patients who responded immediately to FT Colonoscopy and histology: NA QoL: NA Patient acceptance: NA</p>	<p>Treatment with donor feces seems promising for patients who develop repeated recurrence despite adequate therapy and could be valuable in the future during (local) epidemics of the PCR ribotype 027 strain.</p>

Table D.1: Safety and effectiveness of fecal transplantation for the treatment of CDAD (cont'd)

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Louie et al. 2008⁵⁸ (Abstract) Calgary, Canada Study design: single centre case series study (over 11 years) Objective: to describe a method and results of home-based fecal flora infusion in patients with recurrent CD infection</p>	<p>Total number: 45 Consecutive cases: NA Age (yr): mean 62 (range 30 to 91) Gender (M/F): 12/33 Condition: recurrent CDAD for 6 to 24 months Case definition: ≥ 6 months of relapsing CDAD with ≥ 4 relapses with documented EIA positive fecal samples Clinical setting: 44 ambulatory patients (home-based)</p>	<p>Donor: healthy donors, 35/45 related to patients Donor screening: HIV, HCV, HTLV 1 and 2, syphilis, and enteric pathogens Fecal suspension preparation: 300-500 g donor stool obtained over 2-3 days before FT, diluted and dispersed in 1200 mL of pre-reduced PBS Method of administration: rectal catheter with continence balloon Volume/frequency: 1000-1500 mL fecal suspension infused over 20 to 45 minutes; 28 patients received 1 infusion, 16 received 2 infusions, 1 received 3 infusions Length of follow-up: up to 1 year Treatments prior to FT: Antibiotics for C. difficile: oral vancomycin 14 days followed by 3- to 4-day washout period Other: NA</p>	<p>Adverse events: 4 patients experienced irritable bowel symptoms for several months Effectiveness Diarrhea: resolved in 43/45 patients (96%) Testing for C. difficile post-FT: NA Colonoscopy and histology: NA QoL: NA Patient acceptance: NA</p>	<p>Home-based, high-volume, single-dose fecal flora infusion appears to be highly effective and well tolerated in arresting recurrent CD infection.</p>
<p>Faust et al. 2002⁵⁵ (Abstract) Quebec, Canada Study design: single centre, case series study (1992-2001) Objective: to report results of the use of FT in six patients with recurrent pseudomembranous colitis</p>	<p>Total number: 6 Consecutive cases: NA Age (yr): mean 53 (range 34 to 74) Gender (M/F): 1/5 Condition: recurrent pseudomembranous colitis, total 27 episodes: mean 3.5 (range 2 to 6) episodes per patient Case definition: colonoscopy and/or positive cytotoxin assays Clinical setting: NA</p>	<p>Donor: spouse (4), brother (1), son (1) Donor screening: bacterial pathogens on cultures, ova, parasites and <i>C. difficile</i> toxin Fecal suspension preparation: NA Method of administration: NA Volume/frequency: NA Length of follow-up: 9 to 50 months Treatments prior to FT: Antibiotics for C. difficile: metronidazole (11 episodes) or vancomycin (16 episodes) Other: NA</p>	<p>Adverse events: NA Effectiveness: Diarrhea: improved in all patients Testing for C. difficile post-FT: negative in 4 of the 6 patients 1.5 to 13 months post-FT Colonoscopy and histology: NA QoL: NA Patient acceptance: NA</p>	<p>Although seemingly crude or repulsive, fecal transplantation is a logical, simple, and inexpensive therapeutic modality in recurrent pseudomembranous colitis. It has proven to be universally effective in the authors' modest experience.</p>

Table D.1: Safety and effectiveness of fecal transplantation for the treatment of CDAD (cont'd)

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Borody et al. 2003⁵⁶ (Abstract) Australia Study design: single centre case series study Objective: to review a single centre's experience in FT for CD infection, addressing safety, efficacy, and methodology</p>	<p>Total number: 24 Consecutive cases: NA Age (yr): range 19 to 59 Gender (M/F): 11/13 Condition: patients with chronic CDAD who had failed previous CD therapies Case definition: symptoms including fatigue, diarrhea, bloating, flatulence, nausea, vomiting, reflux, abdominal pain, and cramping with positive <i>C. difficile</i> Clinical setting: NA</p>	<p>Donor: related or unrelated healthy individuals Donor screening: Blood tests: transmissible blood diseases and disorders Stool tests: pathogenic bacteria, parasites, cysts and ova Fecal suspension preparation: 200 to 300 g donor stool suspended in 200-300 mL saline Method of administration: colonoscopy and/or retention enema and/or nasojejunal tube; combination of colonoscopy and retention enema used most common (46%) Volume/frequency: fecal suspension delivered daily for 1 day (3/24, 13%), 5 days (11/24, 46%), or 10 days (10/24, 42%) Length of follow-up: 4 to 69 wks Treatments prior to FT: Antibiotics for <i>C. difficile</i>: rifampicin (150 mg, bid), vancomycin (500 mg, bid) or metronidazole (400 mg, bid) for 5 days, and lavage 1 day before FT Other: NA</p>	<p>Adverse events: sore throat (38%), flatulence (29%), rectal discomfort (17%), nausea (13%), abdominal cramping (8%), bloating (13%), headache (13%), and abdominal pain (13%) Effectiveness: Diarrhea: resolved in 6/13 patients (46%) Testing for <i>C. difficile</i> post-FT: negative CD toxin and culture results in 20/24 patients (83%) post-FT Colonoscopy and histology: NA QoL: NA Patient acceptance: NA</p>	<p>The use of FT provides an efficacious method for eradication of <i>C. difficile</i>. Adverse effects of FT are minor and transient, and complications are minimal.</p>

Table D.1: Safety and effectiveness of fecal transplantation for the treatment of CDAD (cont'd)

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Wettstein et al. 2007⁵⁹ (Abstract) Australia Study design: Single centre, retrospective case series study Objective: to report on the efficacy of FT in the treatment and eradication of <i>C. difficile</i> infection</p>	<p>Total number: 16 Consecutive cases: NA Age (yr): ranged from 11 to 87 Gender (M/F): 5/11 Condition: long-standing symptoms of CD infection in patients who failed standard anti-CD antibiotics Case definition: positive stool culture or positive <i>C. difficile</i> toxin A or B Clinical setting: NA</p>	<p>Donor: related or unrelated healthy individuals Donor screening: infectious diseases in blood and feces Fecal suspension preparation: 200 to 300 g feces blended in 200-300 mL saline Method of administration: colonoscopy and retention enema Volume/frequency: 200 to 300 mL fecal suspension delivered to the terminal ileum via colonoscopy on day 1; subsequent infusions administered via retention enema for 5 days (5/16, 31%), 10 days (10/16, 63%), or up to 24 days (1/16, 6%) Length of follow-up: 4 to 6 weeks Treatments prior to FT: Antibiotics for C. difficile: rifampicin (150 mg), vancomycin (500 mg), or metronidazole (400 mg), bid, for 10 days and lavage one day before FT Other: NA</p>	<p>Adverse events: NA Effectiveness: Diarrhea: complete resolution in 8/16 (50%), improved in 7/8 remaining patients Testing for C. difficile post-FT: negative CD toxin A or B and culture in 15/16 patients (94%) 4 to 6 wks post-FT Colonoscopy and histology: NA QoL: NA Patient acceptance: NA</p>	<p>Fecal transplantation cured CDAD in 94% of patients treated. Some symptoms can persist unrelated to CDAD cure. Fecal transplantation is a successful biological therapy for ongoing symptomatic CDAD for patients who have failed available antibiotic therapy.</p>

Table D.1: Safety and effectiveness of fecal transplantation for the treatment of CDAD (cont'd)

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Yoon and Brandt 2008⁶⁰ (Abstract)</p> <p>United States</p> <p>Study design: Single centre, retrospective case series study</p> <p>Objective: to describe six patients with recurrent CDAD treated with FT via colonoscopy</p>	<p>Total number: 6</p> <p>Consecutive cases: yes</p> <p>Age (yr): mean 59 (range 30 to 80)</p> <p>Gender (M/F): 1/5</p> <p>Condition: refractory CDAD</p> <p>Case definition: clinical symptoms and a history of positive fecal CD toxin assay</p> <p>Clinical setting: NA</p>	<p>Donor: NA</p> <p>Donor screening: NA</p> <p>Fecal suspension preparation: NA</p> <p>Method of administration: colonoscopy</p> <p>Volume/frequency: NA</p> <p>Length of follow-up: NA</p> <p>Treatments prior to FT: <i>Antibiotics for C. difficile:</i> NA</p> <p><i>Other:</i> NA</p>	<p>Adverse events: none</p> <p>Effectiveness:</p> <p><i>Diarrhea:</i> immediately and durable response to FT in all six patients (100%)</p> <p><i>Testing for C. difficile post-FT:</i> NA</p> <p><i>Colonoscopy and histology:</i> NA</p> <p><i>QoL:</i> NA</p> <p><i>Patient acceptance:</i> NA</p>	<p>Fecal transplantation via colonoscopy is a safe and effective treatment for refractory/recurrent <i>C. difficile</i>-associated diarrhea.</p>

Table D.2: Safety and effectiveness of fecal transplantation for the treatment of ulcerative colitis

Study	Patient	Intervention	Outcome	Authors' conclusion
<p>Borody et al. 2003⁴⁵ Australia Study design: single centre, retrospective case series Objective: to observe the clinical, colonoscopic, and histologic effects of FT in six selected patients with UC</p>	<p>Total number: 6 Age (yr): mean 36 (range 25 to 53) Gender (M/F): 3/3 Consecutive cases: NA Condition: long-standing (\geq 5 years) idiopathic UC <i>C. difficile</i> test negative in all patients Treatment for UC: moderate to high dose of steroids and anti-inflammatory medications; all patients failed maximum tolerated standard therapies or suffered partially controlled disease that readily relapsed on withdrawal of medication Case definition: UC confirmed by colonoscopy and histology Clinical setting: NA</p>	<p>Donor: healthy unrelated (1) or related (5: 1 partner, 3 brothers, 1 brother-in-law) individuals Donor screening: Blood tests: FBC, LFTs, HAV, HBV, HCV, cytomegalovirus, or Epstein-Barr virus Stool tests: common pathogens; presence of protozoa (trophozoites and cysts), helminths and ova, trematodes, and tapeworms under microscopy Fecal suspension preparation: 200-300 g stool diluted in 200-300 mL saline Method of administration: retention enema Volume/frequency: 200-300 mL fecal suspension administered via retention enema within 10 min of preparation. Patients were encouraged to retain the enema for as long as possible (at least 6 to 8 hrs). Once daily for 5 consecutive days. Length of follow-up: mean 5 (range 1-13) yrs Treatments prior to FT: Antibiotics for <i>C. difficile</i> prior to FT: vancomycin 500 mg, bid, metronidazole 400 mg, bid, and rifampicin 150 mg, bid, for 7-10 days</p>	<p>Adverse events: NA Effectiveness: Diarrhea: improved in some patients within 1 week post-FT; complete reversal of symptoms in all patients by 4 months post-FT Colonoscopy and histology: at 1 to 13 years post-FT and without any medications for UC, no colonoscopic or histologic evidence of UC was found in any patient QoL: NA Patient perception/acceptance: NA Prevention of more aggressive therapy: all medications for UC were discontinued in all patients by 4 months post-FT Reduction in ER visits: NA</p>	<p>Colonic infusion of donor human intestinal flora can reverse UC in selected patients. These anecdotal results support the concept of abnormal bowel flora or even a specific but unidentified bacterial pathogen causing UC.</p>

Table D.3: Safety and effectiveness of fecal transplantation for the treatment of ulcerative colitis complicated by CDAD

Study	Patient	Intervention	Outcome	Authors' conclusion
Borody et al. 2008 ⁵⁷ (Abstract) Australia Study design: single centre, retrospective case series Objective: to review the degree of symptomatic improvement in patients with UC and Crohn's disease whose <i>C. difficile</i> infection was treated by FT	Total number: 6 Age (yr): ranged from 11 to 59 Gender (M/F): 4/2 Consecutive cases: NA Condition: refractory UC + CDAD (4 patients); Crohn's disease + CDAD (2 patients) Case definition: confirmed by stool culture and toxin assay Clinical setting: NA	Donor: NA Donor screening: NA Fecal suspension preparation: NA Method of administration: repeated retention enemas Volume/frequency: NA Length of follow-up: 8 wks Treatments prior to FT: Antibiotics for <i>C. difficile</i>: NA Other: NA	Adverse events: NA Effectiveness: Diarrhea: improved in all patients with UC and CDAD Testing for <i>C. difficile</i> post-FT: negative in all patients with UC and CDAD at 8 wks Colonoscopy and histology: NA QoL: NA Patient acceptance: NA	Fecal transplantation consistently eradicated <i>C. difficile</i> co-infection in refractory UC even when appropriate antibiotics fail. There was marked symptom improvement following <i>C. difficile</i> eradication. Patients with UC respond to anti-UC treatment following <i>C. difficile</i> eradication.

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Bing Guo contributed to study conception and design, data analysis and interpretation, manuscript preparation, and approved the final version for publication.

Christa Harstall contributed to study conception and design, revision of manuscript for critical content, and approved the final version for publication.

Thanh Nguyen contributed to study conception and design, statistical analysis, economic expert review of the literature, revision of manuscript for critical content, and approved the final version for publication.

Arto Ohinmaa contributed to study conception and design, statistical analysis, economic expert review of the literature, manuscript preparation, and approved the final version for publication.

This report examines the clinical research evidence on the safety and effects of fecal transplantation in the treatment of patients with *Clostridium Difficile* –associated disease and ulcerative colitis. This report also provides information on the prevalence and incidence of the two diseases and the availability of fecal transplantation procedure in Alberta and Canada.



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