Faecal Microbial Transplantation in Critically Ill Patients – Structured Review and Perspectives

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Abstract

The human gut microbiota consists of bacteria, archaea, fungi, and viruses. It is a dynamic ecosystem shaped by several factors, which play an essential role in both healthy and diseased states of humans. A disturbance of the gut microbiota, also termed "dysbiosis," is associated with increased host susceptibility to a range of diseases. Because of splanchnic ischaemia, exposure to antibiotics, and/or underlying the disease critically ill patients loose 90% of the commensal organisms in their gut within hours after the insult. This is followed by a rapid overgrowth of potentially pathogenic and pro-inflammatory bacteria altering metabolic, immune, and even neurocognitive functions and turning the gut into the driver of systemic inflammation and multiorgan failure. Indeed, restoring healthy microbiota by means of faecal microbiota transplantation (FMT) in the critically ill is an attractive and plausible concept in intensive care. Yet, available data from controlled studies are limited to probiotics and FMT for severe C. difficile infection or severe inflammatory bowel disease. Case series and observational trials generate hypothesis that FMT might be feasible and safe in immunocompromised patients, refractory sepsis, or severe antibiotic-associated diarrhea in ICU. There is a burning need to test these hypotheses in randomized controlled trials powered for determination of patient-centered outcomes.

Key words: gut microbiota; critically ill; faecal microbial transplantation; multiorgan failure

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Introduction – Defining human gut microbiome

The term microbiota refers to a community of microorganisms (comprising of bacteria, archaea, fungi, protozoa, and viruses) that inhabit a particular environment. Growing attention is attributed to the microbial communities associated with various niches in human body. Their genomes (genes and plasmids) are referred to as microbiome. It is estimated that the microbiota of a healthy human consists of between 500 and 2000 species [1] (Rastelli et al., 2018). The density of microorganisms is highest in the colon and gross majority of bacteria are strict anaerobes [1]. Gut microbiota are indispensable for a range of aspects of the healthy human physiology. Most notably, microbiota influence gastrointestinal motility, regulate mucosal barrier function and epithelial cell turnover, influence immune responses, and suppress pathogen overgrowth. Indeed, they also play important role in the host metabolism, converting dietary fiber to short chain fatty acids (SCFA), which serve as energy substrate for colonocytes. Butyrate producers are also protective against mucosal inflammation and infection [2].

Intestinal microbiota diversity and relation to immunity and inflammation

Gut microbiota is a dynamic ecosystem shaped throughout human lifespan, from prenatal conditions (mothers health and fetus genetic factors), mode of birth (Caesarean section versus vaginal delivery), diet, BMI, weight, environment, antibiotic exposure, to hospitalizations during later life. Gut microbiota of the adults is dominated by taxa belonging to two phyla Bacteroidetes and Firmicutes, with their relative proportions differing among populations. The interindividual variability in microbial composition is remarkable, but most individuals can be categorized into three different enterotypes, probably linked to long-term dietary habits (Wen & Duffy, 2017). One of the most important functional characteristics of human microbiota is its diversity, i.e. species richness. Dysbiosis, a state with low bacterial diversity, in which the homeostasis of the gut microbiome is disrupted, has been associated with a range of diseases [1,3].

Commensal bacteria, and bacteria in the gut in particular, are essential for the development and maturation of the human immune system. Germ-free mice have significantly reduced lymph nodes in gut-associated lymphoid tissues [4]. Microbiota composition can affect immune cells in the gut via microbial components (LPS) or products of microbial metabolism (i.e. SCFA) [4]. Bacteroidetes and other Gram-negative bacteria contain lipopolysaccharides (LPS) in their cell wall, strong immune response activators [2]. Worsening of intestinal barrier function leads to leakage of gut bacteria components or even whole bacteria into the circulation. On the contrary, SCFA reduce pro-inflammatory cytokines production in monocytes and T-cells, and strengthen the tight junctions of gut epithelia cells and butyrate-producing bacteria have beneficial immunometabolic effects [2]. These mechanisms may also explain the link between dysbiosis and autoimmune diseases [5,6].

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Intestinal barrier function

Mucosal barrier is not only essential for the digestion and absorption of nutrients, but it also prevents the entry of diverse exterior antigens (food antigens, commensal bacteria, pathogens, and toxins). In the intestine, the front line of this barrier is only a single layer of specialized epithelial cells that are linked together by tight junctions. Any alteration of gut mucosal barrier increases the translocation of proinflammatory stimuli into the lamina propria, triggering inflammatory cytokine-mediated changes. The "leaky gut" promotes both local and systemic immune responses. The gut barrier disruption creates the way for intestinal microbes to penetrate into the submucosa (Mu et al., 2017). Non-occlusive intestinal ischemia during shock states, resulting in intestinal barrier disruption and bacterial translocation has been associated with immune dysregulation, sepsis, and death in the critically ill (McClave et al., 2018). The gut has been nicknamed a driver of multi-organ dysfunction in this patients' population. (McClave et al., 2018).

Changes in gut microbiota in critically ill patients

Critical illness is an extreme alteration of homeostasis, which requires medical and instrumental life support in addition to the treatment of the underlying disease. As the human microbiome is a result of complicated interplay between the host and gut microbiota, it comes without surprise that critical illness is almost invariably associated with dysbiosis in a degree directly proportional with disease severity (Lamarche et al., 2018). Most prominent is the relative increase in pathogenic bacteria (such as the Proteobacteria, *Enterobacter and Staphylococcus*) and a reduction of SCFA-producing protective microorganisms (such as Firmicutes and Bacteroidetes) and anti-inflammatory species as *Faecalibacterium* (Nakov et al., 2020; Zaborin et al., 2014). The dynamics of this microbiota alteration is astonishing. Ninety percent of the commensal organisms are lost within the first six hours of ICU stay (McClave et al., 2018). Factors contributing to the dysbiosis of the critically ill can be summarized as follows:

1. Artificial instrumentation of upper airways and upper GI tract (endotracheal intubation, nasogastric tube) which overcome natural immune barriers and lead to bacterial colonization of normally nearly sterile surfaces [8].
2. Host responses to critical illness leads to ischemia-reperfusion injury of the gastrointestinal tract. This, in addition to the above discussed barrier disruption, also reduces the production of gastric protective mucus and the secretion of microbial peptides and IgA and reduces partial pressure of oxygen within and near intestinal wall.
3. The lack of luminal nutrients in the gut cause catabolic starvation of bacteria, creating an additional selective pressure.

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4. The effect of medication. Opioids and other drugs, which reduce intestinal motility, and proton pump inhibitors, which alter pH in the stomach, both have the potential to alter microbiota composition. Yet, by far the most disruptive factor is the exposure to antibiotics. The US Centers for Disease Control found out 55% of all hospitalized patients received an antibiotic during their hospital stay. This proportion increases to 70% in the subgroup of patients in ICU (Wischmeyer et al., 2016), (Vincent et al., n.d.). Clinical manifestation of a profound microbiome alteration is antibiotic-associated diarrhea (AAD), which occurs in 5% to 35% of exposed subjects [12]. In addition, exposure to antibiotics increases Clostridium difficile (CD) or multi-drug resistant organisms (MDROs) colonization. Genes of antibiotic resistance then persist in microbiome of the gut. This creates the rationale for the restoration of physiological microbiota by means of FMT, as discussed below.
5. Environmental exposure to disinfectant agents and subtherapeutic concentrations of drugs plays likely a minor role as healthy hospital workers do not seem to have gut microbiota significantly altered (Johanson1969, n.d.).

The effect of dysbiosis on critically ill patients

It is likely that not only the milieu in the human body affects microbiota, but that this relationship also works in the opposite direction. Patients hospitalized with dysbiosis-associated diseases are at significantly increased risk of sepsis and septic shock (Prescott et al., 2015). Altered intestinal microbiota may lead to metabolic, immune, and even neurocognitive disturbances in the critically ill by one or more of the following mechanisms:

1. Dysbiosis reduces fermentation of dietary fibers into SCFA - the main energy source for the colonic epithelium, which preserve gut integrity. In sepsis, there is an association between faecal butyrate concentration, pathogen translocation and increased epithelial apoptosis (Schuijt et al., 2013). Epithelial apoptosis results in diarrhea, malabsorption of nutrients, and fecal energy loss (Nakov et al., 2020).

2. Impaired intestinal barrier function leads to uncontrolled translocation of luminal contents into the body. The microbial products, can cross blood brain barrier and contribute to the development of delirium and sepsis-associated encephalopathy (S. Li et al., 2018a).

3. Dysbiosis reduces specific microbial stimulatory signals for T-helper cells and dysregulates immune system, resulting in infectious complications (Nakov et al., 2020). These are made even more difficult to treat due to resistance genes preserved in the metagenome.

4. Indeed, dysbiosis and MDRO colonization alters bacterial ecology of ICUs and hospital floors, expanding its effect beyond the level of an individual patient.

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Dysbiosis therapy in ICU

In light of these rich bidirectional relations between the critically ill and their gut passengers, microbiota is an attractive potential treatment target. Indeed, the very first step and probably the most important in protecting gut microbiota is a strict **antibiotic stewardship**. Antibiotic overuse has repeatedly been associated with increase morbidity (including but not limited to *Clostridium difficile* infections (Wischmeyer et al., 2016)) and mortality (Vincent et al., n.d.) and with emergence of MDROs (Scott Fridkin, 2014). Yet, in many patients, antibiotic treatment is a necessary and life saving intervention. The question is then whether we can help patients to restore their damaged microbiome and whether such a restoration can improve patient-centered outcomes.

A large body of evidence from non-critical care setting is available for the use of prebiotics, probiotics, and faecal microbiota transplantation (FMT). **Prebiotics** are compounds in food that induce the growth or activity of beneficial microorganisms. **Probiotics** are living non-pathogenic microorganisms. The use of probiotics in critically ill patients may reduce the incidence of ventilator-associated pneumonia and antibiotic-associated diarrhea, but randomized controlled trials gave mixed results regarding the influence on the length of ICU stay or mortality [16]. (Hempel et al., 2012; Manzanares et al., 2016). There were reports of severe sepsis caused by microorganisms contained in probiotics formula, which were subsequently isolated from blood cultures (Muñ oz et al., 2005). Concerns arose in patients with severe acute pancreatitis, where enteral probiotics increased the rate of small bowel necrosis and death (Bongaerts & Severijnen, 2016). The apprehension to administer live bacteria into upper gastrointestinal tract lined with altered epithelial barrier prevented probiotics from wider routine use in intensive care.

Faecal microbial transplantation: Principle and use outside critical care setting

FMT is a procedure during which minimally processed feces from a healthy donor is transferred into a patient's gut. Donor microbiota then engraft in the recipient and increase their microbiota diversity and restores normal bowel function in patients with dysbiosis-associated diseases such as *Clostridium difficile* infections (CDI), inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), or metabolic syndrome [20]. In addition to living microorganisms, several other biologic products in the donor's stool such as bile acids, proteins, bacterial components, and bacteriophages affect intestinal homeostasis after FMT. Most clinical evidence for FMT comes from studies in patients with CDI. Here, rather than treating the CDI with more antibiotics, restoring healthy microbiota which can „fight" with pathogens has been shown effective, in particular in recurrent CDI. Interestingly, one study demonstrated that the transfer of sterile stool filtrates also eliminated CDI symptoms, suggesting the importance of abiotic substance in clinical effects of FMT [21]

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Currently, FMT is recommended for recurrent CDI with cure rate about 90% and as a rescue option in severe and fulminant CDI unresponsive to standard therapy in patients unfit for surgery. For the first episode of CDI, FMT is not yet established treatment beyond the experimental setting (Cammarota et al., 2019; Kelly et al., 2016; McDonald et al., 2018; Quraishi et al., 2017).

Large amount of data from CDI patients allows us to make some assumptions with regards safety and adverse effect of FMT. Even though FMT it appears very safe including in immune compromised patients, there are risks associated with the application procedure, such as aspirations or gut perforation. The application into the lower gastrointestinal tract seems to have a better safety profile [26,27]. Indeed, although FMT is a well-established in the treatment of CDI, there is no international consensus on the search for and testing of suitable donors, nor there are consistent international standard operating procedures for graft preparation (Levy & Allegretti, 2019).

Use FMT in intensive care unit

Severe forms of CDI. Critical illness can be a consequence of severe forms of CDI, for which FMT is a well-established treatment. In critically ill patients, CDI is responsible for 15-25% of nosocomial antibiotic-associated diarrhea. Not only are those patients at risks during their actual hospitalization, but CDI increases the risk of later readmission for sepsis by 70% [29,30]. The European CDI study (ECDIS) shows that one in 10 cases of CDI is either transferred to intensive care unit, necessitates colectomy, or dies. (Fischer et al., 2015; Kelly et al., 2014). The population of critically ill patients is different and data about safety and efficacy of FMT from the studies in general population cannot be directly transferable. In ICU, patients are more vulnerable to developing CDI due to co-morbidities (DM, IBD, liver cirrhosis, CKD, malignancy) and recent GI surgery [32–36] and due to higher exposure to exogenous risk factors such as antibiotics or other medication (immune suppression, PPI, H2 blocker, NSAID, laxatives) or invasive procedures (invasive mechanical ventilation, nasogastric intubation, prolonged use of laxatives). In addition, antibiotic stewardship is more challenging in ICU setting and administered antibiotics often have anti-anaerobic activity [36] or include clindamycin, cephalosporines, and/or fluoroquinolones. All these are associated with increased risk of CDI [37]. The diagnosis of CDI could be challenging due to variety of other possible causes of diarrhea in ICU patients and the difficulty to detect abdominal symptoms in sedated ventilated patients.

Indeed, despite the lack of high-quality evidence, first line treatment for CDI in the critically ill is the same as in general population. Both vancomycin and metronidazole are active against the vegetative forms, but they are not sporicidal. Fidaxomicin besides being active against vegetative forms inhibits sporulation as well and has narrower spectrum, thus less affecting gut microbiota.

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Both these factors translate to lower recurrence rate [1,38,39], but due to high cost, fidaxomicin remains the second line of treatment in most ICUs. In patients with fulminant colitis and/or septic shock refractory to conservative treatment, colectomy is recommended [36]. This invasive procedure bears 50% mortality, which increases with age and severity of physiological deterioration [36]. Therefore, for the patients who do not have an absolute indication for surgery such as colonic perforation, it would be beneficial to have an alternative treatment that would allow avoiding the surgery, mostly for the elderly and the sickest patients [29,40].

There are no randomized controlled trials on FMT for fulminant or severe CDI in critically ill patients and all data comes from 4 retrospective case-cohort studies and uncontrolled studies (case reports and case series) as summarized in Table 1. Indeed, these data can be subjected to selection and publication biases and should be interpreted with great caution. Yet, the available evidence suggests that FMT in critically ill ICU patients with recurrent, severe, or fulminant CDI is feasible and results in a reduction in mortality and morbidity compared with antibiotic therapy alone (Cheng et al., 2020). Importantly, there were no reported serious adverse events related to FMT [23,42–45]. (Table 1).

Of note, rescue FMT was a promising alternative to colectomy in critically ill patients with severe and complicated CDI with primary cure rate 78% (7/9), allowing 88% (8/9) patients to avoid surgery. [46]. There is a burning need of randomized controlled trials comparing standard of care and standard of care plus FMT in severe and fulminant forms of CDI.

Critically ill patients with inflammatory bowel disease. IBD is an intestinal disorder including ulcerative colitis (UC) as well as Crohn's disease (CD) characterized by chronic inflammation of the gastrointestinal tract. A certain degree of dysbiosis is a hallmark of IBD and associated with disease progression [47]. Microbes producing protective short chain fatty acids are reduced in IBD (Oka & Sartor, 2020). Patients with IBD are also at increased risk of developing CDI [49] and have worse outcomes, possibly due to IBD medication (repeated antibiotic courses, immunosuppression), altered immune and nutritional status, and frequent hospitalizations. Up to 20% of IBD flares cases were tested positive for *Clostridium dificille*.

FMT for CDI patients who have underlying IBD has lower success rate compared to patients without IBD, probably because the severity of dysbiosis. Moreover, 26% of patients with IBD experienced a clinically significant flare of IBD immediately after FMT [50,51].

FMT has been attempted to improve microbial dysbiosis in IBD without CDI [52] and as a treatment of active IBD. There are RCTs showing a mild, but statistically significant clinical, endoscopic and histological improvement of active IBD in patients treated by FMT compared to

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placebo [48,53–55]. A proportion of these patients were critically ill. (See Table 2). In addition, there is anecdotal evidence of a successful use of FMT as a rescue treatment to avoid surgery [56]. (Table 2)

In light of this FMT could be considered as a rescue treatment in critically ill patients before surgery in patients with refractory IBD. Most studies used rectal administration rather than upper GI and the procedure appeared safe [51,57].(Borody et al., 2003; Costello et al., 2020; Karakan et al., n.d.; Mocanu et al., 2021; Uygun et al., 2017b). (Chen et al., 2020; Cui et al., 2015; Dang et al., 2020) (Kump et al., 2018; Mizuno et al., 2017; Okahara et al., 2020; Sood et al., 2021; Vermeire et al., 2016) (see table 2).

FMT for septic shock and antibiotic associated diarrhoea. Several case reports and two case series on 31 patients described the use of FMT in septic shock with severe diarrhea in the ICU, mostly using upper gastrointestinal tract as the way to deliver FMT. In these patients FMT was intended to enrich microbiome with commensals (mainly Firmicutes) and reduce opportunistic organisms and by doing so reduce systemic inflammation [26,66,67]. Repeated FMT was also used in the treatment of intestinal failure associated with drug-induced hypersensitivity syndrome [68] and severe antibiotic-associated diarrhea (AAD) [69]. The data is summarized in Table 3.

The uncontrolled nature of published studies does not allow to infer any conclusions about effects of FMT in sepsis or for antibiotic associated diarrhea, but it generate hypothesis that it may be safe and efficient. Although there are also some experimental data supporting the use of FMT in sepsis [70], biological plausibility seems much sounder for AAD, where FMT should be first tested in RCTs.

Critically ill immunocompromised patients. Critically ill patients with immune suppression (HIV/AIDS, hematologic malignancies, on immune suppressive therapy as solid organ transplant recipients or for other reason, etc.) represent a very specific subgroup, where inducing live microorganisms in the form of FMT could be most risky. Surprisingly, the immune suppressed subgroup of patients with severe or fulminant CDI treated with FMT showed similarly high cure rates and no associated bacteremia or signs of worsened systemic inflammation [27,71]. FMT was also successfully used in three patients with severe refractory gastrointestinal acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation[72]

FMT to eliminate colonization by multi/drug resistant organisms. Animal experiments showed that the restoration of microbiome following FMT was associated with an immense reduction in the density of intestinal MDRO, probably by restricting their growt [73]. Indeed, critically ill exposed to

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broad spectrum antibiotics are often colonized with MDRO and in theory, FMT could be a plausible alternative to selective bowel decontamination strategy by using antibiotics alone, offering an advantage of not threatening bacterial ecology of intensive care units. An uncontrolled study of 20 immune compromised haematologic patients demonstrated a total elimination of MDRO from the stool in 15 (75%) patients after FMT [74]. On the other hand, no effect of FMT was observed in RCT. Thirty-nine immune competent patients colonized with MDRO were randomized to receive no treatment or five-day course of nonabsorbable antibiotics followed by FMT. There was no significant difference in colonization rate in stool samples (MDRO eradication in 41% vs. 29% in controls) [75]. Unfortunately, large scale RCTs measuring patient-centred and ecological outcomes are still missing.

Conclusions

FMT is an established treatment method for recurrent CDI and this is also beneficial for patients who are critically ill or develop CDI as a consequence of IBD, immune deficiency or protracted ICU stay. At the current level of evidence, FMT should be considered as a salvage treatment for the sickest patients with most severe forms of CDI in whom colectomy would otherwise be the only alternative. The biggest promise and burning need of RCTs is in the treatment of post-antibiotic diarrhoea as FMT not only seems to eliminate symptoms, but it also may reduce colonisation rate with MDRO and improve systemic inflammation and outcomes. Current data suggest acceptable safety profile of FMT administered into lower gastrointestinal tract to critically ill patients including those who are immune suppressed, but due to uncontrolled nature of most of the available trials, this warrants confirmation in large scale randomised controlled trials.

Appendix: A literature research summarised in Table 1-3 was conducted using PubMed and Web of Science databases, searching for the medical subject headings (MeSH) terms “FMT”, “faecal microbiota transplantation”, “ICU”, “severe illness”, “fulminant”, “sepsis”, “IBD”, “CDI”, and “MODS”. Papers written in English and published between 2003 and 2020 and pertinent to the purpose of the review, were selected. Out of initial 1341 output we finally choose original case reports (n=20), case series (n=25), retrospective cohort studies (n=7), and RCT (n=1)

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Declarations

Authors declare no conflict of interest.

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List of abbreviations:

CD- Clostridium difficile, CDI- Clostridium difficile infection, FMT – Faecal microbiota transplantation, IBD – inflammatory bowel disease, ICU- intensive care unit, MDRO- multi-drug resistant organisms, SCFA- short-chain fatty acids

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Ref.	Study type	Patients				Intervention (faecal microbial transplantation)			Controls	Outcomes	
		N (FMT /controls)// critically ill	Diagnosis	Age	Sex	Way of administration	Frequency	Donor R=related, U=unrelated, ?=Unknown; Fresh, Frozen, ?=Unknown	no FMT therapy	Beneficial	Adverse events (severe/mild)
[76]	Open-label randomised clinical trial	56/0	sCDI	75	17 M/ 39 F	Lg - C	1x 28 pt, 3x on average 28pt	U(71%), R(29%)/ mostly fresh	x	↓AS , ↓D	x/AS
[41]	Retrospective cohort study	225 (50pt FMT)/205	fCDI, sCDI	61.2	123 M/ 102F	Lg-C (98%)	median of 2 FMT	U/Fresh (10%) and Frozen	ATB therapy	↓M	no comment
[77]		17/15	sCDI, cCDI	66,4	18 M/ 14 F	no comments	everage 1.83±0.7	?/?	no more details	↓M	no comment
[43]		66/45	sCDI, scCDI	81 (69–87)	23 M/ 43 F	Ug - NGS	1x51pt, 2x14pt, 3x1pt	R and U/Fresh (46%) and Frozen	Vanco p.o +/- Metro i.v. or p.o. +/i FDX p.o.	↓M	x/AS, F
[42]		16/32	sCDI, fCDI	62,6	7 M/ 9F	Lg - C,S	every 3–5 days until resolution	R and U/?	Vanco p.o. +/− Metro i.v.	↓M	1x bacteremia (6.3%), 1x perforation (6.3%) / no comment
[78]	Case series	14/0	sCDI, refCDI	73.4 (52–92)	5 M/ 9F	Ug-Ngt (93%), Lg-C (7%)	1x10pt, 2x2pt, 3x2pt	R (85.7 %) and U/Fresh.	not applicable	↓AS , ↓D	x/no comment
[79]		75/0	recCDI	76.4	21 M/ 54 F	Lg-C (88%), Lg-S (9.3%)	no comments	R(13.5%) and U/?		↓AS , ↓D	3pt post-procedural hypotension, one case of perforation.
[80]		17/0	sCDI, cCDI	66.4 (38 - 89)	4 M/ 13 F	Lg - C (94%),E,S Ug-Njt	1x14pt 2x 3pt	R (58.8%) and U/?		↓AS , ↓D	x/AS
[46]		9/0	sCDI, cCDI	67.78	6 M/ 3F	Ug-Njt (3x),Peg (1x) Lg-C (1x), Ug+Lg (C+Ngt) 4x	1x 8pt, 2x 1pt	U and R/?		↓AS , ↓D, ↓ Ilf, ↑SA	x/no comment
[81]		328/0 // 42pt sCDI	sCDI, recCDI	61.4 ±19.3	87 M/ 241F	Lg-C (76.9%)	no comments	?/?		no comment	no comment
[82]		64/0 //26pt sCDI	recCDI	74 (29-94)	25 M/ 39 F	Lg - C	1x44pt, multifaecal infusion 20pt	R (44%) and U / Fresh (83%) and Frozen		↓D	no comment
[71]		94/0	sCDI, fCDI + SOTp	56,3	47 M/ 47 F	Ug- Njt, Lg-C (81%),E (17%),S, Caps.	no details	R and U/ Fresh (41%) and Frozen		↓AS , ↓D	3.2% severe diarrhea, AKI, fever, CMV reactivation /22,3% AS,D
[27]		80/0 //36pt sCDI,cCDI,refCDI	sCDI, refCD,recCDI + IC	53 (20–88)	42 M/ 38 F	Lg mostly	1x 62pt, no more comments	?/?		↓AS , ↓D	aspiration, mucosal tear caused by the colonoscopy/ 15% any SAE (AS, IBD flare..)
[44]		57/0	sCDI, scCDI	72 (60 – 79; 25 – 99)	23 M/ 34 F	Lg - C	1x30pt, 2x16pt, 3x 4pt, 4–5x2pt	R and U/Fresh (51%) and Frozen		↓AS , ↓D, ↑ SA	x/no comment

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[45]		146/0 /// s,cCDI 57(38.4%)	rCDI, sCDI, cCDI	78.6 (65 to 97)	46 M/ 10 0F	Lg-C (80,8%),E, S Ug-Gfs, Ent	1x130pt 1x, repeated 16pt (no details)	?/?		↓AS , ↓D	x/D, AS 11pt (7,5%)
[31]		29/0	sCDI, scCDI	65,2 (25-92)	12 M/ 17 F	Lg-C	1x 18pt, 2x 9pt, 3x 2pt	R (36%) and U/?		↓D, ↑ SA	x/no comment
[83]		35/0	sCDI	69 (29–91)	17 M/ 18 F	Lg-C	1x 27pt, multiple 8 pt	R (54%) and U/?		↓AS , ↓D, ↑ SA	no comment
[84]		4/0	sCDI	66-83	1 M/ 3F	Lg - C	1x2pt, 2x2pt	U/Fresh (25%) and Frozen		↓AS , ↓D	no comment
[85]	Case report	1/0	sCDI	65	1 M	Ug-Njt	1x1pt	U/?		↓AS , ↓D	x/no comment
[86]		1/0	fCDI	69	1 M	LG-E	1x1pt	R/Fresh		↓AS , ↓D, ↓ Ilf	x/no comment
[87]		1/0	fCDI	26	1 M	Lg – C	2x1pt	R/Fresh		↓AS , ↓D, ↑SA	x/no comment
[88]		1/0	sCDI	75	1F	Ug-Njt	1x1pt	R/Fresh		↓D, ↓ Ilf	x/no comment
[89]		1/0	sCD, rCDI	65	1 M	Lg – C	1x1pt	R/Fresh		x	SIRS 4 days subsequent to the FMT without detecting an infectious cause
[90]		1/0	fCDI +AML	27	1 M	Lg-S	1x1pt	U/Frozen		↓AS , ↓D	x/no comment
[91]		1/0	CDI+ HIV stage 3	27	1 M	Ug-Njt	1x1pt	R/Fresh		↓AS , ↓D, ↓ Ilf	x/no comment
[37]		1/0	sCDI - liverTx	47	1 W	Ug-caps, Lg-S	2x1pt	R/?		↓AS , ↓D, ↓ Ilf	x/no comment
[92]		1/0	sCDI + SCTx	21	1 W	Ug-Njt	1x1pt	R/?		↓AS , ↓D	x/no comment
[93]		1/0	fCDI +pB Mcht	56	1 M	Ug- Njt, Lg-C	11x1pt (7xC (days 2, 7, 8, 11, 12, 45, 48) + 4 x Njt (days 13, 14, 21, and 24)	U/Frozen		↓AS , ↓D	x/no comment
[94]		1/0	sCDI	71	1 M	Lg-C	1x1pt	R/Fresh		↓AS , ↓D	x/no comment

Table 1. Clinical studies on critically ill patients with Clostridium dificille infections. Note: x- none, pt- patient, D - diarrhea, F - fever, AS - abdominal symptoms, SS- septic symptoms, R- remission, M- mortality, Ilf - inflammatory laboratory findings, SA - surgery avoiding, AE-s - adverse events severe, AE-m - adverse events mild; CDI - Clostridium difficile Infection, sCDI - severe CDI, scCDI - severe complicated CDI, rCDI- recurrent CDI, fCDI - fulminant CDI; Vanco - vancomycin, Metro - metronidazole, FDX – fidaxomicin; SEX - F- female, M- men; Way of administration - Ug -upper GI, Lg-lower GI, Ngt - nasogastric tube, Ngi-nasogastric infusion, Njt - nasojejunal tube, Ent - enteroscopy, C - colonoscopy, S- sigmoidoscopy, E-enema, Caps- capsule; IBD - inflammatory bowel disease - a- active, s-severe, ref-refractory

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			Patient			Intervention (faecal microbial transplantation)			Controls	Outcomes	
	Study type	N (FMT /controls) // critically ill	Diagnosis	Age	Sex	Way of administration	Frequency	Donor R=related, U=unrelated, ?=Unknown; Fresh, Frozen, ?=Unknown	no FMT therapy	Beneficial	Adverse events (severe/mild)
[53]	Double-blind placebo-controlled randomized trial	38/37	aUC	42.2 (FMT)/ 35.8(placebo)	44M/31F	Lg-E	once weekly for 6 weeks	U/ ?	enema with placebo (water)	↑R	1 pt in placebo gr. urgent colectomy, 3pt (1plac. gr. 2FMT gr.) rectal abscess, 1pt in FMT gr. CDI
[95]	Cohort study	17/19	mUC, sUC	40.4y (FMT), 44.8y (ATB)	13M/4F (FMT) 12M/7F (ATB)	Lg-C	1x17pt	U and R/ Fresh	ATB therapy	↓AS	x/AS
[96]		17/10pt //5pt sUC	refUC	44+/-18 (FMT), 36+/-13 (ATB)	14M/3F (FMT), 3M/7F (ATB)	Lg-C+S	5x á 14days (1xC-4xS)	U and R/ Fresh	ATB therapy	↓AS, ↑R	no comment
[97]		55/37 // 52pt(56 %) extensive colitis	refUC, mUC, sUC	41.1±13,9	56M/36F	Lg-C	1x 55pt	U and R/ Fresh	ATB therapy	↓AS	x/12 pt (13.0%) AS,D
[56]	Case series	30/0 //20pt (66.7 %) sIBD	refUC	34.6	14M/16F	Lg-C	1x 27pt, 2x 3pt	U (77%) and R/?	not applicable	↓AS, ↓D, ↑R	x/ AS 7 pt (23.3%)
[98]		14/0	refl BD (8 UC, 6 CD)	28-50y	7M/7F	Ug-Njt (64%), Lg-C, E	2x5pt , 4x9pt (2xNjt +2xC)	U (71%) and R/?		x(CD), ↑R (UC)	1pt aspiration pneumonia / 4pt high fever
[60]		14/0	refUC	47 ± 11	no details	Lg-C	1x 5pt, 2x 1pt, 4x 3pt, 6x 2pt	?/?		↓AS	no comment
[61]		6/0	sUC, recUC	25–53	3M, 3F	Lg-E	daily for 5 days	U/?		↓AS	no comment
[63]		9/0 //6pt (66%) sUC	mUC,sUC	47.90 (31-61)	7M, 2F	Lg-C (55.6%), Ug-Njt (44.4%)	3x (day 1, 3 and 5)	U/?		↓AS, ↑R	X/AS 33.3% (3/9)
[65]		30/0	refCD	38.0 ± 13.83	19M/11F	Ug-Njt	1x30pt	U and R/?		↓AS, ↑R, ↑BMI	x/ F 2pt
[64]		12/0 // 7pt (58.3%) sUC	mUC, sUC	50.5 years (41–65)	M8,/4F	Lg-C	multiple (no more comments)	U/?		↓AS, ↑R	x/x
[51]		67/0 // 15pt	UC, CD +	45.42 +/- 17.33	28M, 39F	Lg-C,S	1x 60pt,	U/ Fresh (88.1%)		↓AS, ↓D	x/AS

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		(22.4%) sIBD	rec CDI				2x6pt, 3x1pt				
[99]		93/0	ref UC, mUC, sUC	34.96± 11.27	58M/35F	Lg-C	7x (week 0, 2, 6, 10, 14, 18, 22)	U/ Fresh		↓AS	x/ AS (30%)
[100]		10/0 // 7pt (70%) sUC	aUC	31 (17–48)	7M/3F	Lg-C	1x 10pt	R/ Fresh		x	x/6pt exacerbation of the UC
[57]		16/0	aUC	37 (18-66)	10M, 6F	Ug-Gfs, Lg-C	3x á 2-3 months	U/ ?		↓AS, ↓Ilf, ↑R	x/no comment
[59]	Case report	1/0	sUC	19	1M	Lg-C,E	3x1pt	U/?		↓AS, ↑R	x/no comment

Table 1. Clinical studies on critically ill patients with inflammatory bowel diseases. Note: x- none, pt- patient, D - diarrhea, F - fever, AS - abdominal symptoms, SS- septic symptoms, R- remission, M- mortality, Ilf - inflammatory laboratory findings, SA - surgery avoiding, AE-s - advers events severe, AE-m - adverse events mild; CDI - Clostridium difficile Infection; Vanco - vancomycin, Metro - metronidazole, FDX – fidaxomicin; SEX - F- female, M- men; Way of FMT administration - Ug -upper GI, Lg-lower GI, Ngt - nasogastric tube, Ngi-nasogastric infusion, Njt - nasojejunal tube, Ent - enteroscopy, C - colonoscopy, S- sigmoidoscopy, E- enema, Caps- capsule; IBD - inflammatory bowel disease - a- active, s-severe, ref-refractory, gr.- group

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		Patient				Intervention			Controls	Outcomes	
	Study type	N (FMT /controls)// critically ill)	Diagnosis	Age	Sex	Way of administration	Frequency	Donor R=related, U=unrelated, ?=Unknown; Fresh, Frozen, ?=Unknown	no FMT therapy	Beneficial	Adverse events (severe/mild)
[101]	case series	18/0	Antibiotic-associated diarrhea, criticall illness	55 (2-91)	12 M/ 6F	Ug-Njt(13),Gfs(4) Lg-E(1)	1x 8pt, 2x7pt, 3x1pt, 4x2pt	U/ ?		↓SS, ↓D, ↓Ilf	x/7pt (38.9%) FMT-related AEs (D,AS)
[66]	case report	1/0	Septic shock, watery diarrhea	44	1 W	Ug-Njt	1x1pt	R/ Fresh		↓SS, ↓D	x/no comment
[67]		2/0	MODS, septic shock, severe diarrhea	65, 84	2 M	Ug-Ngi	1x2pt	U/ ?		↓SS, ↓D, ↓F	x/no comment
[68]		1/0	MODS, drug-induced hypersensitivity syndrome	32	1F	Ug-Ngi	4x -every 6 days	U/ ?		↓SS, ↓D	x/no comment
[102]		1/0	Septic shock, severe dierrhea, UC	29	1F	Ug-Njt	1x1pt	?/?	Not applicable	↓SS, ↓D, ↓F, ↓Ilf	x/no comment
[103]		1/0	MDRO infection, septic shock	57	1 M	Ug-Peg	1x1pt	?/?		-------	the patient died the same day FMT was done
[104]		1/0	High-volume diarrhea (Apoptotic Enterocolitis) on ICU	16	1F	Lg-C	1x1pt	R/ ?		↓D	x/no comment
[105]		5/0	MRSA enteritis, septic shock	28 (19 – 45)	3 M/ 2F	Ug-Njt	3x- once a day for 3 consecutive days	U and R/ Fresh		↓AS, ↓D	x/no comment
[106]		1/0	MDRO Klebsiella, MODS	60	1 M	Ug-Njt	2x - repeated after two weeks.	R/ ?		↓SS, ↓Ilf	x/no comment

Table 1. Clinical studies on critically ill patients with sepsis and septic shock. Note: x- none, pt- patient, D - diarrhea, F - fever, AS - abdominal symptoms, SS- septic symptoms, R- remission, M- mortality, Ilf - inflammatory laboratory findings, SA - surgery avoiding, AE-s - adverse events severe, AE-m - adverse events mild,sCDI - severe CDI, scCDI - severe complicated CDI, rCDI- recurrent CDI, fCDI - fulminant CDI; Vanco - vancomycin, Metro - metronidazole, FDX – fidaxomicin; SEX - F- female, M- men; Way of FMT administration - Ug -upper GI, Lg-lower GI, Ngt - nasogastric tube, Ngi-nasogastric infusion, Njt - nasojejunal tube, Ent - enteroscopy, C - colonoscopy, S- sigmoidoscopy, E- enema, Caps- capsule
IBD - inflammatory bowel disease, UC – ulcerative colitis, MODS - multiple organ dysfunction syndrome, MDRO - multi-drug resistant organisms, MRSA - Methicillin-Resistant Staphylococcus aureus, ICU - intensive care unit,