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WHAT'S NEW IN INTENSIVE CARE

Fecal microbiota transplantation in the ICU: perspectives on future implementations

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Introduction

An increasing amount of evidence has shown that both the intestinal ecosystem, as well as the microbiota that inhabits these niches, can change dramatically during the course of an ICU stay [1–3]. Yet, few data exist on the consequences of these changes on patients' clinical outcome. Recent preclinical studies suggest that severe disruption of the microbiota, otherwise described as dysbiosis, could be associated with a profound state of immunosuppression, as well as an increased risk of organ failure and mortality [4–6]. In addition, it is thought that disruption of beneficial obligate anaerobes in the gut opens the door to colonization with multi-drug-resistant (MDR) pathogens, such as vancomycin-resistant Enterococcus (VRE), and extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) [7, 8]. Therefore, mitigating dysbiosis in the ICU ise a novel field to be explored for its eventual impact on outcome for critically ill patient. Faecal microbiota transplantation (FMT) consists of the infusion of faeces from a healthy donor into the gastrointestinal tract of a patient, aimed at reconstituting the intestinal microbiota and treat disorders associated with dysbiosis. While evidence-based consensus exists that the treatment is extremely effective against recurrent clostridium difficile infection (CDI), the use of FMT for this indication on the ICU remains controversial [9, 10]. A recent retrospective study of 111 patients in France showed that early FMT significantly improved survival in patients with severe CDI, thereby opening the door for further evaluation of FMT in ICU settings [11]. Beyond CDI, studies investigating the role in FMT to improve outcomes of critical illness are largely unexplored. However, we do foresee a potential role for this treatment approach in the restoration of ICU-associated dysbiosis, as well as a future tool to decolonize the gut of MDR organisms.

Only five cases have been described in which FMT has been employed to address disruption of the microbiota in the ICU. All these cases showed that treatment with FMT led to a successful reversal of dysbiosis, with subsequent improvement of outcome. In addition, some cases marked a steep reduction in inflammatory mediators, and normalized Th1/Th2 and Th1/Th17 ratios following FMT. (Supplementary Table 1). Apart from difficulties with extrapolating the data derived from these case reports to the general ICU population, we are far from obtaining conclusive evidence that restoration of dysbiosis in critical illness is beneficial. For example, patients in the relevant studies showed signs of recovery prior to the initiation of FMT, which implies that these patients could have recovered without receiving this experimental therapy. The use of FMT to decolonize the gut with MDR organisms has been studied in several trials in non-ICU settings. (Supplementary Table 2a). The results of the largest and most strictly controlled study did not support the routine use of FMT for purposes; instead, it indicated that larger trials with improved faecal preparation protocols are still warranted [12]. Of interest, other studies examining this procedure are currently ongoing, with one phase 2 open label trial focusing on eradicating MDR bacteria in 10 ICU patients (NCT03350178) (Supplementary Table 2b).

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Practical considerations for implementing FMT in the ICU

Apart from the aforementioned trial, no other studies are currently investigating the safety and feasibility of the use of FMT in the ICU. It is understandable that researcher clinicians have so far refrained from engaging on this subject, as the potential impact of administering live bacteria to a critically ill and potentially immunosuppressed patient has been described as potentially perilous [5]. In addition, numerous practical and technical challenges exist, such as heterogeneity in the selection of patients and donors, modes of faeces preparation, route and type of administration [8, 9, Table 1]. Selection of patients for a potential FMT trial is particularly cumbersome in the ICU, as the majority of critically ill patients receive antibiotics at some point during their ICU stay, potentially nullifying the proposed effect of this specific therapeutic approach. Therefore, investigators are faced with the dilemma to either account for this intervention in initial study design and, therefore, investigate a very narrow subset of ICU patients, or make a daunting commitment to stop any antibiotics during the course of the study, which many clinicians would not be comfortable undertaking.

In addition to the issues with patient selection, appropriate donor screening is equally cumbersome, as transmission of potentially transmittable diseases could be detrimental to an already vulnerable critically ill host [8]. In addition, studies treating inflammatory bowel disorders have shown that failure of FMT can sometimes be attributed to reduced immunomodulatory properties of the donor faeces, leading to the suggestion that donor faeces needs to contain a certain amount of butyrate-producing anaerobic bacteria, such as *Faecalibacterium prausnitzii*, *Roseburia hominis*, and *Coprococcus eutactus*, in order to be effective [13]. Finally, consensus regarding the best route of administration of FMT is currently lacking. Recent evidence states that critically ill recipients who received FMT via a nasogastric tube experienced higher rates of serious adverse events, such as fever and aspiration pneumonia, compared to administration via enema or coloscopy [8]. Potential new administration routes for FMT, such as the use of faecal capsules, lyophilized stool, or faecal filtrate transfer (FFT) could circumvent the current challenges of administration with potentially fewer side effects; however, evidence regarding their efficacy has yet to be established [14, 15]. Table 1 depicts general considerations for FMT in critically ill patients, which, if addressed in future studies, could help the assessment of safety, feasibility and effectiveness of FMT in the ICU setting.

In conclusion, FMT is an interesting but importantly understudied approach that could potentially be effective in improving morbidity and mortality in certain categories of ICU patients. Clinical trials that systematically address the aforementioned issues are needed to provide more insight in the potential safety, feasibility and benefit of this treatment approach in critical illness.

Take home message

FMT has the potential to recover dysbiosis associated with critical illness. Future studies should identify the target population, optimal timing, mode of administration and the ultimate effect on patients' outcome in the ICU setting.

Table 1 Practical considerations for the adoption of FMT in ICU patients. Adapted from Cammarota and colleagues [9]

Facility implementations		Quality of evidence	Strength of recommendation
Clinical requirements and facilities	Referral FMT centres should be implemented in hospitals with appropriate expertise and facilities	Moderate	Strong
	A clinical governance dealing with administrative issues of FMT (e.g., reimbursements, authorisations) is recommended	Low	Strong
	Specific training on FMT processes are encouraged: clinical training (donor and patient selection, patient management after FMT), delivery training (learning of different routes of delivery) and microbiological training (preparation of fresh and frozen faecal material)	Low	Strong
	The availability of the endoscopy service is required. A multidisciplinary team (including gastroenterologists, microbiologists and infectious disease physicians) is encouraged	Low	Strong
Microbiological requirements and facilities	Safe processing of human samples (biosafety level 2: aliquoting, storage and preparation of faeces) is required. Stool banking is encouraged	Low	Strong
	Storage of FMT procedure and donor screening for at least 10 years is required	Low	Strong
Regulatory requirements	Appropriate FMT registries should be implemented, in order to collect data concerning indications, procedure, effectiveness and safety profiles	Low	Strong
	Specific national rules for the classification of FMT should be followed to implement an FMT centre	Low	Strong
Pre-procedure			
Donor selection	Potential donors for FMT have to undergo a medical interview: i) at the beginning of the selection process, and ii) on the same day of the donation. Key issues in the collection of medical history include: risk factors of transmittable diseases, travel history, gastrointestinal/metabolic/neurological disorders, exposure to drugs that can impair gut microbiota composition	Low	Strong
	Potential donors for FMT should undergo blood and stool testing for transmittable diseases at most 4 weeks before donation	Low	Strong
Preparation of faecal material	Fresh stool should be used within 6 h after defecation	Moderate	Strong
	To protect anaerobic bacteria, the storage and preparation should be as brief as possible. Anaerobic storage and processing should be applied if possible	Moderate	Strong
	Until further processing, the stool sample can be stored at ambient temperature (20–30 °C)		
	A minimum amount of 30 g of faeces should be used		
	Faecal material should be suspended in saline using a blender or manual effort and sieved in order to avoid the clogging of infusion syringes and tubes		
	A dedicated space, disinfected using measures that are effective against sporulating bacteria, should be used		
	Frozen faecal material preparation has to undergo a minimum set of general steps		
	At least 30 g of donor faeces and 150 mL of saline solution should be used		
	Before freezing, glycerol should be added up to a final concentration of 10%		
	The final suspension should be clearly labelled and traceable, and stored at − 80 °C		
	On the day of faecal infusion, faecal suspension should be thawed in a warm (37 °C) water bath and infused within 6 h from thawing		
	After thawing, saline solution can be added to obtain a desired suspension volume		
	Repetitive thawing and freezing should be avoided		
During and post-procedure			
Faecal delivery	Recipients should be prepared with bowel lavage by polyethylene glycol before procedure when FMT is performed by upper route or by colonoscopy. For delivery via enema, no preparation instructions have been developed	Low	Weak
	Patients should be able to hold the infused material for at least 30 min. Some study protocols implicate repeated enemas to increase clinical success	Low	Strong
	FMT appears to be safe in immunocompromised and critically ill patients regardless the route of delivery. In case of critically ill patients, faecal infusion by enema(s) should be preferred.		
	the rate of serious adverse events in recipients who received FMT via upper GI tract seems to be higher (aspiration pneumonia due to nausea and vomiting by nasogastric or nasoduodenal tube)		
Clinical management	Short-term monitoring of patients for adverse events (AEs). The most commonly described AEs after FMT for CDI are: diarrhoea, abdominal cramps, belching, constipation, fever, Gram-negative bacteraemia and perforation	Low	Weak
	Long-term monitoring of patients for AEs. Periodicity and length of follow-up for long-term AEs are not determined. Follow-up should include both clinical and analytical data	Low	Weak

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05645-7) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
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