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Faecal microbiota transplantation: from practice to legislation before considering industrialization

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Abstract

Recurrent *Clostridium difficile* infections constitute an important medical concern. Evidence has been provided showing that faecal microbiota transplantation is a more efficient treatment than antibiotics. Serious side effects are unusual, and acceptability is not an obstacle. Nevertheless, protocols are heterogeneous with respect to the selection of donors and the methodology used for the faecal transplantation. Regulations by both the Food and Drug Administration and the French authorities consider stool samples to be drugs, and suggest strict supervision in clinical trials. Donor screening by questionnaire or by blood and stool analysis, which is essential in eliminating pathogens or viruses before transplantation, is similar in different countries, with a few exceptions. The traceability of the faecal transplant and long-term follow-up of the patients in clinical trials are issues that may be difficult to organize. The use of frozen microbiota facilitates transplantation, and the nasogastric route seems to be at least as effective as other invasive methods and avoids the risk of anaesthesia. Synthetic microbiota is an approach that selects a mixture of bacteria, thereby eliminating the risk of transmissible disease; however, this approach is not yet evidence-based. The use of pills, which is currently being tested in clinical trials, will certainly be the starting point for the extensive use and wide industrialization of faecal microbiota transplantation.

Keywords: *Clostridium difficile*, faecal microbiota transplant, industrialization, pills, regulation
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Introduction

Clostridium difficile infection (CDI) is the primary cause of healthcare-associated diarrhoea, with worldwide outbreaks caused by diverse ribotypes [1,2]. The mortality rate ranges from 5% to more than 40%, depending on the strains and clinical status of the host [1,3–6]. For example, the Centers for Disease Control and Prevention estimated that CDI causes 14 000 deaths annually in the USA. Despite antibiotic treatment with metronidazole, vancomycin, or fidaxomicin, the relapse rate is still up to 35% [7]. Faecal microbiota transplantation (FMT) was first proposed empirically in 1958 as a method of treating CDIs [8], and cases series using FMT as a treatment for recurrent infections were reported [9]. FMT has recently been shown to be clearly superior to antibiotics in a randomized clinical study [10]. Indeed, in 2013, Van Nood *et al.* [10] demonstrated better efficacy of FMT than of the conventional treatment with vancomycin in patients with recurrent CDI. Among the 16 patients treated with faeces infusion, none had severe adverse events. Most of the patients had their diarrhoea resolved within 3 h after infusion, and 19% had constipation. Recently, the European Society of Clinical Microbiology and Infectious Diseases strongly recommended the use of FMT in patients with several relapses [11]. The cost-effectiveness of FMT colonoscopy for the management of recurrent CDI was recently demonstrated to be superior to that of the usual antibiotics [12]. Additionally, a recent study demonstrated the efficiency of FMT in recurrent CDI, even in strongly immunocompromised patients, who had initially represented a limited indication [13]. Finally, some scientists

have proposed the use of FMT in other clinical conditions, such as inflammatory bowel diseases, although the results are less encouraging than those obtained for recurrent CDIs [14–16].

Consequently, this alternative and efficient treatment needs regulation and standardization (Fig. 1). However, no consensus exists regarding health safety, legislative aspects, donor screening, and the administration route. We herein provide a review regarding these aspects, which will require standardization before the probable wide-scale industrialization because of the promising number of indications.

Regulation Aspects

Health authorities have been alerted to the absence of faecal transplant status and regulations, given the accumulating evidence showing the effectiveness of such treatments [10]. In France and the USA, authorities have considered FMT to be a drug, in contrast to the UK, Denmark, and The Netherlands. We can also observed the difficulties of authorities, shared between the high pressure from patients and clinical doctors performing FMT, and the necessary regulations [17].

Indeed, in the USA, the US Food and Drug Administration (FDA) stated in the autumn of 2012 that human faeces constituted a drug (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf) [18]. This had the unintended consequence of putting faeces used for FMT under the jurisdiction of hospital pharmacies, requiring storage of the faecal product in the pharmacy [18]. In addition, a time-consuming investigational new drug (IND) status was first proposed for the conduct of studies in humans [19]. The objectives were to improve the safety of and standardize the use of FMT [17]. The FDA noted that the efficacy and safety profiles of this intervention had not yet been fully evaluated in controlled clinical trials, and organized a public workshop to provide a forum for the exchange of experiences among the medical and scientific community about the regulatory issues associated with FMT. After this public meeting and several opinions of different authorities, 6 weeks later, the FDA's guidance documents stated that this protocol including an IND status was suggested or recommended but not required [17,19]. Indeed, the FDA proposed a compassionate exception to allow the many people suffering from CDI to benefit from the use of FMT. The FDA recommended that the treating physician obtain adequate informed consent from the patient or his or her legally authorized representative for the use of FMT. Informed consent should include, at a minimum, a

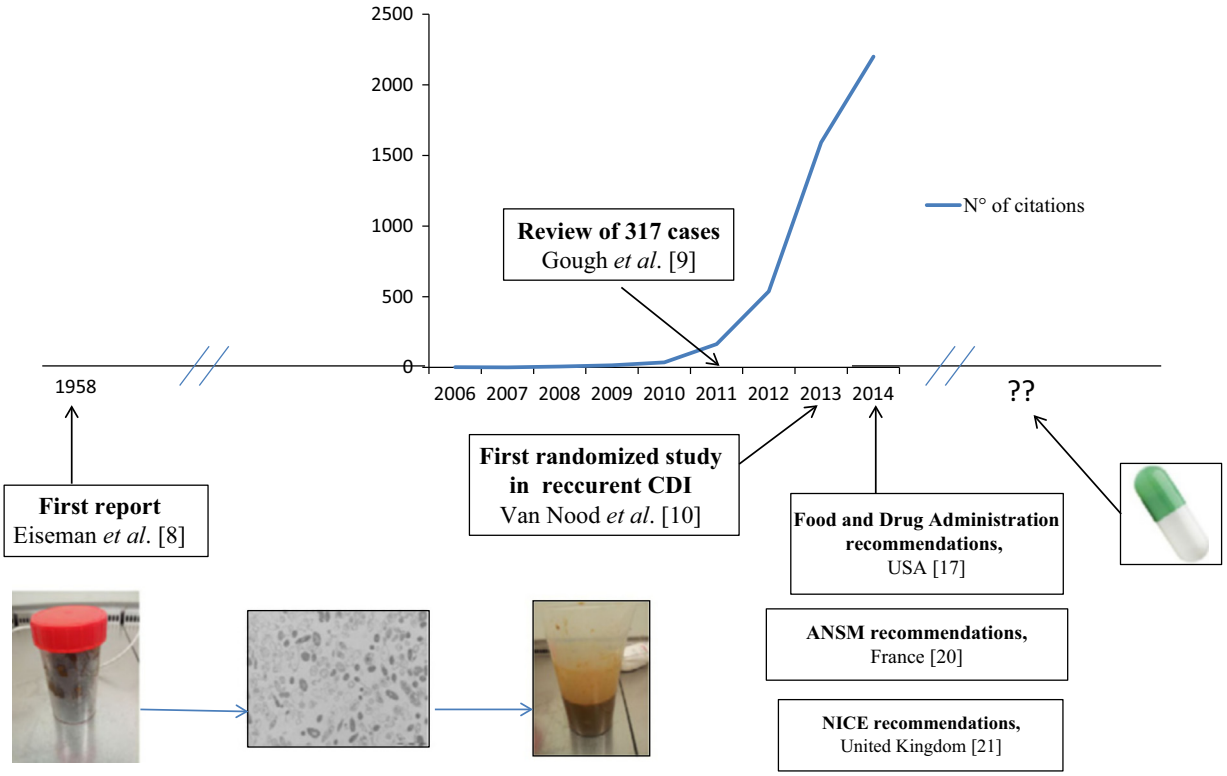

FIG. 1. Scientific and regulatory key events from 1858 to 2014 in faecal microbiota transplantation. We found an increasing number of citations by using the ISI web of knowledge and 'fecal microbiota transplantation' as the keyword. CDI, *Clostridium difficile* infection.