EDITORIAL

Lurking Danger: Emerging Evidence

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"Primum non nocere" is the basic ethical tenet of our medical practice. Despite our best intentions and efforts this if often violated and the patients end up in undesired healthcare-associated adverse events with its attendant consequences. One of such recent and dreadful events is healthcare-associated infection resulting in *Clostridium difficile*-associated diarrhea (CDAD), also referred by some as *Pseudomembranous colitis*. Intestinal dysbiosis and disruption of the gut microbiota are main reasons for this affliction with several other risk factors, one among them is being subjected to hematopoietic stem cell transplantation (HSCT), with a reported incidence of up to 25%.[1] Katrina Ray states in 2012 *Nature* editorial, "we are not just on "friendly" terms with our gut bacteria—the relationship is infinitely more intimate than that—we are married to them," and their imbalances are strongly linked to conditions like inflammatory bowel disease (IBD), cancer, obesity, and cardiovascular diseases.[2] Prevention and treatment of dysbiosis and its consequent disease entities includes probiotics, antibiotics, steroids, and fecal microbiota transplantation (FMT). While probiotics are not derivatives of gut and antibiotics and steroids have their share of issues and limitations, the focus is turning more onto fecal microbiota transplantation, which is offered for recurrent and refractory CDAD and *Clostridium difficile* infection (CDI). A meta-analysis published in 2017 which included 37 studies, seven randomized controlled trials and 30 case series, found that FMT was more effective than oral vancomycin therapy for patients with recurrent or refractory CDAD.[3,4] The idea of fecal transplantation is as old as 4th century AD, and has its origin in China, where severe diarrhea and food poisoning were treated using the "yellow soup." The principle of FMT is to reintroduce the normal flora of the healthy gut of a donor to restore the balance of the recipient's gut flora.[5] This process restores the normal flora of the gut and strengthens the host defence against recurrent *Clostridium difficile* diarrhea and increases the *Bacteroidetes* species and other *Clostridia*. The possible first FMT randomized control trial (RCT) in 2013 compared an initial oral vancomycin regimen (500 mg QID for 4 days), followed by bowel lavage and donor feces solution infusion through a nasoduodenal tube; a standard oral vancomycin regimen (500 mg QID for 14 days); or a standard vancomycin regimen with bowel lavage. This study was stopped after interim analysis due to proven treatment benefit, as in resolution of diarrhea in 15 out of 16 patients in infusion group.[6] Another FMT clinical trial included 43 patients who were given 14 days of FMT via naso-intestinal tubes plus oral vancomycin, followed by oral vancomycin alone and another 14 days with vancomycin coupled with gastric lavage. Symptoms resolved in 81% of patients receiving FMT, 31% of whom were on vancomycin only and another 23% received vancomycin plus gastric lavage.[7] Currently, a number of RCTs are available, which directly compared FMT with either placebo or standard antimicrobial therapy with vancomycin or fidaxomicin for the treatment of recurrent CDI. These studies report efficacy rates of between 44 and 91% for a single treatment and up to 94% for two or more.[8] The possible risks of FMT include transmission of pathogens from donor and implantation of non-organismal elements into the recipient. Stringent donor selection, procurement of fecal sample, and meticulous preparation of final transplantable material are the significant challenges in FMT process. The Federal drug Agency of USA (USDA) in 2013, positioned FMT for recurrent CDI as a therapeutic intervention with patient's consent, and for other indications required an investigational new drug application. In November 2022, USFDA approved the first-ever microbiome therapeutic product with a defined consortium of microorganisms for preventing the recurrence of *C. difficile* infection in adults post-antibiotic treatment. Many European (EU) countries have regulated FMT as a drug, while Finland and UK regulate it as a therapeutic intervention, Italy as tissue and Canada as a biological drug. Some institutions are conducting FMT in India under research purpose, though regulatory approval as a therapeutic intervention is not given yet. According to research done in Mumbai, India has a prevalence rate that ranges from 7.1 to 26.6% with a much lower incidence of fulminant CDI in comparison to the western countries.[9] The European Study Group of *C. difficile* (ESGCD) reported the mean incidence of healthcare-associated CDI as 4.1 per 10,000 hospital patient days.[10] Recent epidemiological reports from the United States implied that *C. difficile* has replaced methicillin-resistant *Staphylococcus aureus* as the most common cause of the healthcare-associated infection.[11] Based on the several reports from US, Canada, and Europe, the incidence of CDI has increased by 2- to 4-fold in the past decade. Going by this data, there seems to be either lesser index of suspicion, or under-reporting of this HAI from our institutions.

Understandably, the cost of extended hospitalization and ensuing treatment is going to be quite burdensome for both the patient and the healthcare system. On the other hand, the resistance patterns of *C. difficile* to vancomycin and metronidazole

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is on the rise. The other drug of choice, fidaxomicin, is not yet available in India.[12] While there has been rapidly increasing number of research publications regarding *C. difficile*-related issues from western countries, there has been very little data emerging out of India. We are still to find out about its true incidence, nature of microbiota, their genomic analysis, their clinical application, and treatment outcomes. Sporadic case reports of FMT intervention for CDI, CDAD, and non-clostridial conditions like IBD such as ulcerative colitis have been published. From this perspective, a single center FMT study published in this edition of IJCCM[13] gains importance and serves as limited window to view these aspects in an Indian tertiary healthcare institution, where 13 hematopoietic stem cell transplant (HSCT) recipients with CDAD received FMT. The authors claim this to be the first study from India using FMT as a therapeutic modality for CDAD. The indications for FMT included: (i) refractory CDAD, (ii) recurrence of CDAD, (iii) presence of both CDAD and Graft versus host disease (GVHD). Resolution of CDAD after FMT was defined as complete cessation of diarrhea without administration of any anti-CDAD therapy or anti-motility agents for at least 48 hours. Either a nasojejunal or a colonoscopy approach was used for FMT implantation. One patient was excluded from this retrospective, observational study due to mortality due to non-infectious complication. Ten out of twelve patients (83%) had resolution of CDAD by the end of 2 weeks following FMT. While one patient had recurrence at 8 weeks, all the 12 patients studied were alive at the end of 28 days. Bacteremia and candidemia was reported in one patient each in first 2 weeks, which were unrelated to the FMT. These results are early and encouraging signs of a novel modality of therapy for the dreaded healthcare acquired infection, which is hopefully not as prevalent in our country as in the west. But, that is yet to be proven by further studies of all aspects of *C. difficile* in our country.

But there is lot of ground to be covered yet and a few hurdles to be crossed. Apart from the lack of regulatory approval, there are other limitations to FMT in India. The FMT donor is India is unlikely to be similar in various characteristics one in the western world. The flora of his fecal sample may be different in various aspects such as the species and their characteristics. There is always a risk of pathogenic multidrug-resistant (MDR) organisms colonized in the gastrointestinal tract of the donor. Then there is lack of technical facilities which are required for preparing a safe sample. In the initial stages, there was a perception that FMT may be very expensive taking into consideration the multiple donor screenings, sample preparation and implantation techniques such as endoscopies. But a recent study disproved this notion.[14] Further, if streamlined well, the cost in Indian setup would be far lower than western countries. If proved successful with further studies such as the one in this journal, therapy with FMT will be far more economical than the management of a drug-resistant hospital acquired infection with attendant complications. We are almost two millennia behind China in deploying "yellow soup," and it is time to catchup. One of the impediments for this therapy is a cultural and human factor. The concept of "consuming" another human's feces may not be acceptable, if not revolting to an average Indian. Regular news about research results of this area, targeted educational counseling and media exposure may bring about change in these attitudes. The small but significant study published in this journal[13] paves way for larger studies and research to be done in this area, not only for *C. difficile*-related issues but other diseases such as inflammatory bowel disorders, alcoholic hepatitis, autism and MDR enteric pathogens, about which case studies are being reported. A national registry for FMT interventions done in our country will also go a long way to have an oversight of this evolving therapy for various conditions, which are otherwise very vexing problems. Data coming from such research and registry may give impetus for quicker regulatory approval for FMT in our country, which will benefit larger population and reduce the burden on healthcare system.

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