Title page

Title: Single Session of Fecal Microbiota Transplantation in Decompensated Cirrhosis: An open-label randomized control trial

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INTRODUCTION

Cirrhosis of liver is the culmination point of long-standing chronic liver disease hallmarked by the cardinal features of liver fibrosis and portal hypertension. The prognosis of patients with cirrhosis is punctuated by the onset of complications which denote the stage of decompensation characterized by ascites, hepatic encephalopathy (HE) and variceal bleeding[1]. Onset of decompensation heralds concomitant complications like renal dysfunction, immune dysregulation, pulmonary and cardiac dysfunction as well as bacterial infections including spontaneous bacterial peritonitis accounting for significant morbidity and mortality[2].

The role of human gut microbiota in health and disease has recieved considerable attention.. The gut microbiome consists of over 1014 microorganisms, including bacteria, fungi, viruses and archaea, which co-exist in a symbiotic relationship.[3]A majority comprises anaerobic bacteria. A healthy gut microbiome enhances metabolism, resilience to infection and inflammation, and resistance to cancer and autoimmunity. The microbiome may mediate these effects by secretion of factors that modulate intestinal permeability, the mucus layer, epithelial cell function, innate and adaptive immunity and intestinal motility. A disruption of this microbial symbiosis is intestinal dysbiosis, which adversely affects these functions and is implicated in the pathogenesis of disease. The gut is connected to the liver by the portal tract, and hence qualitative and quantitative changes in the gut microbiome play a pivotal role in the pathogenesis of alcoholic liver disease, as well as other liver diseases.[3]

Patients with cirrhosis have been demonstarated to have significant changes in their gut microbiota characterized by alteration in the intestinal microbiome (gut dysbiosis) as well as small intestinal bacterial overgrowth (SIBO) [3, 4]. In a study with patients with cirrhosis from China it has been reported that the proportion of phylum *Bacteroidetes* was decreased, and those of *Proteobacteria* and *Fusobacteria*were highly enriched in the faeces of these patients.[5] On the other hand a study from the United States has shown higher prevalanceAlcaligeneceae,

Enterobacteriaceae, and Fusobacteriaceae while those belonging to Ruminococcaceae and Lachnospiraceae were found in a lower proportion.[6] In this perspective a proposed index called cirrhosis dysbiosis ratio (CDR)[8] of the amounts of beneficial autochthonous taxa (Lachnospiraceae + Ruminococaceae + Veillonellaceae + ClostridialesIncertaeSedis XIV) and potentially pathogenic taxa (Enterobacteriaceae + Bacteroidaceae) has been found to core-relate inversely with model of end-stage liver disease (MELD) score and 30 day mortality thus suggesting an integral role of gut dysbiosis in the prognostic outcome of cirrhosis.[8]

Gut dysbiosis has been closely linked to the complications associated with decompensated cirrhosis. Several studies have documented the alteration of gutmicrobiota in patients with hepatic encephalopathy. Liu et al found an overgrowth of potentially pathogenic Escherichia coli (E. coli) and Staphylococcus spp. in the feces of patients with liver cirrhosis (70%–80% related to HBV or HCV) and MHE.[9] Another study showed that patients with cirrhosis and HE had a higher abundance of fecal Enterobacteriaceae, and Alcaligenaceae compared with control subjects.[7]

Therapeutic modalities that restore normal gut flora and stabilize the gut liver axis are being extensively studied in the management of cirrhosis and its complications. Antibiotics, probiotics and long chain fatty acid supplementation are being evaluated as methods to restore gut eubiosis and consequently limit progressive liver damage.

Fecal Microbiota Transplantation (FMT) involves the infusion of intestinal microorganisms by the transfer of stool from a healthy individual into a diseased individual for restoration of normal intestinal flora.[10]Methods to infuse stool include a nasogastric tube or gastroscopy, or into the colon through a colonoscope or rectal catheter.[11] The ultimate goal of FMT is to replace aberrant native microbiota with a stable community of donor microorganisms. The treatment is based on the premise that an imbalance in the community of microorganisms residing in the gastrointestinal tract (i.e., dysbiosis) is associated with specific disease states. FMT has been well-established as a treatment modality to stably modify the gut microbiome and has been shown to be safe and efficacious in several disease states resulting from gut dysbiosis including Clostriumdifficile infection and inflammatory bowel disease.[12, 13]

With this background it is hypothesized that in patients with advanced cirrhosis FMT may reduce the progression to chronic liver failure including jaundice, accumulation of fluid

within the abdominal cavity, bleeding, encephalopathy and the development of infection and organ dysfunction. A trial is proposed to determine whether a FMT from a healthy donor to a patient with advanced cirrhosis is both feasible and safe and to assess its impact on overall survival and prognosis.

2. REVIEW OF LITERATURE

Microbiota refers to the bacteria, archaea, microeukaryotes, fungi and viruses that share the human body space, so as to function in a commensal, symbiotic, or pathogenic relationship with the host. The human microbiota is estimated to contain 10-100 trillion microbial cells.[14]

Microbiome refers to the collective genomes of all the above-mentioned microorganisms. The microbiome is commonly used interchangeably with microbiota – even though this usage is incorrect.[15] The gut microbiota is composed of 100 trillion bacteria of diverse taxonomy . The microbiome has 150-fold more genes than the human genome of which over 99% of the genes are bacterial which is why we study that what is predominant.[15]

Disruption of the healthy microbiota in both composition and functionality is dysbiosis – in which pathogenic species predominate leading to various disease conditions. The term pathogenic species in this context could be better utilized to an increase in numbers and functionality of those that promote/participate in deleterious functional metabolic outcomes that affect the host adversely rather thanjust the numbers of pathogenic species per say – for example pathogenic species such as E.coli and K.pneumonia are all normal components of the gut microbiota in healthy state (probably in lesser numbers) – however, in the presence of a modifying factor, say for example alcohol or high fat diet – their number and functions are adversely modified to promote adverse metabolism/metabolic product accumulation in the host.

Multiple studies have shown association of gut dysbiosis with cirrhosis and its complications. In a study from Wang et al FMT exerted protective effects in hepatic encephalopathy (HE) in rats, and improved the cognitive function with improvement of overall

the liver function indexes.[16] FMT may cure HE by altering the intestinal permeability and improving the TLR response of the liver. This study was the index study to establish a rat model of hepatic encephalopathy and then prospectively carried on the FMT. The results unequivocally hinted that FMT can serve as a kind of new method for the treatment of hepatic encephalopathy.

The first human report of utility of FMT in HE was shown by Kao et al where dramatic clinical improvements, both subjectively and objectively, following serial FMT were observed.[17] This case study demonstrated that serial FMT can result in cognitive improvement in mild HE.

Bajaj et al demonstrated the first trial that showed that FMT from a rationally selected donor reduced hospitalizations, improved cognition, and dysbiosis in cirrhosis with recurrent HE.[18] In this study a specified beneficial population of bacterial community from a stool bank was used.

The following table summarizes the some of the other major studies demonstrating the utility of FMT in cirrhosis

Authors	Methodology	Hallmarks of the study
Chen et al.2011	Controls vs. patients with alcoholic and hepatitis B cirrhosis	First major study of stool microbiome in cirrhosis. Showed that fecal microbiome in cirrhoticsis distinct, including increase in bacteroidetes (Bacteroidaceae) and proteobacteria and reductions in autochthonous taxa, such as Lachnospiraceae. Streptococcaceaeand positively correlated with cirrhosis severity.
Bajaj et al. 2012	Controls vs. all etiology OHE and no OHE cirrhosis.	First study of stool microbiome in cirrhotics with and without Overt Hepatic Encephalopathy (OHE) that looked at correlation-networkanalysis between microbiome, endotoxemia and cognition. HE was associated with reduced abundance ofLachnospiraceae and ruminococcaceae and increased

		Enterobacteriaceae. Increased inflammation andendotoxemiawere noted in HE groups..
Mutlu et al. 2012	Healthy controls vs. alcohol cirrhosis	Study of sigmoidal mucosa microbiome that showed lower median abundance of Bacteroidetes and increased median abundance of proteobacteria in alcoholic cirrhotics
Bajaj et al. 2012	Controls vs. all etiology OHE and no-OHE cirrhosis.	First major study to compare changes in sigmoid mucosal microbiome in all etiology with stool microbiota in cirrhotics with and without OHE. Mucosal microbiota analysis revealed increased enterococcus and Veillonella abundance in OHE. Roseburia was reduced in OHE and, along with other autochthonous microbes, showing positive co-relation with cognition and reduced inflammation in all groups. Enterococcus and Veillonella associated with poor cognition and inflammation.
Bajaj et al. 2014	Cirrhotics followed as outpatient(compensated and decompensated) and during inpatient decompensation.	First major study of cirrhosis stool microbiome comparing cirrhosis in compensated and decompensated state. Increased porphyromonadaceae, Bacterioidaceae, and Enterobacteriaceae with reduced Veillonellaceae, Ruminococcaceae, and Clostridiales XIV (Firmicutes) noted in compensated cirrhosis. Decompensation resulted in increased Enterobacteriaceae, Enterococcaceae, and Staphylococcaceae and reduced Bacterioidaceae. MELD score correlated negatively with Firmicutes and positively with Enterobacteriaceae. Introduction of CDR concept.
Bajaj et al.	Controls vs. all etiology cirrhosis studied before	First major study looking at the influence of PPI use on stool microbiota in cirrhosis. Streptococcaceae abundance was

2014	and after administration of PPI.	relatively increased in controls and cirrhotics after 14 days of PPI. First study that hypothesized oral microbiota could migrate distally secondary to change in intestinal protective mechanisms
Kakiyama et al. 2014	Controls vs. all etiology cirrhosis. Subgroups examined before and after rifaximin therapy.	First major study of role of BAs in gut microbiome modulation in cirrhosis. Showed increased Bacterioidaceae and reduced Veillonellaceae, Lachnospiraceae, and Ruminococcaceae in advanced cirrhosis. CDCA positively correlated with Enterobacteriaceae, while DCA positively correlated with Ruminococcaceae. Post rifaximin, early cirrhotics had reduced Veillonellaceae
Qin et al. 2014	Controls vs. all etiology cirrhosis followed over time.	Major study that cataloged human microbiome genes in cirrhotic stool samples. Increased Veillonella, Streptococcus, Clostridium, and Prevotella, with reduced bacteroides in cirrhosis.
Bajaj et al. 2015	Controls vs. all etiology cirrhosis with and without DM	Major study that compared stool and sigmoid mucosa microbiota in cirrhotics with and without DM. The study showed no change to in decompensated diabetic cirrhotics. Increased Enterococcaceae-relative abundance, reduced Bacteroidaceae, and increased Lactobacillaceae and Enterococcaceae were noted in compensated diabetic cirrhotics at the end of the study period.
Chen et al. 2015	Controls vs. all etiology cirrhosis with ACLF	Study evaluated stool microbiome of cirrhotics with ACLF. ACLF was associated with increased relative abundance of Pasteurellaceae, Streptococcaceae, and Enterococcaceae with decreased Bacterioidaceae, Lachnospiraceae, and Ruminococcaceae. OHE was associated with reduced Lachnospiraceae. On networkcorrelation analysis, strong linkage

		of Lachnospiraceae and Ruminococcacea
Bajaj et al. 2015	Controls vs. all etiology cirrhosis with and without OHE.	First major study that to explored stool and salivary microbiota in detail in all etiology cirrhotics and further explored the changes with decompensation. Significantly increased Enterobacteriaceae and Enterococcaceae, with reduced Lachnospiraceae, Ruminococcacea, and ClostridialesIncertaeSedis XIV noted in the saliva from compensated cirrhotics. Similar microbiota was noted to be prominent in cirrhotics with prior OHE. Streptococcaceae in the saliva was significantly higher in the stool for both groups.
Ahluwalia et al. 2016	Controls vs. alletiology cirrhosis withand without OHE.	Study looked at stool microbiota of cirrhotics with OHE. OHE patients had higher relative abundanceof autochthonous bacteria with higher abundance of Enterococcaceae, Staphylococcaceae,Porphyromonadaceae, and Lactobacillaceae. MR spectroscopy showed autochthonous taxa correlatednegatively and Enterobacteriaceae correlated positively with disease.

Methodologies for FMT

Initially, patients identified their own donors selected from family or friends. Subsequently, some institutions offered the option of an anonymous donor(s). This shifts the burden of donor identification from the patient, creates a pool of tested healthy donors with a track record of cure, and also avoids donors with shared genetic or environmental susceptibilities to the recipient. An approach of using highly filtered human microbiota mixed with a cryoprotectant and then frozen for storage at −80 °C until required for use. This processing removes the fecal smell and reduces the volume of the filtrate. Use of such a

standardized, purified tissue has been shown to have equivalent clinical efficacy in treatment of C difficle infections. [19]

Multiple routes of administration has been tried in FMT including naso-duodenal, transcolonoscopic, or enema based.A systematic review of FMT for C difficle suggested a lower success rate for upper gut administration (76 %), as compared with colonoscopy (89 %) and enema (95 %) administration.[11]

A recent analysis had similar findings, with a trend toward higher CDI resolution rates with lower GI, rather than upper GI, administration (91 % vs. 82 %) although no head-to-head comparison has yet been performed – however, in liver diseases, the routes are not defined, but duodeno-jejunal region has been shown to have maximal dysbiosis.[20]

3. AIMS AND OBJECTIVES

Research question

Does FMT improve liver functions, prevent complications, reduce levels of pro-inflammatory cytokines and lead to an improvement in prognostic scores (CTP, MELD, MELD Na) and short-term survival in patients with DC?

Study Hypothesis:

In patients with DC, FMT may improve liver functions, prevent complications, reduce levels of pro-inflammatory cytokines and lead to an improvement in prognostic scores (CTP, MELD, MELD Na) and 180-day survival.

Aim:

To determine the role of FMT in improving liver function, prognostic scores, and short term mortality and reducing complications in patients with DC

Objectives:

Primary Objective: To assess the difference in 180-day mortality between the FMT group and the SOC group.

Secondary Objective

1. To assess and compare the changes in liver function in both groups based upon

- CTP score at 28 days, 90 days and 180 days
- MELD Score at 28 days, 90 days and 180 days
- MELD Na Score at 28 days, 90 days and 180 days

2. To compare the complications in both groups in a follow-up period of 180 days

3. Changes in inflammatory markers (IL-1b, IL-6) in both groups at 28 days

4. METHODOLOGY

Study design: This will be an institute based prospective pilot study carried out in Postgraduate Institute of Medical Education and Research, Chandigarh from July 2018 to June 2020.

Study period: 15 months (from August 2018 to November 2019)

Recruitment Period: 10 months (August 2018 to May 2019)

Sample Size: 20 consecutive patients satisfying the selection criteria in each arm

Study population

All patients with decompensated cirrhosis who will be admitted to the Department of Hepatology in Medical Ward Unit or Liver ICU of Postgraduate Institute of Medical Education and Research (PGIMER) or will be attending the outpatient department of PGIMER during the period from August 2018 till May 2019 will be screened for eligibility for enrollment after ethical approval from the institute ethics committee. An informed consent will be taken from all the participants. Those patients who satisfy the inclusion and exclusion criteria and provide a valid informed consent will be enrolled in the study.

Inclusion Criteria

1. 18-75 years
2. Confirmed advanced cirrhosis of any aetiology with a MELD score between 12 and 21. The diagnosis of liver cirrhosis will be based on clinical, radiological, or histological criteria
3. Patients must be deemed to have capacity to consent to study.

Exclusion Criteria

1. Ongoing bacterial infection requiring antibiotic treatment.
2. Current or history of significant alcohol consumption for a period of more than 2 consecutive months within 6 months prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average).
3. Treatment with antibiotics or probiotics in the preceding 14 days
4. History of recent spontaneous bacterial peritonitis , gastrointestinal bleeding or overt hepatic encephalopathy (14 days)
5. Previous Liver Transplantation
6. Hepatocellular Carcinoma
7. Human Immunodeficiency Virus (HIV) infection
8. Active or serious medical disease with likely life expectancy less than 5 years
9. Active substance abuse including inhaled or injection drugs in the year prior to screening.
10. Pregnancy, planned pregnancy, potential for pregnancy and unwillingness to use effective birth control during the trial, breast feeding

11. History of severe (anaphylactic) food allergy
12. History of gastroparesis or altered gastric motility
13. Psychiatric disorder
14. Inflammatory bowel disease (IBD)
15. Coeliac disease
16. Immunosuppression e.g. more than two weeks treatment with corticosteroids within 8 weeks of active treatment with tacrolimus, mycophenylate, azathioprine
17. Any other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study

Randomization of patients

Patients with decompensated cirrhosis who will be enrolled in the study after satisfying the selection criteria will be randomized into two groups 1:1 ratio using a random number generator

Group 1(Experimental Arm): Patients with decompensated cirrhosis who will receive Fecal MicrobiotaTransplantation via nasojejunal tube as well as traditional treatment for decompensated cirrhosis.

Group 1(Standard of Care Arm): Patients with decompensated cirrhosis who will receive standard medical treatment for decompensated cirrhosis.

Pre FMT

Participants randomized to the FMT arm will be given pretreatment antibiotics to decrease the host bacterial load, lower diversity, and enable a colonic colonizationof the donor microbiota.Lactulose and rifaximin will becontinued for all patients as per indication. A 5-day broad-spectrum coverage regimen will be used (metronidazole 500 mg orally three timesdaily, ciprofloxacin 500 mg orally twice-daily, andamoxicillin 500 mg orally three times daily) prior to admisnistration of FMT. All antibiotics will be discontinued at least 12 hours before FMTto ensure that these agents would not impact theinstilled microbiota.Participants in the SOC arm will not receive antibiotic pretreatment or FMT,but follow-up will be identical on days 7, 30 and 90 post FMT.postrandomization

DonorSelection Criteria:

Family members will be interviewed and screened for eligibility for being a FMT donor since pooled stool donor facility is not available at our institute. The subjects will be screened for routine laboratory tests, hemogram, fasting blood sugar, liver function tests, lipid profile, stool routine and microscopy for cysts, parasites, ova stool for occult blood, stool cultures, HBsAg, anti HCV, HIV 1 and 2, Clostridium difficile and VDRL. A written informed consent will be taken from the donor to donate fresh stool sample on day of FMT. Donors will be excluded if they had abnormal bowel motions, abdominal complaints, extensive travel history or predisposing factors for potentially transmittable diseases, occasional or chronic alcohol intake, and history of substance abuse or fail to provide consent. Subjects will also excluded if they are less than 18 or more than 60 years of age, had primary or secondary immunosuppressed state, had enteric infections within last 2 months, history of inflammatory bowel disease, prior abdominal surgery, pancreatic disease, gastrointestinal neoplasms in the past, metabolic syndrome, systemic autoimmunity, atopic diseases or on treatment for the same, food and respiratory allergies, chronic neurologic disorders, neuro-developmental disorders, have had antibiotics within the last 2 months. Donors will be advised to eat food based on recommended daily allowance as calculated by dietician and not permitted to eat street foods or attend public functions or eat at family functions or parties. They will not be allowed social consumption of alcohol or tobacco during a period of one week.

Preparation of Donor Stool

Donors will be advised to collect and submit fresh stool sample on the day of FMT after arriving at the hospital in sterile plastic collection containers. All stool samples will be obtained 6 hours before the procedure. Stool specimen (preferably Bristol Stool Type 4 or 5) with a weight of ~30 g (about ~ 2 cm^3) will be considered adequate. 100 mL of sterile normal saline will be added to the stool sample and homogenized with a blender (Morphy Richards ® HBCP Hand Blender @https://www.amazon.in/Morphy-Richards-HBCP-400-Watt-Blender/dp/B0073QIN6C) for 2-4 minutes in pulses of 30 seconds with 10 seconds wait in between each pulse. The homogenous suspension will be then filtered through sterile

gauze pieces, 3-4 times until the filtrate was devoid of roughage. Personnel involved in stool specimen preparation will be required to wear eye shield, masks and fluid resistant gowns.

The FMT Procedure

In the Fecal Microbiota Transplantation procedure 100 ml volume of strained and filtered stool will be delivered through a nasojejunal tube.The recipient patient will be kept nil per oral for at least 4 hours prior to the stool instillation. 100 mL of freshly prepared stool suspension will be given. IV antibiotics will be continued as per treating physician's decision in the event of active sepsis based on culture and sensitivity. The duodenal tube will be flushed with normal saline (30mL) after the stool instillation. The patient will be allowed to consume liquid diet two hours after the procedure. All patients will continue on salt restriction, diuretics, and 1.5g/kg per day of plant and egg based protein and weight based recommended calorie intake as prescribed by the dietician. Intravenous albumin will be continued as indicated during hospitalized period. While rifaximinand other non-absorbable antibiotics will be withheld, disaccharides will be permitted to have 2-3 soft stools per day.

Follow Up post FMT

Follow up of patients will be done at at 7, 30 ,90 and 180 days post FMT. During follow up patients will be evaluated for clinical parameters, routine biochemical monitoring and inflammatory markers for determining status of disease status.

Clinical and Laboratory Assessment

All patients will undergo a detailed clinical evaluation including history and physical examination, and routine biochemical and imaging evaluation. Investigations for etiology of cirrhosis will be performed as required on a case by case basis. Patients will be worked up for chronic liver disease with proper history, clinical examination and investigations which will include viral markers (HbsAg, Anti-HCV, Total anti-Hbc, AIH markers (ANA/SMA/LKM), serum ceruloplasmin, iron profile, celiac work up, NAFLD work up and radiological investigations for cirrhosis and as otherwise indicate

Management post FMT

All patients (experimental arm as well standard of care arm) will be managed by standard medical management in the department of Hepatology, PGIMER. Antibiotics will be given as per protocol and subsequently upgraded according to culture and sensitivity reports. Acute kidney injury will be managed with intravenous 20% human albumin with vasoactive agents if needed and dialysis when indicated. Patients with hepatic encephalopathy will be treated with lactulose and rifaximin. Diuretics will be given for ascites if not precluded by renal failure or hepatic encephalopathy. Inotropes will be given for hypotension and endotracheal intubation with mechanical ventilation will be done for respiratory failure as well as for airway protection for advanced HE.

Assessment of Pro-inflammatory Cytokines

Cytokines (,interleukin [IL]1b, and IL6 will be measured in plasma derived from cirrhoticpatients using specific enzyme-linked immunosorbent assaykits (RayBiotech, Inc, Norcross, GA) according to the manufacturer's protocol. The plate will be read at 450 nm. Absorbance will be converted to picograms per milliliter using a standardcurve prepared with recombinant human IL1b, IL6. Measures will be taken at base line and 28 days post FMT.

4. STATISTICAL ANALYSIS

The results will be expressed as mean ± standard deviation (SD) or median with range. Comparisons between groups will be performed using student's t-test or the Mann–Whitney U test. For categorical data chi-square test or Fisher's exact test will be applied. A value of $P < 0.05$ will be taken as significant. The results will be analyzed at baseline and at day 7, 30 and 90 of the study. The in hospital survival curves will be made by the Kaplan-Meier method and compared with the log-rank test. All statistical tests will be done by Microsoft Excel and SSPSS Software version 18.

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ANNEXURE 1

ETHICAL CONSIDERATION

According to guideline setup by ICMR (2000) and Helsinki declaration (modified 2008) the following will be adhered to in all patients/ volunteers involved in the study.

1. All the possible treatment options will be given and none will be withheld.

2. Patients will be enrolled in the study with their knowledge, and study will be done by utilizing known investigation modalities, regarding which proper information will be provided to the patients.

3. Patient will be informed about all the major and minor risk factors and the remedies thereof and a refusal to participate in this study will not interfere with patient-doctor relationship.

4. Patient will be given the option of quitting from the study at any point during the study if he or she so desires and no element of compulsion will be exerted.

5. Confidentiality of data collected from contribution source or individual will be maintained.

6. Written informed consent will be obtained from all the patients included in the study after informing them about the aims and method of the study and the institutional affiliation of the researcher.

7. In the cases where the patients are legally incompetent minors or are not eligible for giving consent due to poor neurological status, consent of the close relative available will be taken.

8. There will be no difference in the management of the patients and all the patients will be treated by standard protocol of the Department of Hepatology, PGIMER, Chandigarh in the best interest of the patient.

9. In publication of the results of this study all efforts would be made to preserve the accuracy of both the positive and negative results of this study.

10. At conclusion of study every patient entered in to this study will be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by this study.

This study titled has been planned with due ethical justification and the study will be completed in accordance with the ICMR guidelines.

ANNEXURE

PATIENT CONSENT FORM

Fecal Single Session of Fecal Microbiota Transplantation in Decompensated Cirrhosis: An open-label randomized control trial

Name of the participant: _____

Name of the Investigator: DrAkash Roy

Name of the Institution: PGIMER, Chandigarh

Documentation of the informed consent

Consent for Fecal Microbiota Transplantation (FMT)

1. I _____ or _____ for
(Patient name) (Legal guardian)

_____ authorize the performance of FMT to be administered by
(Patient name)

Dr. _____ and/or his assistants or designees.

2. I understand that FMT may be performed through a nasoduodenal tube inserted via the nose into the first part of the small intestine. FMT is administered to treat decompensated cirrhosis. FMT consists of introducing normal bacterial flora contained in stool collected from a healthy donor into the diseased gut where the flora is missing.

3. The nature, purpose, risks and benefits of this procedure has been discussed with me. I understand that the donor will be screened for a possible history of exposure to a communicable infectious agents through a detailed health questionnaire, and also undergo blood and feces testing for occult infectious pathogens as some infectious diseases may be silent or clinically undetectable.

I have discussed all alternative treatments for decompensated cirrhosis with my physician, and understand the risk and benefits of the alternative treatments. I understand that my condition could improve, worsen or stay the same with each of the alternative treatment options, including FMT. I understand that individuals who are severely ill with FMT have a high risk of dying from their illness, regardless of what treatment is used. I understand that at the current time the cumulative experience with FMT is limited and that FMT is therefore considered investigational.

In choosing to proceed with FMT I understand that a solution of donor stool will be infused into the beginning of my small intestinal tract via a hollow tube inserted through the nose

4. The risks of FMT procedure has been discussed in detail with me. I understand that complications may arise as a result of FMT. Complications may include but are not limited to:

- ·Transmission of infectious organisms contained in stool (bacteria, viruses, fungi, parasites)
- ·Allergic reactions to constituents (antigens) contained in the donor stool
- ·Mechanical complication related to the insertion and presence of the tube, such as potential perforation of the lining of the esophagus, stomach, or duodenum, or aspiration of stool into the lungs (for the nasoduodenal tube)

I understand that the outline above is not a complete list of potential complications, and that unforeseen risks that have not been discussed with me may exist.

5.I understand that the above risks, as well as other complications, may require additional procedures or operations and that these issues have been discussed with me. I give my consent to undergo additional procedures which my physician deems necessary.

6.I am aware that the practice of medicine is not an exact science. I acknowledge that no guarantee or promise can be made by my physician as to the outcome of my treatment.

7.I acknowledge that the entire content of this form has been explained to me, and that I understand the contents.
I have had the opportunity to ask questions, and all of my questions have been answered to my satisfaction.

Signature: _____
Date _____ Time _____

(Patient or legal guardian)

Signature: _____ Date _____ Time _____

(Stool donor)

Provider's Acknowledgement:

I confirm that I have fully explained to the above patient or legal representative the nature and purpose of Fecal Microbiota Transplantation and the possible risks and benefits of FMT and treatment alternatives.

Printed name:
_____
(Provider)

Signature: _____
(Provider)

Date: _____ Time: _____

Interpreter's Acknowledgement (when applicable):

I confirm that consent to proceed with FMT, as explained above, has been given by this patient or legal guardian.

Printed name: _____ Signature: _____
(Interpreter) (Interpreter)

ANNEXURE

INFORMED CONSENT FORM-DONOR

I ,.....EXERCISING MY FREE POWER OF CHOICE HEREBY

GIVE MY CONSENT TO BE INCLUDED AS A FECAL DONOR IN THE STUDY of "Single Session of Fecal Microbiota Transplantation in Decompensated Cirrhosis: An open-label randomized control trial

" I have been informed to my satisfaction by the attending physician the purpose of the study and the nature of the test to be done.

I have been informed that there will be no payment for participation in this study. My patient's identity shall be kept confidential and in case the data is published, identity shall not be revealed. I also understand that participation in the study is entirely voluntary and I am / my patient is free to opt out of the study at any point of time without having to give reasons for doing so and this will not jeopardize my patient receiving treatment in the future. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and my questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate in this research.

ANNEXURE- II

PATIENT INFORMATION FORM

TITLE: - Single Session of Fecal Microbiota Transplantation in Decompensated Cirrhosis: An open-label randomized control trial

Name of Participant: .....

You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

The purpose of this research is to assess how fecal microbiota transplantation from a healthy donor to a patient with decompensated cirrhosis affects their overall prognosis, by means of assessing parameters of prognosis commonly used in patients of liver disease, as well as their survival at 3 months so that this could aid in the future management of similar patients with fecal microbiota transplantation so that the overall mortality and morbidity could be benefitted.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

The alternatives you have

If you do not wish to participate, you still will get the standard treatment for your condition.

Compensation: Nil

Reimbursement: You will not be paid to participate in this research study.

What should you do in case of injury or a medical problem during this research study?

Your safety is the prime concern of the research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form. You will be provided the required care/treatment.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, its advisable that you talk to the research team prior to stopping the treatment. You may be advised about how best to stop the treatment safely. If you withdraw, you may be asked to undergo some additional tests to which you may or may not agree. Though advisable that you give the investigators the reason for withdrawing, it is not mandatory.

Can the investigator take you off the study?

You may be taken off the study without your consent if you do not follow instructions of the investigators or the research team or if the investigator thinks that further participation may cause you harm.

Right to new information

If the research team gets any new information during this research study that may affect your decision to continue participating in the study, or may raise some doubts, you will be told about that information.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, institutional ethics committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

Contact Persons:

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