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Fecal microbiota therapy in recurrent and refractory clostridium difficile infections has been associated with positive results in immunocompromised patients

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Fecal microbiota therapy in recurrent and refractory clostridium difficile infections has been associated with positive results in immunocompromised patients

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ABSTRACT A critical appraisal and clinical application of Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. *The American Journal of Gastroenterology*, 2014;*109*(7):1065-71. doi: 10.1038/ajg.2014.133.

Keywords: *fecal microbiota transplantation, clostridium difficile, immunocompromised, HIV, AIDS*

Clinical Context

Michael Thomas (pseudonym), a 56 year-old man with a past medical history of medical non-adherence, Intravenous drug use, poorly controlled HIV/AIDS (with a CD4 count of 52), and stage IV chronic kidney disease originally presented to a major urban emergency department after being found lying on the ground confused. He was admitted to the floor for concerns of acute encephalopathy of unknown etiology. Mr. Thomas underwent a complicated hospital course. He was found to have cryptococcal meningitis, developed acute respiratory distress as well as bacteremia, and was treated with multiple different antibiotics. He later would develop further episodes of bacteremia as well as an empyema. Throughout his hospitalization, he was treated with multiple broad-spectrum antibiotics, he received a tracheostomy as well as a percutaneous endoscopic gastrostomy tube for a total hospital stay of greater than 2 months.

About 4 weeks into his hospital stay, Mr. Thomas began having severe watery diarrhea and PCR for Clostridium Difficile returned positive. He was started on oral Vancomycin 125mg every 6 hours for a 14-day course for treatment of a Clostridium difficile infection (CDI). During the 14-day course, Mr. Thomas had some resolution of symptoms; however, by the end of the course his watery diarrhea had returned. Mr. Thomas was then started on a 12-day course of Fidaxomicin 200mg twice daily for treatment of the now treatment resistant CDI. Throughout the duration of this course of Fidaxomicin, the patient continued to experience watery diarrhea. Our Infectious Disease team was then consulted for recommendations of treatment resistant CDI. After discussing different options for therapy, it was decided that the patient was to be restarted on oral Vancomycin 12mg every 6 hours which was to be continued 5 days beyond the last day of parenteral antibiotics the patient received during hospitalization. The Infectious disease team also discussed the possibility of recommending a fecal microbiota transplantation (FMT) for therapy in treatment resistant CDI in the immunocompromised population. Discussions with Mr. Thomas concerning this option of therapy would have been beneficial but could not be performed due to his's clinical status. The option was discussed and explored further.

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Clinical Question

What is the efficacy and safety of FMT for the treatment of CDI in a patient who is immunocompromised secondary to HIV/AIDS?

Research Article

Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. *The American Journal of Gastroenterology*, 2014;109(7):1065-1071. doi: 10.1038/ajg.2014.133

Related Literature

A literature search was then conducted utilizing Pubmed. The keywords “clostridium difficile” and “fecal transplant” and “HIV” were used yielding seven results. Of these results there were no articles that discussed fecal transplantation in HIV individuals specifically but only as a subgroup in an immunocompromised population. The keywords “clostridium difficile” and “fecal microbiota transplant” and “immunocompromised” were then used overlapping many of the results from the previous search. Overall, 24 results were found and, of those results, there were no randomized control trials or prospective cohort studies.

Articles were rejected if they focused on a specific immunocompromised population outside of HIV such as patients with Inflammatory Bowel Disease (IBD)[1] or patients with solid organ transplants(SOT).[2] These were rejected as they did not align with the etiology of the patient’s immunocompromised state. Articles were also rejected if they did not focus on the efficacy or safety of using FMT in the immunocompromised population. For example: some articles discussed the way the FMT was performed[3,4] or the patients perspective on FMT.[5]

A systematic review was published on this topic in September 2018 gathering information for 44 different case reports, case series, and retrospective studies.[6] The review looked at both the efficacy and safety FMT in immunocompromised patients. It gathered information on 243 immunocompromised patients treated for CDI with FMT that 93% experienced successful treatment after one or multiple FMT. When it comes to adverse events there were 19 reported including 2 deaths. The 44 articles cited by this paper were also reviewed. The majority were case studies or case series which were too small on their own to make any conclusions. One larger cohort study was not selected as it was specifically focused on patients who were immunocompromised secondary to treatment for IBD.[7]

A retrospective study conducted at a single institution by Alrabaa, S et al. looked at outcomes of fecal microbiota transplantation in immunocompetent compared with immunocompromised individuals.[8] 13 patients qualified for this study: 6 were immunocompetent and 7 were immunocompromised. This study was not chosen due to its small sample size and therefore decreased power.

Another single-center retrospective study conducted by Mandalia, A et al. compared immunocompromised patients with immunocompetent patients who received FMT for the treatment of recurrent or refractory CDI.[9] The study was unable to find a difference in either efficacy or safety of FMT for CDI between the immunocompromised and immunocompetent populations. This study was not chosen as it did not provide specific data on the characteristics of the patient population selected. With this information lacking it was difficult to determine if our patient was similar to the patients included in this study.

Critical Appraisal

A retrospective cohort study which collected data from multiple centers was conducted by Kelly, C et al and published in 2014.[10] Their team looked at the efficacy and rates of adverse events in immunocompromised patients treated for CDI with FMT. This study provides level 3 evidence according to the Oxford Center for Evidence-Based Medicine as it is a retrospective cohort study.[11,12]

When it was published, this study was the largest cohort study to look at efficacy and safety FMT in immunocompromised patients suffering from CDI. This study’s purpose was to establish baseline observational data and to identify any dramatic correlations. It also acknowledged its own limitations and the need for further, more definitive data.

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The study included 16 different facilities who all used a standardized protocol to identify immunocompromised patients who received FMT for the treatment of recurrent, refractory, severe, or complicated CDI. Patients qualified for the study if they had met one or more of the set definitions for recurrent, refractory, severe, or complicated clostridium difficile infections established by the American College of Gastroenterology. Patients were determined to be immunocompromised based on set inclusion criteria: an established HIV infection despite CD4 count, AIDS with CD4 count of less than 200, another inherited or primary immune disorder, or a medical condition for which patient is currently taking or has received in the past 3 months treatment with an anti-neoplastic or immunosuppressant medication. The study also required that 12 weeks of follow-up information after administration of the FMT be available for each patient. This was to capture any likely recurrence of signs and symptoms of infection as well as possible related adverse events.

This study design looks at a very diverse patient population of which our patient would be included. However, such a diverse population introduces many potential confounding variables. Although potentially outside of the scope of this paper, it does limit the usefulness of the information in establishing correlations between the population and the results. The diversity of the inclusion criteria for the immunocompromised status allows the paper to reach more people at the cost of specificity of correlations.

The primary goals of the study were to look at the cure-rate from the infection (resolution of diarrhea and no need for further therapy for the infection) and to document the rate of adverse events that occurred. All adverse events were recorded whether the events seemed to be related or unrelated. Adverse events were further stratified between “adverse events” (Any clinically evident changes from a patient’s baseline status whether that be signs or symptoms related or unrelated to the fecal transplant) and “severe adverse events” (any death, life-threatening event, or unintended hospitalization).

This paper effectively measures the observed efficacy of therapy in the population studied. This information is helpful is determining a correlation between therapy and resolution of symptoms.

The paper is limited in determining the degree of adverse events experienced by the patients receiving FMT. Without a control population it is difficult to determine whether the adverse events reported were secondary to the therapy or were unrelated to therapy.

The study included 80 patients. 94% of the patients were adults with 6% pediatric patients. The mean age of the adult patients was 53 years of age. All of the patients were immunocompromised albeit for different reasons: 45% were on immunosuppressants for IBD, 24% were solid organ transplant recipients, 19% with specified chronic medical conditions (eg. Rheumatoid arthritis), 9% with cancer being treated or having been treated with antineoplastic within 3 months of fecal transplantation, and 3% were immunocompromised due to HIV/AIDS. 55% of patients were treated for recurrent infection, 11% for a refractory infection, 1% for a severe or complicated infection, and 33% for some combination of the previous indications.

The number of patients included in the study was an important factor in deciding to review this article. This population size was among the largest found decreasing the likelihood of a type II error.

The two primary outcomes for the study were efficacy and safety of fecal transplantation in immunocompromised patients. The study showed the overall success rate using FMT in their population was 89%. Adverse events occurred in 24 (30%) patients. Of those 24, twelve were reported as having severe adverse events with two patient deaths recorded. One death occurred 13 days after fecal transplantation and was due to a progressive pneumonia. The other was due to respiratory failure secondary to aspiration which occurred while the patient was being anesthetized for the fecal transplant procedure. Other adverse events ranged from nausea to catheter infection.

As a retrospective study there were many innate limitations to the conclusions that could be made pertaining to the results from the study. This is seen most evidently in the adverse events reported with no control group to compare the information to. However, this study has provided the medical community with a foundation of preliminary data in which further research can be performed. It has shown that the treatment of recurrent, refractory, severe, and/or complicated CDI with FMT was associated with a resolution of 89% of CDI in immunocompromised patients. The study also showed that, although the adverse events could not definitively be assessed as relating to FMT or not, there were likely minimal severe adverse events associated with the action of FMT itself ignoring the procedural component of the therapy.

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Clinical Application

The study conducted by Kelly C, et al. gave basic safety and efficacy data that aided in the clinical decision to pursue fecal transplantation.[10] Although Mr. Thomas was not specifically well represented by population collected in the study, there was data to show that similar patients with decreased immune systems had successfully undergone therapy with fecal transplant in the past with limited adverse effects. Also, the consequences of continuing current therapy that had shown few results up to this point were also considered. Unfortunately, at the time of the infectious disease consultation for the patient's Clostridium difficile infection, the patient's clinical status had deteriorated causing him to be sedated, ventilated via a tracheostomy tube, and placed in the medical ICU. This made communication with Mr. Thomas difficult. The decision was made to recommend the primary to consult the physician in charge of fecal microbiota transplantation at the hospital in question. The infectious disease team decided that fecal transplant was would be an appropriate next step in therapy for his infection.

Learning points:

1. Treatment of refractory clostridium difficile infections with fecal microbiota transplantation has been shown to be associated with positive outcomes and few adverse events although more research must be done to further this question.

2. Clostridium difficile infections are more commonly seen in immunocompromised individuals compared with immunocompetent individuals.

3. Retrospective studies can be used but must be used with caution when making medical decisions.

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