Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis

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CRD summary

This review evaluated the safety and efficacy of faecal microbiota transplantation in patients with *Clostridium difficile* infection. The authors concluded that this treatment had considerable promise in patients with recurrent infection, but results were based largely on non-controlled observational data. Well-designed randomised controlled trials were recommended. The authors' cautious conclusion is likely to be reliable.

Authors' objectives

To evaluate the safety and efficacy of faecal microbiota transplantation in patients with *Clostridium difficile (C. difficile)* infection.

Searching

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched (1946 to March 2012) for full text, peer-reviewed publications in any language. Search terms were reported. The bibliographies of relevant papers were searched for additional studies.

Study selection

Eligible for inclusion were studies of faecal microbiota transplantation via any delivery modality in patients with laboratory or endoscopically confirmed *C. difficile* infection. The primary outcome of interest was clinical resolution of diarrhoea (regardless of the number of faecal microbiota transplantation per patient). Case series were included, provided there were 10 or more patients.

Most studies included in-patient and ambulatory patients. The mean/median age was over 65 years, and most patients were women. Co-morbidities, *C. difficile* strain type and whether infection was acquired in a health-care facility or community setting were not well reported. Approximately half of the studies focused on recurrent *C. difficile* (defined by the authors). Most studies used patient-selected donors (spouse or close relative). Faecal microbiota transplantation delivery modality varied, with approximately half focusing only on colonoscopy. Other modalities included gastronomy tube, gastroscopy, nasogastric/nasojejunal delivery and retention enema. Faecal microbiota transplantation dose and protocols also varied, and the timing of the intervention (where reported) ranged from six to 24 hours after stool donation. Second faecal microbiota transplantations were administered in some cases of clinical failure.

Two reviewers independently selected the studies for inclusion.

Assessment of study quality

The assessment of study quality was based on checklists from the Centre for Reviews and Dissemination (CRD), and (for case series) the National Institute of Clinical Excellence (NICE). The NICE total score (maximum eight points) was used for subgroup analysis (a total score of at least four was considered to be higher quality; lower than four was low quality).

Two reviewers independently assessed study quality.

Data extraction

Data were extracted to enable the calculation of clinical resolution rates. Data on adverse events were also collected.

Two reviewers independently extracted the data. A third reviewer compared the data extraction forms. A fourth reviewer resolved any discrepancies, where necessary.

Methods of synthesis

Unweighted and weighted pooled clinical resolution rates, with 95% confidence intervals, were calculated using random-

effects meta-analysis (DerSimonian and Laird). Statistical heterogeneity was assessed using Cochrane Q and the I^2 statistic ($Q < 0.10$ or $I^2 > 50\%$ represented significant heterogeneity). Subgroup analyses were carried out using the unweighted and weighted proportion difference to compare upper and lower gastrointestinal delivery, type of donor, and the impact of study quality.

Results of the review

Eleven studies (273 patients) were included in the review. There were no randomised controlled trials; data were derived largely from non-controlled observational studies. None of the studies met all of the CRD criteria. None of the studies scored eight using NICE criteria (seven studies scored 4 or more, and four studies scored less than 4). Follow-up ranged from three weeks to eight years.

Faecal microbiota transplantation achieved clinical resolution in 245 out of 273 patients. The weighted pooled resolution rate was 89.1% (95% CI 84.0% to 93.3%; 11 studies; I^2=33.7%). Success rates were similar when data were re-examined using the review authors interpretation of clinical resolution.

In subgroup analyses, lower gastrointestinal delivery (using colonoscopy/enema) of faecal microbiota transplantation was favoured compared with upper gastrointestinal delivery (un-weighted rate proportion difference 9.1%, 95% CI -0.1% to 22.1%; weighted rate proportion difference was not statistically significant). Higher quality studies showed significantly improved clinical resolution compared with lower quality studies (un-weighted rate proportion difference 11.7%, 95% CI 3.7% to 21.5%; weighted rate proportion difference 12.3%, 95% CI 3.5% to 21.1%). There were no statistically significant differences in clinical resolution rate between patient-selected versus anonymous healthy donors.

There were no adverse events related to faecal microbiota transplantation, but this was not a primary outcome in any of the studies.

Authors' conclusions

Faecal microbiota transplantation had considerable promise as a therapy for recurrent *C. difficile* infection.

CRD commentary

The research question was clear and inclusion criteria were potentially reproducible. Appropriate databases were searched, and attempts were made to minimise language bias. There was no apparent search for unpublished studies and no assessment of publication bias, which meant that relevant studies might have been overlooked. The review process was conducted with sufficient rigour to minimise error and bias. Appropriate quality assessment criteria were applied to the included studies. The clinical variability of study characteristics did not appear to have impacted on the main finding in terms of statistical heterogeneity, and the chosen method of synthesis seemed appropriate.

The authors' cautious conclusion reflects the evidence presented and is likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that the efficacy and safety profile of faecal microbiota transplantation needed to be confirmed in the appropriate population before the approach could be widely advocated. Where this treatment was administered, patients should be counselled on the known and unknown risks.

Research: The authors stated that well-designed randomised controlled trials with long-term follow-up registries were needed, along with cost-effectiveness evaluations on faecal microbiota transplantation. Future research should include *C. difficile* strain typing. It should also seek to establish the definition of recurrent *C. difficile* infection and develop methods to distinguish this from post-infectious irritable bowel syndrome.

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