The 'ins and outs' of faecal microbiota transplant for recurrent *Clostridium difficile* diarrhoea at Wits Donald Gordon Medical Centre, Johannesburg, South Africa

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Background. *Clostridium difficile*-associated diarrhoea (CDAD) is a potentially life-threatening condition that is becoming increasingly common. A persistent burden of this infectious illness has been demonstrated over the past 4 years at Wits Donald Gordon Medical Centre (WDGMC), Johannesburg, South Africa, through implementation of active surveillance of hospital-acquired infections as part of the infection prevention and control programme. Oral treatment with metronidazole or vancomycin is recommended, but there is a major problem with symptomatic recurrence after treatment. Replacement of normal flora by the administration of donor stool through colonoscopy or nasogastric/duodenal routes is becoming increasingly popular.
Objectives. To identify risk factors for the development of CDAD in patients referred for faecal microbiota transplant (FMT) and evaluate the safety of administration of donor stool as an outpatient procedure, including via the nasogastric route.
Methods. A retrospective record review of patients with recurrent CDAD referred for FMT at WDGMC between 1 January 2012 and 31 December 2016 was conducted.
Results. Twenty-seven patients were identified, all of whom fulfilled the criteria for recurrent CDAD. One-third were aged >65 years, and the majority were female. The most common risk factors were prior exposure to antibiotics or proton-pump inhibitors and underlying inflammatory bowel disease. Three procedures were carried out as inpatients and 24 in the outpatient gastroenterology unit. At 4-week follow-up, all patients reported clinical resolution of their diarrhoea after a single treatment and there were no recurrences. The FMT procedure was associated with no morbidity (with particular reference to the risk of aspiration when administered via the nasogastric route) or mortality.
Conclusions. This case series confirms that FMT is a safe and effective therapy for recurrent CDAD. In most cases it can be administered via the nasogastric route in the outpatient department. We propose that the recently published South African Gastroenterology Society guidelines be reviewed with regard to recommendations for the route of administration of FMT and hospital admission. Meticulous prescription practice by clinicians practising in hospitals and outpatient settings, with particular attention to antimicrobials and chronic medication, is urgently required to prevent this debilitating and potentially life-threatening condition.

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Clostridium difficile-associated diarrhoea (CDAD) is becoming increasingly common. It is a potentially life-threatening condition with mortality as high as 33% and a 28% possibility of relapse.[1] Risk factors for acquiring CDAD include increasing age (>65 years), multiple antibiotic treatments, lengthy stays in hospital and concurrent proton-pump inhibitor (PPI) therapy.[2] Most infections are healthcare associated, occurring in hospitals and long-term care facilities, but outpatient acquisition has also been described.[3] The disease is spread via the faecal-oral route by ingestion of acid-resistant spores. Meticulous hand hygiene on the part of of healthcare workers, by washing with soap and water or disinfectants to help remove spores, is extremely important, and isolation of patients with acute diarrhoea can limit the spread of the disease in healthcare facilities.

The burden of this condition has been demonstrated clearly at Wits Donald Gordon Medical Centre (WDGMC), Johannesburg, South Africa (SA), through established active surveillance of hospital-acquired infections as part of the infection prevention and control programme (Fig. 1).[4]

Much effort has been focused on patient therapies to prevent symptomatic disease. Probiotics have been used in the treatment of CDAD, but their role remains uncertain. A meta-analysis conducted in 2010 suggested that there may be a benefit to using probiotics in addition to standard therapy for the management of patients with severe or relapsing *C. difficile* infection (CDI) or to prevent infection. However, the studies included in the review were small and there are currently insufficient data to support the use of probiotics in patients with CDAD.[5] Recommended treatment for the disease is via the oral route using metronidazole or vancomycin, to which 90% of patients respond and experience no further symptoms.[6]

The major problem with CDAD is symptomatic recurrence after antimicrobial therapy is complete. The frequency of recurrence has

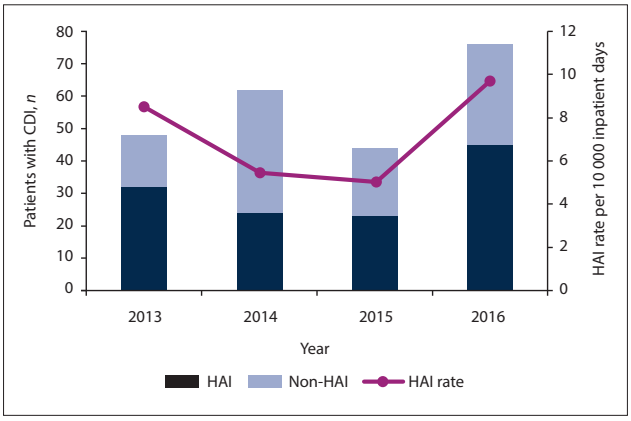

Fig. 1. Clostridium difficile *infection rates at Wits Donald Gordon Medical Centre, 2013 - 2016. (CDI =* C. difficile *infection; HAI = hospital-acquired infection.)*

been reported to be as high as 50%, and if a patient has experienced one recurrence, the risk of subsequent recurrence is even higher.[7] Disruption of the normal gut microbiota is the main cause of susceptibility to and recurrence of infection. Replacement of normal flora is becoming an increasingly popular therapeutic intervention, and treatment by the administration of donor stool through colonoscopy or the nasogastric/duodenal route is well described.[7-9] Faecal microbiota transplant (FMT) is considered a safe and effective treatment for recurrent CDAD and has a reported success rate of 80 - 90% from one infusion of donor stool.[7] While there are many published case series and reports confirming the efficacy of the treatment, to date there have only been two randomised controlled trials comparing FMT with current treatment, which includes extended vancomycin therapy. In both studies, early termination was recommended because the superiority of FMT made continuation unethical.[10,11] It is also noteworthy that patients who receive FMT experience minimal or no short-term complications, although the long-term consequences are unknown.[12]

There are no absolute contraindications to faecal transplantation. The choice to undergo faecal transplant has been positively influenced by its cost-effectiveness compared with continuing antibiotic treatment, as well as its success rate. Patients typically respond well to the idea of faecal transplantation, once the benefits of the procedure are explained to them, but the idea of the procedure is an obstacle to some.[13] The most acceptable and safe methods of administering FMT are nasogastric via insertion of a nasogastric tube (NGT), and into the large bowel via colonoscopy. Nasogastric administration is cost-effective, readily accessible as an outpatient and easy to perform, and does not require bowel preparation (lavage). An added advantage of nasogastric over colonic administration is potentially greater exposure of gut surface area to the new flora.[13] Reported complications have been related to the insertion of the NGT itself rather than the transplantation. Exceptions to eligibility for nasogastric administration are delayed bowel transit, ileus and small-bowel Crohn's disease. Colonoscopic insertion delivers faecal matter directly into the large bowel after standard lavage and is the preferred route for severe CDAD complicated by ileus.[13,14]

Preparation of the faeces for both methods is to liquidise the stool and blend it with saline or water, making a faecal suspension which is then filtered to remove any fibrous particles that may cause blockage of the NGT or colonoscopic channel.[13,14] A smaller volume of this suspension is used for NGT administration (30 - 50 mL), whereas larger volumes are used for colonoscopic insertion (400 mL). All modes of administration require that concurrent antimicrobial treatment be discontinued 24 - 48 hours before the procedure. When the nasogastric route is used, a PPI should be administered for 24 - 48 hours prior to transplantation to render the stomach achlorhydric and increase survival of the new organisms.[15]

The definitive role of FMT as a therapeutic intervention is evolving, such as whether it should be considered at the time of initial diagnosis of CDAD or only after recurrence occurs. The preferred route of administration of FMT is also under investigation and may depend on the severity of the associated symptoms, as well as patient preference.

Objectives

WDGMC, an academic specialist referral hospital, is one of few centres in SA that offers FMT for recurrent CDAD. In this article, we report on the clinical profile and outcomes of a case series of FMT recipients. We hope to create awareness in the healthcare profession of who may be at risk and the importance of judicious antibiotic prescription to prevent this condition. We highlight clinical methods utilised at our hospital that appear to make FMT safe, successful and cost-effective. Finally, we discuss funding issues in the private health environment and relate these to the recently published South African Gastroenterology Society (SAGES) guideline.[16]

Methods

Permission for this study was obtained from the Human Research Ethics Committee (Medical), University of the Witwatersrand (ref. no. M150319). A retrospective record review of patients with recurrent CDAD referred for FMT between 1 January 2012 and 31 December 2016 was conducted. Patients were referred by local clinicians to a medical gastroenterology practice at WDGMC. The following data were collected: age at time of referral, gender, associated risk factors, prior antibiotic treatment received for CDAD, relationship of recipient to donor, method of administration of FMT, and results of 4-week follow-up for remission. Laboratory reports confirming CDI were obtained, where possible. The definitions used and treatment regimens prescribed are according to published guidelines.[17,18]

Clinical remission was assessed 4 weeks after FMT and defined as complete resolution of clinical symptoms (mostly diarrhoea). Patients were also requested to submit a stool specimen for laboratory confirmation of clearance of *C. difficile*.

Private laboratory testing for *C. difficile* was mainly performed through molecular tests (polymerase chain reaction (PCR)) that detect the toxin genes (*tcdA*/*tcdB*) responsible for producing toxins A and B. Testing for the actual toxin was sometimes also performed.

Each patient was asked if they could source a potential donor from family members (related), spouses/partners or friends (unrelated but known). If a patient was unable to source a donor, the attending clinician sourced an anonymous donation (unrelated and unknown) from previous donors. The donor was approached if they were still within 6 months of their last screening. If agreeable, they were questioned to ensure that they had remained well during this period, and that they had not received antibiotics or had any new piercings, tattoos or sexual partners.

For the evaluation of each potential donor, a confidential screening interview was conducted to identify any risk factors that may preclude donation as per the SAGES guideline.[16] If eligible, the donor then gave a full medical history and underwent examination. Donors were excluded if they had any of the following: history of antibiotic use in the past 3 months; history of irritable bowel syndrome or irregular bowel habits; history of any major gastrointestinal

disease (such as inflammatory bowel disease or malignancy); diabetes mellitus; morbid obesity; use of any immunosuppressive or chemotherapeutic agents; recent piercings or tattoos; or a history of high-risk sexual behaviour. All donors were then screened for HIV, hepatitis A, B and C and syphilis. Donor stool was tested to exclude infection with ova, cysts, parasites and *C. difficile*. Additional screening tests were performed at the discretion of the attending physician. Donors were prescribed a single dose of an osmotic laxative containing macrogol (polyethylene glycol) to be taken with water the night before the planned stool donation.

On the day of the procedure, the fresh stool specimen was liquidised with 200 - 400 mL normal saline (depending on the volume of the sample) and passed through a gauze filter to remove particulate matter. For the nasogastric method, a PPI was administered to each recipient 48 hours prior to the procedure. After insertion of the NGT, placement was checked via auscultation and aspiration. A 60 mL volume of the sample was administered slowly and flushed with a further 60 mL normal saline. The NGT remained *in situ* for a further 20 minutes and was then removed. Each patient was observed for a further 30 minutes before discharge. The total time taken for the procedure was 60 - 120 minutes. To minimise the risk of aspiration, no sedation or local anaesthetic throat spray was used and the procedure was performed with the patient in a seated position. For the colonoscopic method, standard bowel preparation was performed prior to the FMT procedure. During the FMT procedure, 300 mL of the total 400 mL faecal sample was placed in the terminal ileum, provided the terminal ileum was intubated, with the remaining 100 mL dispersed on withdrawal of the colonoscope. If terminal ileal intubation was not achieved, 300 mL of the faecal sample was instilled into the caecum and the remaining 100 mL sprayed on withdrawal.

Study data were collected and managed using Research Electronic Data Capture (REDCap) which is a secure, web-based application designed to support data capture for research studies hosted at the Faculty of Health Sciences, University of the Witwatersrand.[19] Sample size estimation was based on the key research question to be answered, in this case the estimation of proportions (e.g. the proportion of females in the study group). Based on worst-case (for sample size) estimates of 50%, 5% precision and the 95% confidence level, an ideal sample size of 385 would be required.[20] The actual sample size of 27 corresponds to a precision of 19% (rather than 5%), which is a limitation of the study. Descriptive data analysis was carried out using SAS version 9.4 for Windows.

Results

All 27 patients in this study group fulfilled the criteria for recurrent CDAD and, at the time of presentation, 72% had had between one and three previous infections. Three procedures (11%) were performed as inpatients, two from the intensive care unit (ICU) and one from the general ward. The remainder (24/27) were done in the outpatient gastroenterology unit. Laboratory-confirmed reports of CDI were available in 21/27 cases. Most of these (86%) were diagnosed by PCR, 29% with demonstration of *C. difficile* toxin and three patients by both methods. All patients with known previous treatments (26/27) had been treated with vancomycin, while 65% had also been treated with metronidazole. One patient had received a previous faecal transplant. In 24/27 of the patients, data were available for the median time between diagnosis of the first episode of laboratory-confirmed CDAD and FMT, which was 4 months (interquartile range (IQR) 3 - 7, range 0.2 - 25).

The majority of the patients in this study group were female (20/27, 74%), the median age at first visit was 57 years (IQR 37 - 72, range 19 - 88), and 9/27 (33%) were aged >65 years. In this sample, the main risk factors for the development of CDAD, in decreasing frequency, were prior antibiotic use (15/25, 60%), chronic use of PPIs (11/25, 44%) and comorbid inflammatory bowel disease, which included ulcerative colitis and Crohn's disease (11/25, 44%) (Fig. 2). Forty percent of the patients had three or more risk factors. In those with prior antibiotic use, antibiotics had been prescribed for the following conditions: gastrointestinal (5/15, 33.3%), respiratory (4/15, 27%), and skin/soft tissue (each 3/15, 20%).

Of the faecal donor pool, approximately two-thirds were either related (9/27, 33%) or known to the recipients as a spouse/partner or friend (10/27, 37%). The remainder were unknown to the recipients and were sourced from previous donors (7/27, 26%). The donor-recipient relationship could not be determined in one case. The most common route of administration was via NGT (21/27, 78%), with 4/27 (15%) procedures done by colonoscopy and 2/27 (7%) nasoduodenal. Both the nasoduodenal insertions were for ICU patients and were administered in the radiology unit under X-ray guidance, not via endoscopy. There were no serious procedure-related complications, notably aspiration. One patient vomited 3 hours after administration, but the transplant was still effective. Another reported feeling nauseous, but this settled on symptomatic treatment. The majority of FMT recipients (23/27, 85%) returned for a follow-up visit after 4 weeks. The others were contacted telephonically. All the recipients experienced clinical resolution of their diarrhoea by 4 weeks, and there were no recurrences or deaths. Of those who submitted a stool sample for *C. difficile* PCR at 4 weeks (23/27), 20 tested negative (87%) and 1 tested positive (4%); 2 results could not be found.

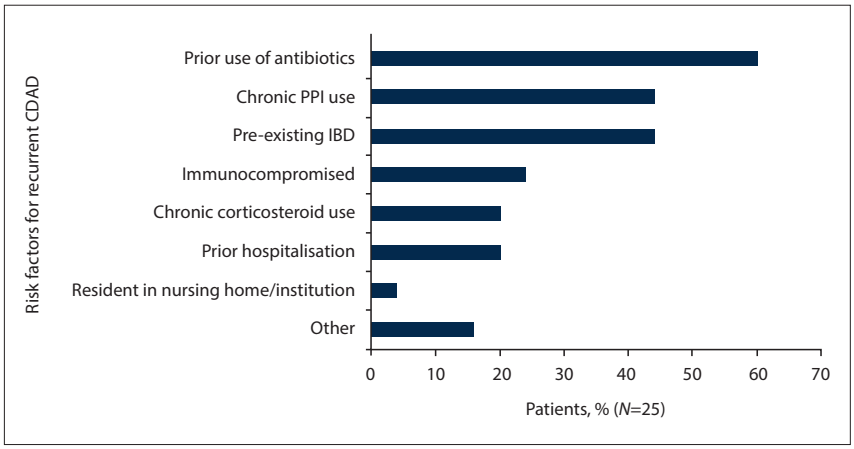

Fig. 2. Risk factors for the development of recurrent Clostridium difficile*-associated diarrhoea in patients referred to Wits Donald Gordon Medical Centre for faecal microbiota transplant. (CDAD =* C. difficile*-associated diarrhoea; PPI = proton-pump inhibitor; IBD = inflammatory bowel disease; immunocompromised = individuals with comorbidity that required immunosuppressive therapy other than corticosteroids; other = 1 patient with diabetic gastroparesis, 2 with surgical procedures relating to colon cancer and 1 with surgical site sepsis after caesarean section.)*

Discussion

To date, this is the largest case series published from SA that has described the role of FMT in the management of recurrent CDAD. The success of the procedure in our context is significant, given the persistent burden of disease observed at WDGMC (Fig. 1). It is important to note that the increase in the number of infections in 2016 may be attributable to the status of the hospital as a referral facility, previous diagnostic barriers in diagnosis of CDAD and mechanisms for laboratory reporting (which may have led to underreporting), or a combination thereof.[21] While there are no national surveillance data to confirm the trend at our hospital, it reflects similar findings internationally and adds urgency to the implementation of the South African Antimicrobial Resistance Strategy Framework.[22] This comprises a regulatory framework within which surveillance and antimicrobial stewardship in combination with infection prevention and control are prioritised to reduce morbidity and mortality associated with antibiotic-resistant infections.

While a regulatory framework is essential, clinicians need to be far more aware of the impact of CDAD on the individual and the healthcare system in which they seek care. The findings in this study are sobering. At the time of referral, the majority of our patients had suffered from between one and three infections requiring at least two courses of antibiotics over a median period of 4 months. Of the identified risk factors, prior antibiotic exposure and chronic PPI and corticosteroid use predominated. All these are potentially modifiable and even preventable with judicious prescription practice. With regard to the non-modifiable risk factors, namely female gender, older age (one-third of the patients were aged >65 years) and underlying inflammatory bowel disease, our findings are consistent with the published literature, but we had far fewer patients from long-term care facilities.

At WDGMC the preferred mode of administration for FMT is via the nasogastric route in the outpatient unit. This means that no gastroscopy or bowel preparation is required (as in the case of colonoscopy) and the need for hospital admission is eliminated. The results from this series confirm unequivocally that this is safe and effective. Nasoduodenal or colonoscopic routes are only considered if nasogastric administration is not feasible. This method has evolved over the past 5 years from clinical experience based on good patient tolerance, the success rate and ease of administration. However, it counters the recently published SAGES guideline[16] that recommends duodenal or colonoscopic administration and inpatient observation overnight.

The administration of FMT via the nasogastric route at WDGMC also evolved from difficulties regarding funding in the private healthcare sector. There is currently no procedural code for FMT, as it is not a registered form of treatment. This forces clinicians to code for alternative 'proxy' procedures which, besides being ethically problematic, results in wide variations in cost to the funder and the patient. There is also no funding mechanism for evaluation of the donor, which results in most recipients carrying the costs themselves.

Study limitations

The limitations of the study are its retrospective design, small sample size and restriction to the private sector.

Conclusion

This case series confirms that FMT is a safe and effective therapy for recurrent CDAD. In most cases it can be administered via the nasogastric route as an outpatient. We propose that the recently published SAGES guideline be reviewed regarding recommendations for the route of administration of FMT and hospital admission. We hope that by making our experience available, we can assist healthcare funders to formalise billing procedures for FMT that include the costs of the donor evaluation.

More broadly, this study highlights an urgent need for the medical community to address antimicrobial prescription at all levels – governmental health policy and regulation, implementation in healthcare institutions, and bedside practice. It is incumbent upon each clinician to critically review prescription practice and implement appropriate changes that minimise the risk of patients developing these debilitating and potentially life-threatening conditions.

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Conflicts of interest. None.

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