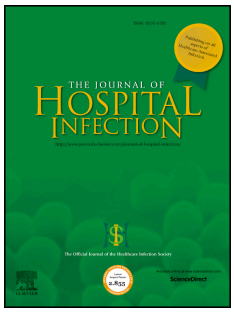
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TITLE PAGE

Article title

Treatment of *Clostridium difficile* infection: a national survey of clinician recommendations and the use of faecal microbiota transplantation

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Abbreviated title

C. difficile: treatment approaches

Keywords

Clostridium difficile ; treatment ; adherence ; faecal microbiota transplantation

Summary

Adherence to *Clostridium difficile* infection treatment guidelines is associated with lower recurrence rates and mortality as well as cost savings. Our survey of Irish clinicians indicates that patients are managed using a variety of approaches. FMT is potentially underutilised despite its recommendation in national and European guidelines.

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TEXT

Introduction

C. difficile infection (CDI) is characterised by reductions in microbial diversity of the complex gut microbiota, and stool transplantation from healthy donors (faecal microbiota transplantation, FMT) is increasingly recommended for treatment of patients with recurrent CDI.[1, 2]

CDI is a mandatory notifiable infection under Irish public health legislation. In 2014, 155/1613 (8.5%) of cases were classified as recurrent CDI (i.e. CDI that occurs within 8 weeks following the onset of a previous episode),[2] though sub-classification on the number of recurrences is not reported.[3] Irish guidelines recommend metronidazole, vancomycin or fidaxomicin (following infection specialist consultation) for the first non-severe CDI episode and the first non-severe recurrence, with FMT recommended as an option for second and subsequent recurrences.[2] Given the quality of evidence available, this is given a Grade A recommendation. However, FMT is likely underutilised, possibly due to logistical difficulties, regulations, or perceived patient aversion.[4]

We performed a national survey to assess CDI management practices to inform the national CDI guideline implementation process.

Methods

In September 2015 a ten question survey was developed principally based on a previous United Kingdom survey and following a literature review.[7] The aim was to design a short questionnaire that would take no longer than three minutes to complete, targeting senior decision makers. Questions regarding current management of CDI, experience with and

beliefs about FMT were included. The full questionnaire is available as a supplementary file. The survey was formulated using an online survey tool (www.surveymonkey.com) and circulated via the relevant professional societies to Irish hospital consultants in specialties most likely to regularly manage CDI (Irish Society of Clinical Microbiologists, Irish Society of Gastroenterology, Infectious Disease Society of Ireland, Irish Society of Physicians in Geriatric Medicine, Irish Association of Coloproctology). Responses were accepted up until the close of the survey in February 2016.

Results

Ninety-four surveys were completed by gastroenterologists (n=42), microbiologists (n=26), infectious diseases physicians (n=10), geriatricians (n=8) and general/colorectal surgeons (n=8).

CDI treatment options selected by respondents are summarised in Table I. Oral metronidazole was most commonly selected for the first episode of non-severe CDI. Vancomycin was most frequently recommended for the first and second non-severe recurrence. Both FMT and fidaxomicin were more frequently recommended for the third or subsequent recurrence than for earlier recurrences.

Fidaxomicin was most frequently recommended by an infection specialist (i.e. a microbiologist or infectious diseases consultant), particularly for earlier episodes (i.e. first episode and first recurrence).

Fourteen respondents (14.9%) reported previous FMT use, mostly in the previous year (10/14). One respondent, a microbiologist, reported recommending FMT on more than 10 occasions. In contrast to its low usage, the majority had seen potential FMT candidates in the past year, principally patients with recurrent CDI and, in some instances, severe CDI. (Table

1) Twenty-eight had not seen any patients in the previous year who they considered suitable FMT candidates.

Factors which influenced respondents to recommend FMT included: the availability of prepared stool (64/94; 68.1%), donor selection logistics (50/94; 53.2%), availability of a national agreed protocol (46/94; 48.9%) and patient acceptability (45/94; 47.9%). Patient safety concerns, overall cost of the procedure and antimicrobial resistance as a result of the procedure were less likely to influence decision making (9/94 (9.6%), 7/94 (7.4%), 4/94 (4.3%), respectively).

Enablers that would facilitate respondents either recommending or performing FMT included: availability of donor stool (76/94; 80.9%) and a national agreed protocol (69/94; 73.4%), patient information resources (43/94, 45.7%), laboratory resources / logistics (39/94, 41.5%) and endoscopy resources / logistics (35 /94, 37.2%).

Discussion

Adherence to CDI treatment guidelines is associated with lower recurrence rates and mortality as well as cost savings.[5, 6] Irish CDI patients are managed using a variety of approaches. National guidelines recommend metronidazole for the first episode or first recurrence of non-severe CDI, with fidaxomicin or vancomycin as alternatives.[2] It is notable that vancomycin is more commonly recommended for the first CDI recurrence, versus metronidazole for the first episode. The frequent recommendation of probiotics (by a quarter of respondents) despite insufficient evidence to support their use was a significant variation from guidelines.[2] Multiple reasons for these variations in prescribing may exist, such as local policy and personal preference. These reasons were not examined here and, given the small numbers in each specialty group, analysis of prescribing practices between specialties was not performed. This discordance is not unique to Ireland, with other studies reporting similar

findings.[5, 6] Few studies explore prescribers' rationale for these discordances, though lack of guideline awareness may be a major factor.[6]

This survey highlights the desire by Irish clinicians to use FMT in CDI management. It also indicates that FMT is potentially underutilised despite its national and European recommendations.[1, 2] Similar findings have been reported elsewhere.[4, 7] A United Kingdom survey reported that 94% of hospital specialists had seen at least one patient for whom they would recommend FMT; however only 22% reported using FMT in the last 10 years. Similar to our findings, the availability of regional guidelines and pre-screened stool were factors considered to facilitate FMT. [7]

Logistical issues, specifically availability of prepared screened stool, donor selection logistics, and availability of a national agreed protocol, were the most likely factors to be taken into account when consideration was given to recommending FMT. It follows, therefore, that the ready availability of donor stool was considered the main factor to facilitate wider use of FMT. Issues such as patient safety concerns and antimicrobial resistance were of less concern, suggesting that respondents believe that FMT is a safe procedure. Using a directed donor model (i.e. where an individual is identified as a stool donor, followed by local donor / sample screening for potentially transmissible conditions) can be time consuming, expensive and needs to be well-regulated to minimise any potential risk to the patient.[8] This approach could result in patient treatment delays, assuming the donor sample is considered suitable. Indeed, when rigorous screening protocols are applied only a small percentage of would-be donors are ultimately selected – 10% in one study.[9] Hence the introduction of standardised stool banks modelled on the universal donor model, to help overcome limitations related to donor selection and screening logistics. At present in the Republic of Ireland there is no nationally agreed FMT policy or guidance should a hospital wish to set up a stool banking service, nor is there a national or regional stool banking

service. In a country such as ours (4.5 million population) with a low absolute number of patients with recurrent CDI,[3] further evaluation is needed to explore the logistical challenges and costs associated with a national or regional stool banking service. Although national CDI surveillance collects data on recurrent CDI,[3] there are no data on second or more recurrences, i.e. those for whom FMT is recommended. A full economic assessment would therefore be required to examine the option of a national / regional service against availing of an established service from abroad. The universal donor model is already used in many U.S. centres, with frozen donations acquired from stool banking organisations such as OpenBiome. These preparations, which are non-inferior to freshly prepared samples with regard to rates of clinical resolution, can be stored and available for use as needed.[10] This approach is a worthy consideration where a national stool banking service is not in operation.

Although not explored in this survey, factors that should be taken into account at an institutional level when commencing an FMT service are the national regulatory frameworks that FMT falls under (i.e. as a drug or biological material), ethics of donor screening and long term safety of microbiome manipulation. In Europe, the regulation of FMT is currently at the discretion of individual EU member states. Currently in Ireland no such national regulation exists. The United States Food and Drug Agency (FDA) views FMT as an investigational new drug (IND) meaning that the drug is normally made available through a clinical trial. Up to recently they have exercised enforcement discretion in this regard, however recent guidance suggests this is to change, particularly in situations where the FMT recipient does not know the donor (e.g. where the sample has been obtained from a stool bank). Where stool bank donation samples are to be used IND regulations are to be adhered to. This change in enforcement discretion may impact service provision, particularly in centres where samples for donation are routinely obtained from stool banking services. It does however ensure ongoing compliance with best practice in the relation to the obtaining of specimens and

screening of donors. It remains to be seen if future planned EU regulation of FMT donor material will hinder its widespread use. This may depend on whether it is regulated as a drug or bodily tissue. In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHRA) recently classified FMT as a medicinal product, not tissue, thus regulation of FMT changed from the Human Tissue Authority (HTA) to the MHRA. For any trial utilising FMT, MHRA approval should be sought. Again, this may impact on service provision and also the development of future research. Institutions need to ensure they are working within their national and EU frameworks and regulations. Where national regulations are absent, comparisons should be made to international standards to ensure the highest level of safety. This survey did not explore issues regarding protocols / regulations being followed in individual institutions. It is clear however that improved clarity at a national / European level is required.

Planning a local FMT service should involve multidisciplinary input (e.g. laboratory, pharmacy and endoscopy services) and must consider legislative requirements. It is not always possible for national protocols to take into account local nuances such as resources and administration processes. Therefore locally agreed protocols, based around available national guidance, which considers these local variations will be crucial in determining success of the service.

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LMcD, DK, SC: no conflicts of interest relevant to this article.

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Table I: *Clostridium difficile* infection (CDI) Management Practices of 94 Irish Clinicians

Agents recommended for CDI treatment (by CDI episode)	First episode -non-severe. [n (%)]	First recurrence-non-severe [n (%)]	Second recurrence-non-severe [n (%)]	Third / subsequent recurrence - non-severe [n (%)]	Severe CDI [n (%)]
Oral metronidazole	92 (97.9)	36 (38.3)	12 (12.8)	3 (3.2)	19 (20.2)
Intravenous metronidazole	2 (2.1)	8 (8.5)	7 (7.4)	4 (4.3)	48 (51.1)
Oral vancomycin	5 (5.3)	58 (61.7)	55 (58.5)	38 (40.4)	84 (89.4)
Oral fidaxomicin	10 (10.6)	22 (23.4)	34 (36.2)	41 (43.6)	15 (16.0)
Probiotics	15 (16.0)	12 (12.8)	14 (14.9)	13 (13.8)	9 (9.6)
Faecal microbiota transplantation	0 (0)	4 (4.3)	8 (8.5)	29 (30.9)	12 (12.8)
Colectomy	0 (0)	2 (2.1)	0 (0)	0 (0)	22 (23.4)
Intravenous immunoglobulin	0 (0)	1 (1.1)	1 (1.1)	6 (6.4)	22 (23.4)
Rifaximin	0 (0)	0 (0)	5 (5.3)	12 (12.8)	2 (2.1)
Respondents who would have recommended / performed FMT in the past year if readily available (by CDI episode)	0 (0)	7 (7.4)	20 (21.3)	41 (43.6)	22 (23.4)