Faecal microbiota transplantation for *Clostridium difficile* infection in the United Kingdom

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**Abstract**

Faecal microbiota transplantation (FMT) has been shown to be highly effective in treating recurrent *Clostridium difficile* infection, but to date there have been no data from the United Kingdom. An electronic survey was developed at Portsmouth Hospitals’ National Health Service (NHS) Trust and sent out to UK hospital specialists utilizing the contact databases of the British Infection Association and the Royal College of Gastroenterologists. A total of 162 responses were received, representing nearly one in every seven of the United Kingdom’s infection specialists and a response from one in every two UK NHS acute trusts or boards. Ninety-six per cent believe that the evidence base supports the use of FMT, and 94% reported consulting on at least one patient a year in whom they would recommend FMT. However, only 22% reported FMT use in their institution in the last 10 years, and 6% reported performing more than ten FMTs in the last 10 years. Concerns with patient acceptance, donor selection, availability of screened faecal solution, feasibility of procedure and availability of local expertise were reported as inhibiting the use of FMT. More than 90% of respondents would like access to regional guidelines, prescreened faecal solution and expert advice to facilitate implementation, and more than two thirds of respondents would support a regional FMT referral centre. A large gap exists in the United Kingdom between physicians desire to use FMT and the ability and facilities to provide it as a therapy at the bedside.

**Keywords:** *Clostridium difficile* infection, faecal microbiota barriers, faecal microbiota physician attitudes, faecal microbiota transplantation, faecal microbiota uptake

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**Introduction**

*Clostridium difficile* infection (CDI) is a major cause of mortality and morbidity. *C. difficile* was recorded as the underlying cause of death for 10 258 patients in England and Wales between 2007 and 2011, and a contributing factor in a further 12 687 deaths. Between 2009 and 2011, 91% of CDI deaths in England and Wales occurred in National Health Service (NHS) hospitals. Most deaths occur in older people, with those aged 85 and over having the highest mortality rate (1099 per million population in 2009–2011) ([http://www.ons.gov.uk/ons/dcp171778_276892.pdf](http://www.ons.gov.uk/ons/dcp171778_276892.pdf)). Mortality estimates have varied widely, and rates have generally reported to have increased with the widespread circulation of the 027/NAP1/BI strain, with 30 day all-cause mortality of 23% to 29% in an endemic setting [1–3]. Mortality rates in hospitalized CDI patients from Holland in a nonendemic setting were recently published, with a 30-day all-cause mortality rate of 13% and a 1-year mortality rate of 37% [4].

A review of the economic burden of CDI in 2012 reported the cost of a single case of CDI to be between £4577 ($6943) and £8843 ($13 414) at 2010 values (approximately £5000 to £10 000 in 2014), with an average hospital length of stay of...
between 17 and 37 days [5]. Patients with multiple recurrent episodes of CDI may cost the local healthcare economy significantly more than this [6,7]. Faecal microbiota transplantation (FMT) has been shown to be highly cost effective compared to standard therapy, with an incremental cost-effectiveness ratio of over £10 000 ($17 016) relative to oral vancomycin [8].

Recurrence occurs in approximately 22% of patients after a first episode of CDI [9,10]. FMT has increasingly been reported as an effective treatment for recurrent CDI, with a 2011 systematic review of 317 patients across 27 case series and reports showing an overall cure rate of 92% [11]. In 2013, a Dutch group reported the first randomized controlled trial of FMT for recurrent CDI, which showed an overall cure rate of 94% compared to 31% for standard therapy with high-dose vancomycin [12].

Although FMT appears to be effective, uptake may be hampered by patient and physician concerns over the procedure. Attitudes in the United Kingdom are unknown, but concerns over the ‘yuck’ factor [13], as well as the disconnect between physician beliefs and patient willingness to accept FMT [14], have been explored in the United States. A survey of gastroenterologists and infectious diseases physicians in the Houston, Texas, area in the United States published in 2013 showed a desire for a local referral centre for FMT [15].

We developed a survey to explore the uptake of FMT within the United Kingdom and to identify any barriers that might prevent the use of FMT. We also asked about the desire for support through availability of prescreened donor faecal solution, expert advice and regional referral centres.

The NHS provides free healthcare to all UK citizens and legal immigrants, and supports a network of primary, secondary and tertiary care providers. Portsmouth Hospitals’ NHS Trust is a secondary and tertiary care provider for over 650 000 individuals on the south coast of England.

Methods

Survey development

The survey was developed at Portsmouth Hospitals’ NHS Trust following a literature review of research and opinion articles concerning FMT. It was designed to be completed in approximately 5 minutes and to explore the current uptake and need for FMT and the attitudes of physicians to FMT. It asked about current use of FMT and other common therapeutic measures by UK physicians, asked physicians to determine how many FMTs they might foresee using and asked about their beliefs regarding FMT. After literature review, and from peer discussion, 11 factors were identified that might influence FMT uptake, and questions regarding these factors were incorporated. The survey was administered using the web-based KwikSurveys (http://www.kwiksurveys.com) site. The survey data was downloaded to a CSV file and analysed using descriptive statistics within Microsoft Excel.

Survey participants

The survey was targeted at consultants and senior trainees in infection and gastroenterology. A short request for help completing the survey with an attached hyperlink was forwarded via e-mail with the help of the British Infection Association and the Royal College of Gastroenterologists. Mailings occurred in December 2013 and June 2014, with survey responses accepted up until collation of results in July 2014.

Results

Characteristics and caseload of respondents

A total of 161 complete or nearly complete (>75%) responses were returned from 86 unique acute hospital trusts or NHS boards. One incomplete response was excluded. A total of 142 responses were received from infection specialists, and a further 19 responses were received from gastroenterologists via the Royal College of Gastroenterologists. One hundred sixty responses were from the United Kingdom, and 159 were from physicians primarily working within the NHS. Table 1 shows the grade and specialty of respondent and the average number of CDI consults performed per month.

Current treatment for CDI

Respondents were asked which therapies for CDI they had personally recommended (Table 2), with 160 (99.4%) reporting oral vancomycin, 112 (69.6%) fidaxomicin, 43 (26.7%) colectomy and 33 (20.5%) FMT.

When asked about current FMT use, 34/161 (21.1%) had used it in the last year, and 36/161 (22.4%) had used it in the last 10 years. Of those who had used FMT in the last year, 28/161 (17.4%) had performed one to four FMTs, three (1.9%) had performed five to nine FMTs and a further three (1.9%) more than ten FMTs. Only nine respondents (5.6%) from four unique trusts or boards (4.4%) reported performing more than ten FMTs in the last 10 years.

Perceived need for FMT

In contrast to the low current usage of FMT, 130 (94.1%) of respondents indicated that they saw at least one patient a year who would be suitable for FMT in their institution, and 50 (37.0%) saw more than five per year. Only eight (5.8%) reported seeing no suitable patients in a year; these eight were all consultant infection specialists.
TABLE 1. Specialty and grade of respondent

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Grade</th>
<th>n (%)</th>
<th>0</th>
<th>1–2</th>
<th>3–5</th>
<th>6–10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Consultant</td>
<td>104 (65)</td>
<td>1 (1)</td>
<td>41 (39)</td>
<td>43 (41)</td>
<td>15 (14)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Consultant</td>
<td>25 (16)</td>
<td>2 (8)</td>
<td>13 (51)</td>
<td>9 (36)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>Senior trainee</td>
<td>4 (2)</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

Average no. of CDI cases consulted per month

Table 2 shows the therapy used for CDI:

- **Vancomycin (oral)**: 160 (99.4)
- **Metronidazole (oral)**: 155 (96.3)
- **Metronidazole (intravenous)**: 145 (90.1)
- **Fidaxomycin (oral)**: 112 (69.6)
- **Intravenous immunoglobulin**: 82 (50.9)
- **Vancomycin (per rectum)**: 54 (33.5)
- **Colectomy**: 43 (26.7)
- **Faecal microbiota transplant**: 33 (20.5)
- **Rifaximin (oral)**: 27 (16.8)
- **Cholestyramine**: 6 (3.7)
- **Fusidic acid/sodium fusidate (oral)**: 3 (1.9)
- **Teicoplanin (oral)**: 2 (1.2)
- **Netazoxanide (oral)**: 1 (0.6)
- **Bacitracin (oral)**: 0 (0.0)

C. difficile infection.

When asked about the place of FMT in treatment, 132/141 (93.6%) would recommend FMT in patients who had recurrent CDI and whose CDI had failed to respond to 10 days of high-dose pulse/tapered vancomycin, 72 (51.1%) in patients with CDI and whose CDI had failed to respond to high-dose vancomycin, 50 (35.5%) in patients with fulminant CDI, 18 (12.8%) in patients with a first recurrence and five (3.5%) as primary therapy. Five (3.5%) would never consider recommending FMT.

**Facilitators and barriers for FMT use**

Respondents were asked to report how 11 different factors influenced their view of FMT (Table 3). A total of 133/138 (96.4%) believed that the evidence base supported the use of FMT, but a majority reported that patient acceptance, donor selection, lack of availability of screened faecal solution, feasibility and local expertise inhibited the uptake of FMT.

When respondents were asked about factors that might facilitate the uptake of FMT, 135/140 (96.4%) would like access either on or off site to a physician experienced in FMT during initial implementation of an FMT programme and 97 (69.3%) would use prescreened faecal solution if it were available regionally, 131 (93.6%) would like access to a regional protocol and patient information sheet for FMT, 136 (97.1%) would use prescreened faecal solution, 135/140 (96.4%) believed that the evidence base supported the use of FMT, but a majority reported that patient acceptance, donor selection, lack of availability of screened faecal solution, feasibility and local expertise inhibited the uptake of FMT.

Discussion

C. difficile costs society dearly in lives, bed-days, and financial expenditure. FMT is an option that may reduce mortality, shorten hospital stays and save the healthcare economy money. This survey provides the first data on UK physician attitudes to FMT and provides insights into the uptake, beliefs and desires of those treating these patients at the bedside. There is clearly a strong risk of selection bias in this form of survey, but it includes views from 104 of the 746 consultant infection specialists in the United Kingdom (Royal College of Physicians, https://www.rcplondon.ac.uk/sites/default/files/2011_census_-_registrar_census_-_intro_and_r1-r20.pdf, and Royal College of Pathologists, http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/C/careersleafletundergraduates.pdf), and the whole survey represents a response from nearly one in two (86/183) of all NHS acute trusts or boards. This survey suggests that uptake of FMT in the United Kingdom is currently low, with FMT being recommended less frequently than colectomy, but that there is a recognition that more patients would benefit from this therapy, with almost every respondent reporting one or more suitable patients a year at their place of work.

**TABLE 2. Therapy used for CDI**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Vancomycin (oral)</td>
<td>160 (99.4)</td>
</tr>
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</tr>
<tr>
<td>Bacitracin (oral)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**TABLE 3. Factors influencing use of faecal microbiota transplantation**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favours use, n (%)</th>
<th>Inhibits use, n (%)</th>
<th>Neither, n (%)</th>
<th>Don’t know, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base</td>
<td>133 (96.4)</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Benefit vs. risk</td>
<td>128 (90.8)</td>
<td>1 (0.7)</td>
<td>8 (5.7)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Overall cost</td>
<td>59 (41.8)</td>
<td>14 (9.9)</td>
<td>42 (29.8)</td>
<td>26 (16.8)</td>
</tr>
<tr>
<td>Antimicrobial resistance</td>
<td>86 (61.0)</td>
<td>5 (3.5)</td>
<td>41 (29.1)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Patient safety</td>
<td>78 (55.3)</td>
<td>17 (12.1)</td>
<td>37 (26.2)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Patient acceptance</td>
<td>33 (23.4)</td>
<td>58 (41.1)</td>
<td>37 (26.2)</td>
<td>13 (9.2)</td>
</tr>
<tr>
<td>Donor selection</td>
<td>13 (9.3)</td>
<td>67 (47.9)</td>
<td>45 (32.1)</td>
<td>15 (10.7)</td>
</tr>
<tr>
<td>Cost to local laboratory</td>
<td>14 (10.0)</td>
<td>10 (7.5)</td>
<td>64 (45.7)</td>
<td>16 (11.4)</td>
</tr>
<tr>
<td>Availability of prepared stool</td>
<td>47 (33.6)</td>
<td>66 (47.1)</td>
<td>16 (11.4)</td>
<td>11 (7.9)</td>
</tr>
<tr>
<td>Feasibility and practicability of procedure</td>
<td>35 (24.8)</td>
<td>81 (57.4)</td>
<td>19 (13.5)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Local expertise</td>
<td>45 (32.1)</td>
<td>64 (45.7)</td>
<td>24 (17.1)</td>
<td>7 (5.0)</td>
</tr>
</tbody>
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Physicians overwhelmingly believe that the evidence base favours FMT and that the benefit of this form of therapy outweighs the risk. There appears to be understanding about the high cost of treatment for recurrent CDI—not only a financial cost, but also a cost in terms of antimicrobial resistance in normal gut flora. However, there remains a belief that patients may not want FMT, despite evidence to the contrary [13]. Physicians are also rightly concerned about appropriate donor selection, availability of prescreened stool and the practicality and feasibility of performing FMT. There is also a recognition that expertise in the United Kingdom is currently lacking. When asked if access to regional protocols, patient information leaflets, prescreened stool and expert advice would be welcomed, there was an overwhelmingly positive response, and two thirds of respondents would be happy to refer patients to a regional centre for FMT.

The development of artificial faecal solution [16] and neater delivery methods are already in development, but in the interim, carefully screened donor faeces appears safe in the short term [11]. The use of frozen faecal solution [17] will improve accessibility to prescreened stool and appears to have a similar efficacy [18]. Delivering frozen FMT via oral capsule has recently been reported to have resulted in good outcomes in a small group of patients. This approach is less invasive, is less time-consuming and is likely to improve patient acceptability [19].

FMT was recently incorporated into the European Society of Clinical Microbiology and Infectious Diseases’ treatment guidelines for recurrent CDI [20]. However, there is an increasing need for clear national and international guidelines standardizing the approach to donor screening, as well as the subsequent preparation, storage and delivery of FMT [21,22]. The governance structures around FMT are yet to be clearly defined in many countries. In the United States, the US Food and Drug Administration classed FMT as a drug in May 2013, requiring an investigational new drug (IND) application to be submitted before performing FMT. However, shortly afterwards, the FDA effectively dropped this requirement (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm361379.htm) after concerns that the IND application was so onerous that it would greatly restrict uptake of FMT. The FDA guidance is currently in draft, and further clarification is expected to follow. In the United Kingdom, FMT is regulated under the Human Tissue Act of 2004 and is overseen by the Human Tissue Authority, which does not currently provide FMT-specific guidance. The European Medicines Agency does not recognize FMT as a drug, and as such has no specific guidance (personal correspondence).

With regard to funding, the United Kingdom remains behind the United States, where remuneration for FMT through coding now recognizes not only the cost of performing the procedure but also the cost to the laboratory of donor selection and stool screening (http://www.gastro.org/practice/coding/aga-provides-fmt-coding-guidance), whilst the UK National Institute for Clinical Excellence coding guidance covers the cost of the procedure only. Centres performing FMT must be able to recoup their costs or the NHS may end up spending more by buying from private providers.

The United Kingdom should benefit from having a single, unified healthcare provider, and for FMT, this benefit should be exploited. Service development between the NHS and the Royal Colleges could lead to national protocols, consent forms and information. Regional centres could provide FMT or could act as donor banks for faecal solution, sending out frozen stool aliquots as required. Awareness amongst primary care and secondary care physicians could be raised and patient education supported. As interest in FMT for other common conditions increases [23], this would potentially put healthcare services on the front foot.

**Transparency declaration**

Both authors report no conflicts of interest relevant to this article.

**References**


