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BRIEF REPORT

Early Economic Assessment of Faecal Microbiota Transplantation for Patients with Urinary Tract Infections Caused by Multidrug-Resistant Organisms

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ABSTRACT

Introduction: The use of faecal microbiota transplantation (FMT) to eradicate intestinal carriage of multidrug-resistant organisms (MDRO) has been described in case reports and small case series. Although few in numbers, these patients suffer from recurrent infections that may exacerbate both the patients' comorbidities and their healths. In the current study, we hypothesized that FMT for MDRO-related urinary tract infections (UTIs) reduces hospitalisations and associated costs.

Methods: In a cohort of patients referred for FMT from 2015 to 2020, we selected all patients who had consecutively been referred for eradication of MRDO carriage with UTIs. An early economic assessment was performed to

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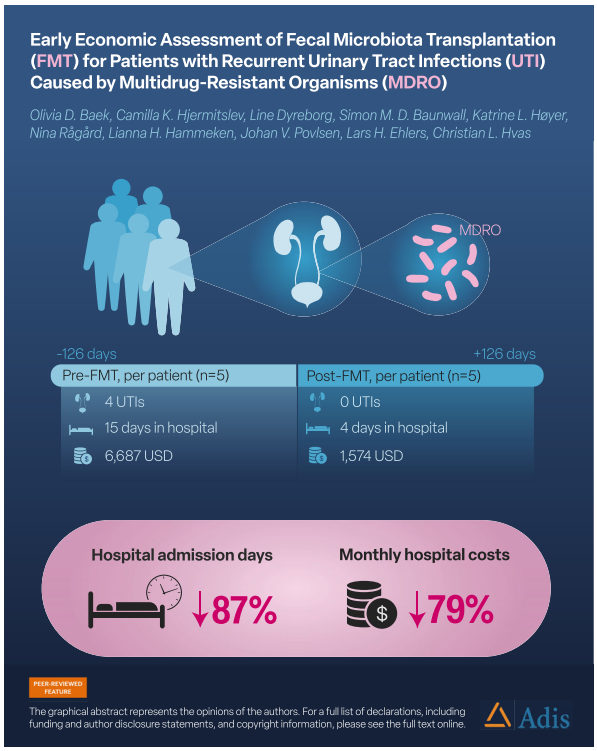
calculate hospital-related costs. The overall study cohort was registered at ClinicalTrials, study identifier NCT03712722.

Results: We consecutively included five patients with UTIs caused by MDROs. Four of the patients were renal transplant recipients. Patients were followed for median 126 days (range 60–320), where the follow-up duration for each patient was aligned with the number of days from the first UTI to FMT. The median number of UTIs per patient dropped from 4 to 0. Investigating hospital costs, hospital admission days dropped by 87% and monthly hospital costs by 79%.

Conclusions: FMT was effective in reducing the occurrence of UTIs and mediated a marked reduction in hospital costs. We suggest that this strategy is cost-effective.

Trial Registration: ClinicalTrials, study identifier NCT03712722.

Graphical Abstract:



Keywords: Early economic assessment; Faecal microbiota transplantation; Hospital cost; MDRO; Multidrug resistance

Key Summary Points

Faecal microbiota transplantation (FMT) may eradicate intestinal carriage of multidrug-resistant organisms (MDROs) that lead to clinical infection.

Investigating hospital costs in five consecutively included patients who received FMT for MDROs causing urinary tract infections (UTIs), we calculated that hospital admission days dropped by 87% and monthly hospital costs by 79%.

FMT to eradicate MDRO carriage may be a cost-effective strategy to reduce both the number of infections and hospital costs.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.22341232.

INTRODUCTION

Multidrug-resistant organisms (MDROs) frequently cause urinary tract infections (UTIs), causing an increase in hospital costs from frequent hospitalisations, medication use, and patient mortality [1, 2]. Immunosuppressive treatment may further increase infection susceptibility, rendering solid organ recipients particularly vulnerable if they become colonised with MDROs [2, 3]. The health burden related to antimicrobial resistance, highlighted by the World Health Organization as a key challenge [4], calls for new and better treatments.

Faecal microbiota transplantation (FMT) is the transfer of a complete intestinal microbiome from a healthy donor to a recipient. FMT is highly effective for recurrent *Clostridioides difficile* infection [5], and small case series

suggest that FMT may improve the clinical outcome of patients who suffer from MDRO-related recurrent UTIs [6–10]. Although currently regarded as an experimental last resort, FMT may both reduce the frequency of UTIs caused by MDROs and improve antibiotic sensitivity in the organisms causing the UTI [7].

Economic evaluations may provide useful input for the prioritisation of scarce healthcare resources because they help decision makers measure the costs and consequences of alternative interventions [11]. To provide relevant information on allocative efficiency, economic evaluations must be based on the best available clinical and economic evidence, preferably on data from randomised controlled trials. Early economic evaluations performed without a solid evidence base, i.e., from randomised clinical trials, may indicate and guide the value of emerging technologies and guide further research and development decisions, provided that they address uncertainties and potential benefits of further research [12]. No previous study evaluated the early economic benefits of FMT for MDRO-related UTIs.

In this single-centre cohort study, we aimed to perform an early economic assessment of FMT for patients with UTIs caused by MDROs, measuring the number of UTIs, days of admission, hospital contacts, and hospital-related costs to guide the potential use of FMT.

METHODS

This was a subgroup analysis including patients from a cohort study, carried out in a Danish public gastroenterology referral centre from 2015 to 2020. In addition to including patients referred for recurrent *Clostridioides difficile* infection, we consecutively included patients who were referred for FMT due to intestinal MDRO carrier status and a medical history of UTIs where urine cultures had revealed growth of an MDRO. All patients received at least one FMT from one thoroughly screened donor [13], administered either by colonoscopy or capsules. The cohort was a subgroup of all patients referred for FMT at our institution, and the overall cohort study was registered at ClinicalTrials.gov (study identifier NCT03712722).

Routine follow-up was carried out in all patients at 1 and 8 weeks following FMT. Patient-specific data collection was extended into equal periods before (pre-FMT) and after FMT (post-FMT) to allow for comparison and to include the longest possible follow-up time for each patient. The pre-FMT period included the period from the first MDRO-related UTI until the day of FMT. The post-FMT period was defined as the period from the FMT treatment until a follow-up period matching the length of the pre-FMT period.

The Danish diagnosis-related group (dkDRG) tariffs were used to estimate the costs for inpatient and outpatient hospital contacts. In Denmark, a dkDRG must be assigned to every hospital discharge and course of treatment and covers all hospitals in Denmark. The dkDRG tariffs are mean cost estimates of treatment courses, and the tariffs represent the reimbursement for a patient on the basis of the patient's primary diagnosis, secondary diagnosis, age, sex, and length of hospital contact or admission.

The clinical health outcomes, including the number of UTIs, days of admission, and hospital contacts per patient, were identified by reviewing electronic patient records. In Denmark, the electronic patient file holds all information related to hospital contacts. All hospital contacts were evaluated and calculated to a monthly average cost. The cost of FMT was not included as an expense in any of the periods.

Paired t-tests were applied to compare clinical health outcomes, and a Wilcoxon signed-rank test was applied to compare the costs for the pre-FMT and post-FMT periods. Clinical health outcomes are reported as median and range, while costs are reported as mean and 95% confidence intervals (CI). A p-value of < 0.05 was considered statistically significant. All data were exported from the Research Data Capture system, REDCap 9.1.8 (www.redcap.au.dk). Statistical tests were conducted using STATA/MP 16.0 (STATA Corp.). The exchange rate of 1 DKK = 0.1649 USD from 31 December 2020 was applied.

Table 1 Clinical characteristics of patients referred for faecal microbiota transplantation (FMT) due to urinary tract infections (UTI) secondary to carriage of multidrug-resistant organisms (MDROs)

Patient no.	Age	Sex	RTX	Charlson Comorbidity Index	Days from index UTI to FMT	Number of UTIs pre-FMT	Number of UTIs post-FMT[a]	Causative organism	Resistance factor
1	65	M	Yes	6	153	6	0	*Klebsiella pneumoniae*	ESBL
2	76	M	Yes	7	126	2	0	*Klebsiella oxytoca*	ESBL
3	57	M	Yes	6	126	4	0	*Klebsiella oxytoca*	ESBL
4	70	M	Yes	9	320	9	1	*E. coli*	ESBL
5	87	F	No	4	60	1	0	*Klebsiella pneumoniae*	ESBL

ESBL extended-spectrum beta-lactamase, *FMT* faecal microbiota transplantation, *RTX* renal transplant, *UTI* urinary tract infection

[a]The follow-up period was patient specific and equal to the number of days from index UTI to FMT, making pre-FMT and post-FMT periods comparable for each patient

The robustness of the base case results was assessed using one-way deterministic sensitivity analyses; one excluding the least expensive patient, and another where the most expensive patient was excluded.

The study was conducted according to the principles stated in the Declaration of Helsinki. All patients were treated according to routine clinical care. All patients provided written informed consent to registration in a central database, making up a consecutive cohort. The study was conducted as a quality improvement study, and access to medical records was approved by the board of directors at Aarhus University Hospital. All patients further provided specific written informed consent to the publication of this report. Data collection was approved by Aarhus University Hospital board of directors, and because no experimental therapies were involved and no biological material was collected, approval from the Regional Ethics Committee was not required according to Danish law. The project was registered with the Danish Data Protection Agency in Central Denmark Region (j.no. 1-16-02–224-16).

RESULTS

In a consecutive cohort of patients referred for FMT between 2015 and 2020 and where the main indication was *Clostridioides difficile* (306 patients in total), we also included five consecutively referred patients suffering from MDRO-related UTIs. This subgroup was made up of four men and one woman, with a median age of 70 years (Table 1). Four of the five patients were kidney transplant recipients and received triple immunosuppressive treatment with prednisolone, tacrolimus, and mycophenolate mofetil. All five patients had several comorbidities, with a median Charlson Comorbidity Index score of 6 (range 4–9). The individual aligned pre- and post-FMT periods for the five patients ranged from 60 to 320 days with a median of 126 days.

The median number of UTIs per patient was 4 (range 1–9) in the pre-FMT period and 0 (0–1) in the post-FMT period, corresponding to a median reduction of 4 (1–8) UTIs after the FMT treatment ($p = 0.031$) (Tables 1 and 2). The number of admission days per patient dropped from a median of 15 (12–47) days in the pre-FMT period to a median of 4 (0–7) days in the post-FMT period and a median reduction of 13 (8–40) days per patient after the FMT treatment ($p = 0.030$) (Table 2). The number of hospital contacts, composed of admissions, outpatient visits, telephone contacts, and emergency room visits, dropped from a median of 28 (3–33) to a median of 11 (4–12), corresponding to a median

Table 2 Clinical health outcomes, hospital costs, and sensitivity analysis in five patients with multidrug resistant organism-related urinary tract infections, before (pre-FMT) and after (post-FMT) faecal microbiota transplantation

	Pre-FMT	Post-FMT	Difference	*p*-value
Base case (n = 5)				
Clinical health outcomes	Median (range)	Median (range)	Median (range)	
Number of UTIs per patient	4 (1–9)	0 (0–1)	−4 (−8 to −1)	0.031
Number of admission days per patient	15 (12–47)	4 (0–7)	−13 (−40 to −8)	0.030
Number of hospital contacts per patient	28 (3–33)	11 (4–12)	−21 (−24 to −1)	0.045
Cost outcomes	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Monthly average cost per patient (USD)	6687 (1996–11,379)	1574 (0–3920)	−5113 (−8841 to −1386)	0.043
Sensitivity analysis, excluding the most inexpensive patient (n = 4)				
Clinical health outcomes	Median (range)	Median (range)	Median (range)	
Number of UTIs per patient	3 (1–6)	0 (0–0)	−3 (−6 to −1)	0.061
Number of admission days per patient	13.5 (12–47)	3 (0–7)	−12.5 (−40 to −8)	0.089
Number of hospital contacts per patient	30 (3–33)	7.5 (4–12)	−21 (−24 to 1)	0.068
Cost outcomes	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Monthly average cost per patient (USD)	7495 (1396–13,594)	1598 (0–5068)	−5897 (−10,375 to 1419)	0.068
Sensitivity analysis, excluding the most expensive patient (n = 4)				
Clinical health outcomes	Median (range)	Median (range)	Median (range)	
Number of UTIs per patient	3 (1–9)	0 (0–1)	−3 (−8 to −1)	0.094
Number of admission days per patient	13.5 (12–27)	3 (0–6)	−12.5 (−21 to −8)	0.016
Number of hospital contacts per patient	23 (3–33)	8 (4–12)	−13.5 (−24 to 1)	0.128
Cost outcomes	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Monthly average cost per patient (USD)	5679 (109–11,249)	1723 (0–5141)	−3955 (−6746 to 1165)	0.068

UTI urinary tract infection, *CI* confidence interval, *FMT* faecal microbiota transplantation

reduction of 21 (1–24) hospital contacts per patient (p = 0.045) (Table 2).

The monthly average costs per patient in the pre-FMT period were USD 6687 (95% CI 1996–11,379) and in the post-FMT period USD 1574 (95% CI 0–3920). We found a reduction in the monthly average cost per patient of USD 5113 (95% CI 1386–8841, p = 0.043) for the population in the post-FMT period compared with the pre-FMT period (Table 2).

The sensitivity analyses testing the robustness of our findings demonstrated that the clinical health outcomes remained unchanged both when excluding the most inexpensive patient and when excluding the most expensive patient (Table 2). However, the costs showed no

statistically significant differences in either of the sensitivity analyses.

DISCUSSION

In this single-centre cohort study, we performed an early economic assessment of the hospital-related costs in patients treated with FMT for MDRO-related UTIs. We found a statistically significant reduction in the overall hospital costs per patient and in the number of UTIs, admission days, and hospital contacts per patient. Although limited to five study participants, the statistically significant reductions in both admissions and hospital-related costs indicate uniform and marked beneficial effects. FMT application was associated with both reduced number of MDRO-related UTIs and hospital admission days, even despite the immunosuppressive therapy used by four of five patients.

Several small studies investigated the use of FMT in patients carrying MDROs in their intestines, such as ESBL-producing *E. coli* or multidrug-resistant *K. pneumoniae* [6, 7, 9, 10]. In accordance with these studies, we found a marked reduction in the number of UTIs per patient. A recent study showed a significant reduction in admission days post-FMT [10]. Combined with the findings in our study, we hypothesize that fewer UTIs lead to fewer admissions and hospital contacts, indicating an improvement in the population's clinical health but not necessarily eradicating the MDRO [14].

In the present study, we used DRG tariffs to value hospital contacts. Because the costs for a specific patient may differ from average costs, using a micro-costing approach could have improved the precision of our cost estimates. We consider it unlikely that more precise estimates would change the conclusions of this early economic assessment. Costs directly related to applying FMT should be considered when evaluating cost-effectiveness. We previously calculated total costs related to donor recruitment and screening, laboratory processing, and clinical application of donor faeces in an early development stage of FMT service [15] and recently published updated cost estimates in a fully developed FMT service [16]. In the present study, we did not include FMT costs in the hospital cost calculations because these vary considerably with the level of development and application method. Comparing the total costs of USD 3519 per colonoscopic FMT with the reduced monthly hospital costs per patient of USD 5113 in the present study indicates that the use of FMT is highly cost-effective. As the application of FMT is refined, e.g., by using encapsulated formulations, this may further improve the effectiveness of the treatment, and cost evaluations should be undertaken in future patient cohorts.

MDRO carrier status remains an investigational indication for FMT. Obtaining high-level evidence for the use of FMT in these patients is challenging because patients are few and heterogeneous, yet still pose a heavy economic burden. A recent multicentre randomised clinical trial was stopped prematurely due to insufficient patient inclusion [14]. While the patients included in our study may not be representative of all patients with MDRO-related UTIs, the marked health economic benefits of FMT demonstrated in our small patient sample underpins the potential of FMT as a cost-effective option. Regardless, the individual patient's health benefits gained from FMT should lead to the development of patient-tailored regimens. The significant clinical improvements indicate a potential for improvements in the quality of life, and future studies should evaluate this impact of FMT on perceived health-related quality of life and additional societal costs.

CONCLUSIONS

The use of FMT to eradicate MDRO carriage markedly reduced the occurrence of UTIs and associated hospital costs. We suggest that this strategy is cost-effective.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, take responsibility for the integrity of the data, and have approved this article to be published.

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Disclosures. Olivia D. Baek, Camilla K. Hjermitslev, Line Dyreborg, Simon M. D. Baunwall, Katrine L. Høyer, Nina Rågård, Lianna H. Hammeken, Johan V. Povlsen, Lars H. Ehlers and Christian L. Hvas declare no conflicts of interest. Lars Holger Ehlers changed his institutional affiliation during the completion of the manuscript from Danish Centre for Healthcare Improvements, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark, to Nordic Institute of Health Economics, Aarhus, Denmark.

Compliance with Ethics Guidelines. The study was conducted according to the principles stated in the declaration of Helsinki. All patients were treated according to routine clinical care. All patients provided written informed consent to registration in a central database, comprising a consecutive cohort. The study was conducted as a quality improvement study, and access to medical records was approved by the board of directors at Aarhus University Hospital. All patients further provided specific informed written consent to the publication of this report. Data collection was approved by Aarhus University Hospital board of directors, and because no experimental therapies were involved and no biological material was collected, approval from the Regional Ethics Committee was not required according to Danish law. The project was registered with the Danish Data Protection Agency in Central Denmark Region (j.no. 1-16-02-224-16).

Data availability. The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request and following anonymisation as required by data protection directives.

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