Infection Prevention in Practice 6 (2024) 100340

Available online at www.sciencedirect.com

Infection Prevention in Practice

journal homepage: www.elsevier.com/locate/ipip

Case Report

Faecal microbiota transplantation for multidrug-resistant organism decolonization in spinal cord injury patients: a case series

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ARTICLE INFO

Article history:
Received 20 July 2023
Accepted 18 December 2023
Available online 27 January 2024

Keywords:
Spinal cord injury
Colonization
Antibiotic resistance
Isolation
Microbiota

SUMMARY

Introduction: The increase of multidrug-resistant (MDR) bacteria in healthcare settings is a worldwide concern. Isolation precautions must be implemented to control the significant risk of transmitting these pathogens among patients. Antibiotic decolonization is not recommended because of the threat of increasing antibiotic resistance. However, restoring gut microflora through faecal microbiota transplantation (FMT) is a hopeful solution.

Patients and method: In 2019—2022, FMT was indicated in seven patients of the Spinal Cord Unit at University Hospital Motol who were colonized with MDR bacterial strains. Five patients tested positive for carriage of carbapenemase-producing *Enterobacteriaceae*, and two were carriers of vancomycin-resistant enterococci. Isolation measures were implemented in all patients. Donor faeces were obtained from healthy, young, screened volunteers. According to local protocol, 200—300 ml of suspension was applied through a nasoduodenal tube.

Results: The mean age of the patients was 43 years. The mean length of previous hospital stay was 93.2 days. All patients were treated with broad-spectrum antibiotics for infectious complications before detecting colonisation with MDR bacteria. MDR organism decolonization was achieved in five patients, and consequently, isolation measures could be removed. Colonization persisted in two patients, one of whom remained colonized even after a third FMT. No adverse events were reported after FMT.

Conclusion: FMT is a safe and effective strategy to eradicate MDR bacteria, even in spinal cord injured patients. FMT can allow relaxation of isolation facilitates, the participation of patients in a complete rehabilitation program, their social integration, and transfer to follow-up rehabilitation centres.

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https://doi.org/10.1016/j.infpip.2024.100340

Introduction

The sharp rise in carbapenemase-producing *Enterobacteriaceae* (CPE) and vancomycin-resistant enterococci (VRE) is becoming a serious global concern [1]. Individuals colonized with these bacteria are at high risk of infection and, simultaneously, pose a risk of pathogen transmission to other patients in healthcare settings. The care of patients colonized with drug-resistant bacterial strains is challenging and requires the implementation of specific measures; these may include strict adherence to isolation precautions and screening of contacts. The isolation regime can adversely affect the scope of care, but it also has a negative impact on the patient's mental health due to the limitation of social contact [2]. It often results in prolonged hospital stays and delays in transfer to a follow-up healthcare facility [3]. Multidrug-resistant (MDR) organism decolonization and treatment of MDR infections are complex and are usually managed by systemic antibiotics, which can be toxic to the patient [4]. In addition, they may not be fully effective and may, in turn, increase antimicrobial resistance due to high selection pressure [5].

The role of the gut microbiota in preventing colonization by antibiotic-resistant pathogens has long been known [6]. The association between antibiotic (ATB) treatment and subsequent detection of resistant strains in the stool, due to gut dysmicrobia has also been observed. These considerations pointed to the potential benefit of decolonization by restoring healthy gut microbiota. Faecal microbiota transplantation (FMT), long used in the management of *Clostridioides difficile* infection (CDI), has proved to be an effective strategy [7]. In recent years, several case reports and case studies have been published evaluating the effect of FMT on eliminating MDR gut bacteria [8–11].

Patients after spinal cord injury (SCI) are at particularly high risk of gut colonization with MDR strains. This risk is associated with frequent stays in intensive care units (ICU), prolonged mechanical ventilation, recurrent respiratory, urinary, or bloodstream infections requiring ATB therapy, and other complications such as skin defects or neurogenic bowel [12]. On the other hand, the implemented isolation regimes interfere with rehabilitation interventions and complicate the operation of rehabilitation facilities. Therefore, we have started using FMT as a promising therapeutic option for our patients colonized by MDR bacteria. Here, we report the outcomes of using FMT for MDR decolonization of the gut in seven patients with SCI.

Patients and method

Patients

In 2019–2022, we identified seven patients of the Spinal Cord Unit at Motol University Hospital in the Czech Republic for faecal bacteriotherapy. Five patients were colonized with CPE, out of which three were colonized by *Klebsiella pneumoniae* (two with CPE New Delhi metallo-beta-lactamase (NDM) and one with CPE oxacilinase (OXA)), and two were colonized by *Escherichia coli* (one with CPE NDM and one with CPE OXA). Two other patients were colonized with VRE. In addition, MDR *Acinetobacter baumannii* was found in two patients. MDR bacteria were first detected in the stool of four patients, in the urine of two patients, and in the respiratory tract of one patient.

Microbiological methods

The presence of CPE or VRE was confirmed using rectal swabs. Each rectal swab was cultured on specific media (CHROMagar CARBA or CAP agar, OXOID). Strain identification was done using Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight (MALDI-TOF) mass spectrometry. Carbapenemase was detected by immunochromatographic rapid test NG-Test CARBA 5 (NG Biotech), and was validated by MALDI-TOF mass spectrometer.

Isolation precautions

Upon detection of MDR bacteria carriage, colonized patients were placed in a separate isolation room, and the Institutional Public Health Officer was notified. Those identified as close contacts were also isolated until negative rectal swab culture results were obtained. Isolation patients received a bath every other day in a separate bathroom. They were allowed to continue their standard rehabilitation program in their room only, however, without the use of out-of-room equipment (e.g. sling system, tilt table, MOTOmed). As a precautionary measure, the staff and visitors were required to wear protective personal equipment (PPE), including surgical gowns, face masks, and gloves, before entering the room. The staff were instructed to maintain hand hygiene and avoid cross-contamination by using separate containers to collect biological specimens. During the follow-up period, stool cultures from isolated patients were collected weekly.

Faecal transplant preparation

All patients isolated due to colonization with MDR bacteria were considered eligible for FMT. The inclusion criteria were confirmation of MDR bacterial colonization by two consecutive rectal swabs, even if the first detection of MDR bacteria was in a different location. Additionally, one positive rectal swab the week before the FMT was required. ATB therapy for any other indication should have been completed at least one week before the FMT. Patients who were candidates for FMT were informed about the procedure, and they signed a consent form upon agreement.

Donor protocol

The closest young healthy relative was eligible as a stool donor for the first patient. An unrelated young healthy volunteer provided a stool for the second patient as no relative was willing to contribute. Both donors completed an anamnestic

questionnaire and underwent a general blood test, serology, and stool examination for intestinal pathogens, including MDR bacteria and parasites. Within six hours of defecation, stool homogenization and filtration were performed to make it ready for use. In other patients, frozen stool samples from a newly established stool bank were used for FMT. These donors were first and second-grade students from the Faculty of Medicine who were initially screened using a questionnaire addressing risk factors for potentially transmissible diseases. They had no underlying diseases and had not taken any ATBs in the last three months. They underwent a physical examination and blood tests. Serology screening was performed to test for HIV, syphilis, and hepatitis A, B, and C. Stool analysis was conducted for the presence of pathogenic bacteria (including MDR strains), viruses, ova, and parasites. Stool samples were donated, and 50g samples were mixed with 100 mL of sterile normal saline and stored as concentrated glycerol stocks at −80°C. After three months, the examination of the donors was repeated.

Treatment protocol

The patients were required to fast from midnight prior to FMT and were given a proton pump inhibitor both in the morning and evening on the day of the procedure. Under gastroscopic control, a nasoduodenal probe was inserted, and 200−300 ml of the extract was applied to the duodenum. Three hours after the procedure, the patient was given one Imodium tablet and instructed to stay seated if possible. He was allowed to take fluids immediately and food two hours after the procedure.

Follow-up procedures

Following FMT, the patient continued in a standard rehabilitation program while in isolation. Stool samples and samples from previously MDR-positive sites were collected weekly. If three consecutive cultures were negative for MDR strains, the patient was considered to be decolonized. To discontinue isolation precautions, the patient was transferred to a clean bed in a different room after taking a bath. No further cultures were needed. In the case of two consecutive positive rectal swabs, repeated FMT was considered. The procedure could be modified as per the guidelines of the Institutional Public Health Officer.

Results

Seven patients underwent FMT (Table I). The mean age of patients was 43 years (19.1−55.8 years). All of them were men and had a motor complete traumatic spinal cord lesion. Six patients were in the post-acute stage of SCI, and one patient in the chronic stage of SCI was admitted for surgical management of extensive trochanteric decubitus ulcer. The mean length of previous hospital stay in acute patients was 93.2 days (26−176 days). Two patients were transferred from the Spinal surgery departments, while four were admitted from long-term ICU. All SCI patients had recurrent infectious complications managed with broad-spectrum ATBs. The average duration between the last use of ATBs and FMT was 20.1 days (7−21 days). None of the previous infections were caused by MDR organisms.

The mean time from the pathogen detection to bacteriotherapy was 32.1 days (range: 13−81 days). Five patients underwent a single FMT, one patient had two, and one had three FMT procedures. The last two patients subsequently received ATBs for urinary tract infection and wound infection, respectively. Decolonization was achieved in five patients, and patient isolation was terminated after a mean of 38.6 days following FMT, based on the above-mentioned criteria. Two patients continued to be positive for MDR strains. One patient with a tracheostomy cannula had *E. coli* CPE OXA in the upper airways; the other patient, who subsequently received ATBs for wound infection, had *K. pneumoniae* CPE NDM persisting in their stool even after the third FMT. The former required early transfer to another healthcare facility, and the latter was discharged home. None of the patients reported any adverse events after FMT.

Discussion

Antimicrobial resistance caused by ATB selective pressure is a growing threat worldwide. Antibiotic resistance is emerging faster than new ATBs are being developed [5]. Over a decade ago, infections caused by pan-resistant strains, refractory to any available ATB were reported [13]. Even when appropriate ATBs are found, they may be less effective and result in recurrences, prolonged hospital stays, and increased mortality [4]. All this is associated with a substantial economic burden.

ICUs are hot spots for the emergence and spread of MDR infections. Severe trauma patients are susceptible to infections due to invasive procedures and an impaired immune response. They often require broad-spectrum ATBs [14]. All patients in our cohort were transiently hospitalized in the ICU and developed post-injury infectious complications that had to be managed with a combination of broad-spectrum ATBs. In addition, four patients had a long-term tracheostomy cannula, and four patients had a decubitus ulcer. Because of neurogenic lower urinary tract dysfunction, permanent urine drainage was achieved via a transurethral catheter in six patients and a suprapubic catheter in one patient.

The primary site of MDR organism colonization is the intestinal tract, which serves as their reservoir [15]. Various decolonization protocols, combining interventions such as isolation regimes, environmental disinfection, systemic use of ATBs and probiotics, and other measures have been developed with varying efficacy [6]. The definitions of decolonization also differ, e.g., in the number of negative samples [5]. Colonization with MDR organisms is limited by the normal gut bacterial flora, referred to as the gut microbiome. A mechanism for this limitation may be the influence of gut bacteria on gut wall permeability. Other mechanisms considered are competition with MDR bacteria for nutrients, pH modification, mucus expression, or effect on cellular immunity [4]. This knowledge resulted in attempts to manage MDR decolonization by restoring the gut microbiome.

Since the involvement of individual bacterial species in the protection against MDR bacteria is currently unknown, the most effective approach appears to be gut microbiota transfer from a healthy individual. Faecal microbiota transplantation restores the microbiota's diversity and complexity, inhibiting pathogenic microorganisms' colonisation. The use of FMT in patients with severe diarrhoea was mentioned for the first time

Table I
Characteristics of spinal cord injury patients colonized with carbapenemase-producing *Enterobacteriaceae* and vancomycin-resistant enterococci and outcomes of faecal microbiota transplantation

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	40,5	55,5	50,9	19,1	54,5	55,8	24,7
Sex	M	M	M	M	M	M	M
Cause of injury	Fall	Sport	Traffic accident	Fall	Sport	Traffic accident	Traffic accident
Neurological level of injury	C5	C4	T3	L1	C5	T10	T5
ASIA Impairment Scale	A	A	A	B	B	A	B
Previous hospitalization (days)	70	142	52	26	93	-	176
Previous infections	Pneumonia, recurrent UTI	Recurrent pneumonia	Catheter sepsis	Recurrent pneumonia, septic shock	Recurrent pneumonia, recurrent UTI	Decubital sepsis, osteomyelitis	Recurrent pneumonia and UTI, sepsis
Prior use of ATB before FMT	MEM, PTZ, CAZ, SAM, AMK, MTZ, FLU	PTZ, AMK, COL, TGC	PTZ, CIP, AMP, SXT, ERT	GEN, PNC, MEM, PTZ, CIP	SXT, MEM, VAN, GEN, AMP, CIP, VAN, SAM	VAN, TGC, SAM, RIF, OFX, LZD, OFX	COL, MEM, PTZ
Time from ATB to FMT (days)	50	20	17	7	19	7	21
Subsequent use of antibiotics	-	-	-	-	FEP, AMK	-	PTZ
Comorbidities	Tracheostomy, esophageal perforation	Tracheostomy, pressure injury, swallow disorder	Pressure injury	Polytrauma, abdominal cavity revision	Tracheostomy, pressure injury	Pressure injury	Polytrauma, tracheostomy
Bacterial species	CPE KP OXA+	CPE EC OXA+	VRE	CPE KP NDM+	CPE KP NDM+, MRAB	VRE	CPE EC NDM+, MRAB
Primary specimen	Stool	Sputum	Stool	Urine	Stool	Stool	Urine
Duration of carriage before FMT (days)	53	15	13	14	81	35	14
Stool donors	Relative	Non-relative	Stool bank - B19	Stool bank - B51	Stool bank - B60, B58, B63	Stool bank - B64	Stool bank - B56, B59
Number of FMTs	one	one	one	one	three	one	two
Time to decolonization (days)	35	-	27	18	-	55	58

UTI, urinary tract infection; ATB, antibiotics; FMT, faecal microbiota transplantation; MEM, meropenem; PTZ, piperacillin/tazobactam; CAZ, ceftazidime; SAM, ampicillin/sulbactam; AMK, amikacin; MTZ, metronidazole; FLU, fluconazole; COL, colistin; TGC, tigecycline; CIP, ciprofloxacin; AMP, ampicillin; SXT, trimethoprim/sulfamethoxazole; ERT, ertapenem; GEN, gentamicin; PNC, penicillin; VAN, vancomycin; RIF, rifampicin; OFX, ofloxacin; LZD, linezolid; FEP, cefepime; CPE, carbapenemase-producing *Enterobacteriaceae*; KP, *Klebsiella pneumoniae*; OXA, oxacilinase EC, *Escherichia coli*; VRE, vancomycin-resistant enterococci; NDM, New Delhi metallo-beta-lactamase; MRAB, multidrug-resistant *Acinetobacter baumannii*.

in the fourth century in China [16]. In the last twenty years, FMT has been used as a standard therapeutic option for CDI, with success rates between 70 and 90% [17]. Multidrug-resistant strains also colonized some CDI patients, and FMT resulted in MDR decolonization. Therefore, it was assumed that FMT could also work for other pathogens and prevent difficult-to-treat infections. In 2015, the first case report was presented of an 82-year-old woman in whom FMT led to CPE decolonization, which facilitated rehabilitation and the transfer to a follow-up care centre [18]. Subsequently, FMT has been proven effective in eradicating both CPE and VRE [19]. As the intestinal tract is a reservoir of MDR pathogens, gut decolonization may also eliminate these pathogens from other areas [8]. This was also the case in some of our patients with primary detection of MDR bacteria in the urinary tract.

The use of FMT in SCI has been reported mainly in experimental medicine. Various studies have evaluated the effect of FMT in mouse models with SCI on improving neurological outcomes [20] or preventing anxiety-like behaviour [21]. In clinical medicine, only one case of FMT use for gut decolonization after SCI has been reported. A case report was presented of a 65-year-old SCI patient who developed severe recurrent CDI after receiving ATB for pneumonia. Following FMT, the patient developed systemic inflammatory response syndrome and required multiple ATB treatments [22]. Our study introduces the first application of FMT to decolonize MDR organisms in the SCI population. In our hospital, FMT is used as a standard therapeutic option for recurrent CDI. The reason for introducing this method for MDR bacteria eradication is the implementation of strict anti-epidemic measures in our hospital, requiring an isolation regime for all colonized patients. After the decolonization of our five patients through FMT, we were able to discontinue isolation precautions, which had a significantly positive impact on their subsequent treatment. They could move out of isolation rooms, which improved their mental state and increased their cooperation with therapists. Moreover, they were able to use out-of-room equipment such as the sling system, tilt table, and MOTOmed. The use of devices like the Cough Assist, Pneuven, or electrical stimulator also became simpler, as these can be difficult to move to an isolation room. Finally, it was easier to use imaging methods for these patients and to transfer them to the next facilities.

Different studies have reported varying success rates of FMT in eradicating MDR pathogens. In a literature review, Yoon *et al.* [23] reported the overall success rates of FMT in eradicating carriage of Gram-positive and Gram-negative MDR bacteria to be 68.2% and 70.6%, respectively. More precisely, the success rates of FMT were 67.4% for CPE and 63.2% for VRE. In our study, FMT had an overall success rate of 71.4% for CPE and VRE combined. The success of MDR eradication can also be affected by other factors. Antibiotics given after FMT seem to be a significant cause of decolonization failure. Bilinski *et al.* [11] found FMT significantly less effective in patients treated with ATBs within the first week after FMT. In our study, one patient had decolonization failure due to subsequent ATB treatment of wound infection.

Yoon *et al.* [23] further summarized different FMT procedures, namely the application into the small bowel by nasogastric or nasojejunal tube or capsule or into the colon by colonoscopy or enema. As no study has compared the effectiveness of different procedures, the most effective strategy has not been identified yet. However, prospectively, the capsule form might prevail due to better tolerability, although capsules need to be administered in large quantities due to their small size. In our study, we use the application route via a nasoduodenal probe inserted under gastroscopic control.

Wang *et al.* [24] presented a systematic review of 50 papers on adverse events during FMT, reporting an overall incidence of 28.5%. The most common adverse event was abdominal discomfort, more often associated with the application in the upper GI tract. No adverse events were observed in our study.

Limitations of the study

Our study has several limitations that must be considered. First, the small number of patients, as well as the presence of various types of MDR organisms, makes it difficult to interpret the results. Secondly, we did not apply a follow-up period to confirm MDR bacteria decolonization after three consecutive negative cultures. Although there is a possibility of recolonization over time, our primary focus was discontinuing isolation precautions to allow for the patient's rehabilitation, change of environment, and improvement of their well-being. Thirdly, we do not use polymerase chain reaction testing to confirm the presence of CPE genes, but we acknowledge that the MALDI-TOF mass spectrometer method is sufficiently sensitive.

Conclusion

FMT is a safe therapeutic option with a high success rate in eradicating MDR bacteria colonisation. It has also proved effective in our small cohort of hospitalized SCI patients. Decolonization of MDR organisms is an essential prerequisite for the relaxation of isolation regimes, which significantly extends rehabilitation options and positively affects patients' mental health. More specifically, following FMT and subsequent MDR bacteria decolonization, our SCI patients benefited from moving out of their rooms, using rehabilitation devices more extensively, and transferring easily to follow-up facilities without any restrictions.

Ethics

All participants received written and oral information about the study before giving their written consent. The study was approved by the Ethics Committee of the Motol University Hospital (No: EK - 441/23).

Acknowledgments

NA.

Conflict of interest

The authors declare no conflict of interest.

Funding statement

The preparation of this paper was supported by the "Movement without Help" foundation.

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