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NOVEL ID CASES

Transmission of Antibiotic-Susceptible *Escherichia coli* Causing Urinary Tract Infections in a Fecal Microbiota Transplantation Recipient: Consequences for Donor Screening?

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Fecal microbiota transplantation (FMT) has been reported to decrease the incidence of recurrent urinary tract infections (UTIs), presumably by restoring microbiome diversity and/or uropathogen competition. We report a 16-year-old female with recurrent UTIs caused by multidrug-resistant *Klebsiella pneumoniae*, for which frequent intravenous broad-spectrum antibiotic treatment was necessary. The patient was treated with FMT from a well-screened healthy donor without multidrug-resistant bacteria in the feces. After FMT, she developed several UTIs with an antibiotic-susceptible *Escherichia coli* that could be treated orally. The uropathogenic *E. coli* could be cultured from donor feces, and whole genome sequencing confirmed donor-to-recipient transmission. Our observation should stimulate discussion on long-term follow-up of all infections after FMT and donor fecal screening for antibiotic-susceptible Enterobacterales.

Keywords. fecal microbiota transplantation; FMT; MDRO; ESBL; uropathogen; urinary tract infection.

Fecal microbiota transplantation (FMT) is recommended for patients with multiple recurrent *Clostridioides difficile* infections. In these patients, FMT also seems to decrease the load of antimicrobial resistance genes and the phylum Proteobacteria (which includes Enterobacterales) [1]. FMT has been explored for gut decolonization in patients with colonization and/or infections with multidrug-resistant organisms (MDROs). However, success rates for decolonization are heterogeneous while spontaneous decolonization has also been described [2, 3]. Recently, gut microbiome dysbiosis has been linked to recurrent urinary tract infections (UTIs) [4]. Several case reports and an observational study suggest that FMT may be an effective treatment to prevent recurrent UTIs [5–12].

Although FMT is generally considered safe, severe adverse events with transmission of multidrug-resistant *Escherichia coli* [13] and Shiga toxin–producing *E. coli* have been reported [14]. Consequently, the US Food and Drug Administration (FDA) issued safety warnings and recommends enhanced screening of donor stool. Here, we report a pediatric patient who underwent FMT because of recurrent MDRO UTIs and highlight transfer of a uropathogenic *E. coli* causing UTIs in the recipient.

CASE REPORT

An FMT was requested for a 16-year-old female with recurrent febrile UTIs and gut colonization with a multidrug-resistant (MDR) *Klebsiella pneumoniae*: extended-spectrum β-lactamase (ESBL)–producing, susceptible to fosfomycin, colistin, and meropenem, with variable susceptibility to nitrofurantoin. The medical history included familial holoprosencephaly, epilepsy, correction of scoliosis due to spasticity, cystic renal dysplasia, and feeding problems for which she had a percutaneous endoscopic gastrostomy tube. The past 2 years she had been regularly admitted for intravenous (IV) meropenem treatment for, on average, 1 UTI every 1–2 months.

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Other treatments included oral fosfomycin and intravesical gentamicin administration, yet without sustained response. The MDR *K. pneumoniae* was repeatedly isolated from urine, perineal swabs, and feces. While urine culture was negative directly following meropenem, fecal cultures were positive for *K. pneumoniae,* suggesting bacterial translocation from the gut via ascension in the urinary tract as underlying mechanism for the recurrent UTIs. However, the patient also had dysfunctional voiding as a possible contributing factor to recurrences, due to severe psychomotor retardation. No signs of focal infection were demonstrated on repeated ultrasound of the kidneys.

The UTIs led to renal scarring documented by DMSA (dimercaptosuccinic acid) scan. Multiple prolonged admissions for IV antibiotic therapy had a profound impact on the quality of life of the patient and her family. Two courses of meropenem within 1 month prompted a request for FMT via the compassionate use program of the Netherlands Donor Feces Bank (NDFB) to attempt gut decolonization and/or decrease the frequency of recurrent UTIs with the MDR *K. pneumoniae*. With no viable alternative treatment option left, the multidisciplinary NDFB working group deemed the patient eligible for FMT. Informed consent was obtained from the parents.

The patient received the FMT (198 mL, prepared from 60 g of feces) via an endoscopically placed duodenal tube under general anesthesia. Prior to FMT, a gram-negative gut decolonization scheme with polymyxin/neomycin 500 000 international units/125 mg orally 4 times daily combined with nitrofurantoin 100 mg orally twice daily was given for 4 days and stopped 24 hours pre-FMT. One day prior to FMT, 2 L of macrogol/electrolytes was administered via the percutaneous endoscopic gastrostomy tube. No complications occurred during the FMT procedure.

The clinical course is summarized in Figure 1. One month post-FMT, the patient was admitted with pyelonephritis caused by an amoxicillin/clavulanic acid–susceptible *E. coli*. After empiric meropenem treatment for 3 days (pending urinary culture results), she was discharged with amoxicillin/clavulanic acid orally (7 days). Three months post-FMT, a second episode of *E. coli* pyelonephritis was treated ambulatory with ciprofloxacin (14 days), though a perineal swab revealed return of the MDR *K. pneumoniae*. At 4 months, a *Klebsiella* pyelonephritis required IV meropenem (10 days). At 5 months, a suspected UTI was treated empirically with IV meropenem (1 day), but this was switched to fosfomycin (10 days) when deemed uncomplicated. At 11 months, pyelonephritis due to a ciprofloxacin- and amoxicillin/clavulanic acid–resistant *E. coli* was treated with IV meropenem. At 14 months, asymptomatic bacteriuria with the MDR *K. pneumoniae* was not treated.

MICROBIOLOGICAL ANALYSIS

We hypothesized that the *E. coli* associated with 3 UTI episodes post-FMT had been transmitted via donor feces. Feces from donor and patient were examined for the presence of antibiotic-susceptible and MDR Enterobacterales. Of the patient, 2 pre-FMT fecal samples were available: before (day FMT −4) and after (day FMT −1) antibiotic pretreatment, and 3 samples after FMT: 1, 8, and 17 months post-FMT. In addition, 2 different *E. coli* isolates cultured from a urine sample 3 weeks post-FMT were available: 1 ciprofloxacin-susceptible and 1 ciprofloxacin-resistant *E. coli* (minimum inhibitory concentration [MIC] ≤.25 mg/L and 1 mg/L, respectively). Both *E. coli* isolates were resistant to trimethoprim-sulfamethoxazole (TMP-SMX) (MIC >320 mg/L) and susceptible to amoxicillin/clavulanic acid (MIC ≤2 mg/L).

Culture

Raw feces aliquots were stored at −80°C. After thawing at room temperature, 10 µL was cultured with enrichment broth with subsequent plating on growth media, as previously described [15]. Colonies morphologically suspect for Enterobacterales were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Microflex, Bruker Daltonik, Bremen, Germany). Susceptibility testing was performed with the VITEK2 system (bioMérieux; Marcy-l'Étoile, France) using European Committee on Antimicrobial Susceptibility Testing breakpoints. ESBL production was confirmed using the double disk method.

The donor feces contained an *E. coli* with a similar antimicrobial resistance pattern as the *E. coli* detected in the patient's urine, resistant to TMP-SMX (MIC ≥320 mg/L) with a ciprofloxacin MIC of 0.5 mg/L. Additionally, a TMP-SMX–susceptible *E. coli*, a non-MDR *K. pneumoniae*, and *Enterobacter cloacae* were cultured from the donor feces.

In the pre-FMT feces sample of the patient before antibiotic pretreatment (day FMT −4), the MDR *K. pneumoniae* was detected, in contrast to the sample after antibiotic pretreatment (day FMT −1). The MDR *K. pneumoniae* was again cultured from feces 1 month and 17 months post-FMT, but not at 8 months. The pre-FMT fecal sample and all post-FMT fecal samples of the patient were negative for the presence of the antibiotic-susceptible *E. coli*.

Whole Genome Sequencing

Whole genome sequencing (WGS) of *E. coli* isolates from the donor feces (n = 2, D1 and D2) and clinical patient urine sample (n = 2, P1 and P2) was performed to assess the relatedness between the strains and the presence of urovirulence factors and antibiotic resistance genes. DNA isolation and sequencing were performed as previously described [15].

The 4 *E. coli* isolates belonged to multilocus sequence typing (MLST) sequence type 69 and differed with a maximum of 4 alleles based on an in-house whole genome MLST scheme (comprising 4503 genes) of the Dutch National Institute for Public Health and the Environment (RIVM)

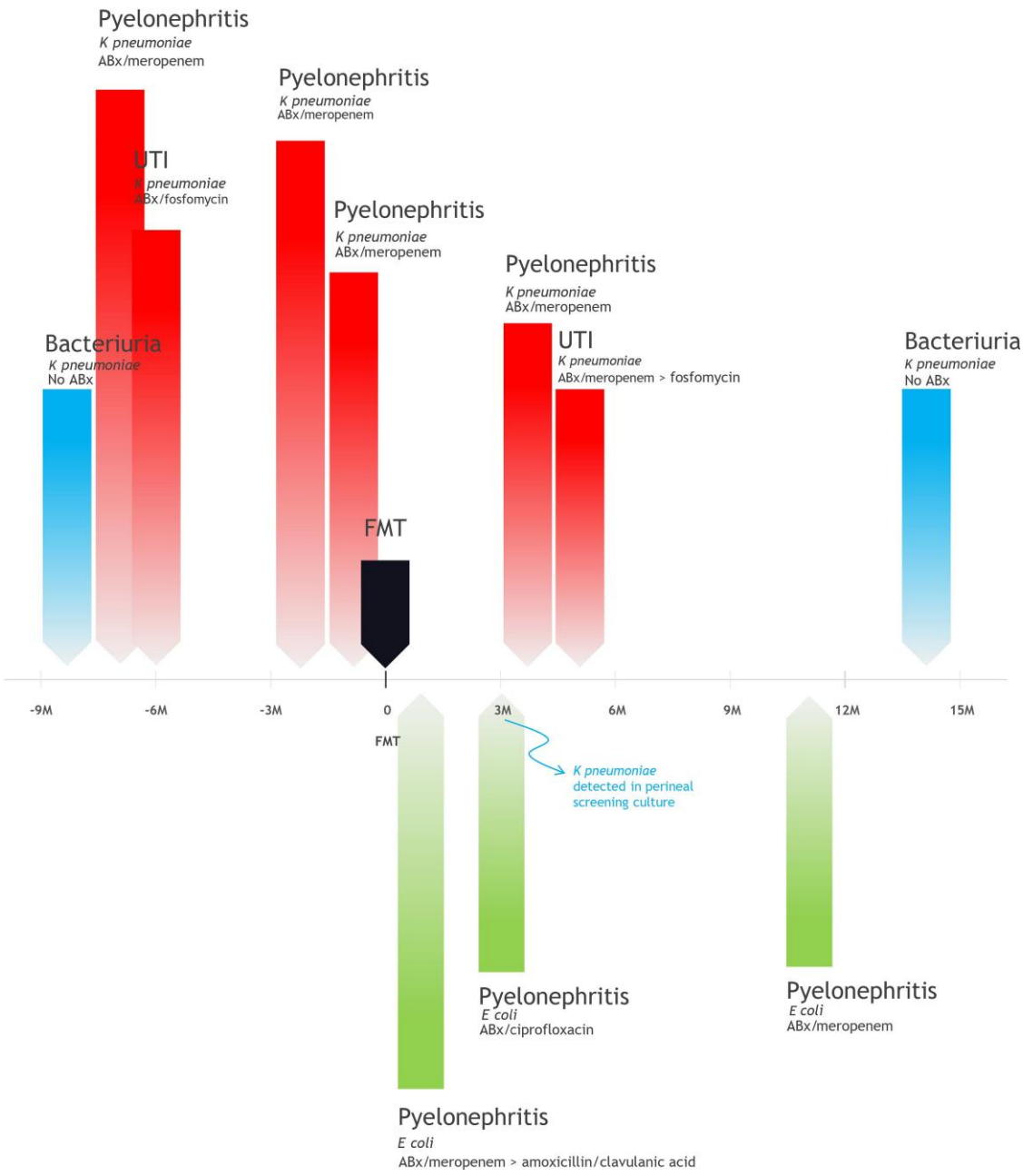

Figure 1. Clinical course of a patient who underwent fecal microbiota transplantation (FMT) for recurrent urinary tract infections (UTIs). Red bars indicate UTIs with positive urine cultures with multidrug-resistant (MDR) *Klebsiella pneumoniae* for which antibiotic treatment was given, blue bars indicate positive urine cultures with MDR *K. pneumoniae* that were not treated, and green bars indicate positive urine cultures with *Escherichia coli* that were treated. Abbreviations: ABx, antibiotic treatment; FMT, fecal microbiota transplantation; M, months relative to transplant; UTI, urinary tract infection.

[16]. This indicates clonal relationship since the cluster cut-off was established at ≤25 alleles. Single-nucleotide polymorphism (SNP) analysis using CLC Genomics workbench version 22 resulted in a maximum difference of 6 SNPs. The isolates formed a separate cluster when compared with MDR *E. coli* isolates from the national database of the RIVM, and belonged to Clermont phylotype D, which is associated with uropathogenicity [17]. Thirteen putative urovirulence factors (PUFs) and 8 additional urovirulence factors were identified (see Supplementary Table 1). Results of genomic antibiotic resistance analysis with the ResFinder database are shown in Table 1.

Table 1. Antimicrobial Resistance Genes Identified in *Escherichia coli* Isolates From Donor Feces and Patient Urine

	Donor *Escherichia coli*		Patient *Escherichia coli*	
Antimicrobial Resistance Gene	D1	D2	P1	P2
aadA5		X	X	X
dfrA17		X	X	X
mdf(A)	X	X	X	X
mph(A)		X	X	X
gacE		X	X	X
qnrB19	X	X	X	X
sitABCD	X	X	X	X
sul1		X	X	X

In 1 donor isolate (D1), only fluoroquinolone resistance (*qnrB19*), multidrug efflux pump (*mdf(A)*), and hydroxide peroxide resistance (*sitABCD*) genes were detected. These genes were also detected in donor isolate D2 and patient isolates P1 and P2, with additional presence of genes for antiseptic (*gacE*), macrolides (*mph(A)*), aminoglycosides (*aadA5*), trimethoprim (*dfrA17*), and sulfonamide (*sul1*) resistance. Abbreviation: X, gene present.

In addition, WGS was performed on *K. pneumoniae* isolates cultured from patient feces pre-FMT (P3) and 1 month post-FMT (P4), and clinical *K. pneumoniae* isolates cultured from urine pre-FMT (P5 and P6) and from a perineal swab 3 months post-FMT (P7). Core genome MLST analysis with Ridom SeqSphere+ indicated clonal relationship of the *K. pneumoniae* isolates: all isolates belonged to sequence type 307 with a maximum number of 5 alleles' difference.

Microbiota Analysis

Microbiota analysis was performed by 16S ribosomal RNA (rRNA) gene amplicon sequencing. After DNA extraction from fecal samples, the 16S rRNA gene was amplified by polymerase chain reaction (PCR). The PCR products (amplicons) were then sequenced. Next, the sequences were assigned to bacterial species at the genus level (eg, *Klebsiella* or *Escherichia/Shigella*). The protocol for DNA extraction from feces and control samples and the protocol for microbiota analysis are described in the Supplementary Data. Results are shown in Figure 2*A* and 2*B*. Before FMT, the order Enterobacterales was abundant in the recipient's feces, but was reduced after antibiotic gram-negative decolonization and FMT. Eight months post-FMT, there was a notable increase in the genus *Akkermansia*. The genus *Klebsiella* could not be identified in the donor feces or any of the patient samples with this technique.

DISCUSSION

A pediatric patient underwent FMT to treat intestinal colonization and multiple recurrent febrile UTIs with MDR *K. pneumoniae*. The assumed source of the recurrent *K. pneumoniae* infections was the gut, illustrated by positive fecal cultures after UTI treatment. Reinfection due to infected renal cysts cannot be excluded. However, after FMT, 3 UTIs with *E. coli* were diagnosed, counterarguing the latter. The *E. coli* could not be cultured from post-FMT fecal patient samples. However, WGS analysis showed that donor and patient *E. coli* (from urine) were genetically identical, confirming FMT transmission of *E. coli* from donor to patient. WGS suggested uropathogenicity of the *E. coli* by assignment to Clermont phylotype D and the presence of PUFs and additional urovirulence factors

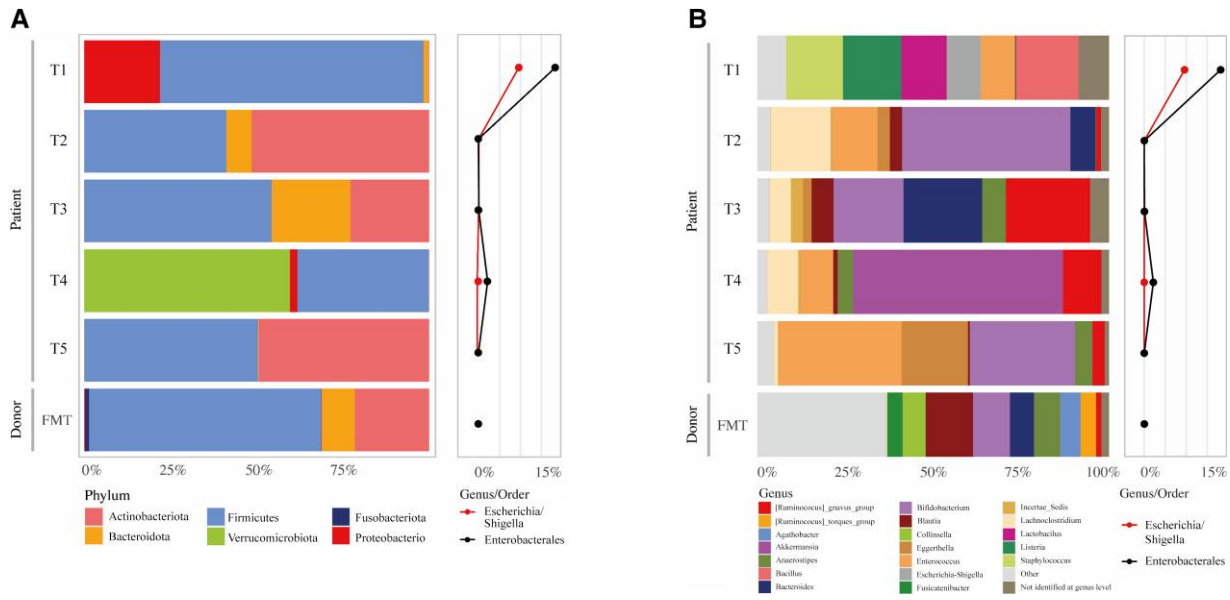

Figure 2. Microbiota composition of donor and patient samples at different sampling timepoints, at the phylum level (*A*) and the genus level (*B*). Abbreviations: FMT, fecal microbiota transplantation; T1, 4 days pre-FMT; T2, 1 day pre-FMT; T3, 1 month post-FMT; T4, 8 months post-FMT; T5, 17 months post-FMT.

[17, 18]. Three months after FMT, the MDR *K. pneumoniae* recurred in a perineal screening culture: WGS analysis confirmed that this *K. pneumoniae* was genetically identical to the ones causing UTIs before FMT.

We hypothesize that the *K. pneumoniae* was temporarily suppressed under the threshold of microbiological detection by the gram-negative gut decolonization (enteral) antibiotics and possibly FMT, but we cannot rule out recolonization from the environment or from a body niche other than the gut. Although FMT was ineffective for resolving recurrent UTIs by MDR *K. pneumoniae* and decolonization in the long term, several *E. coli* UTIs after FMT could be successfully treated with oral antibiotics. Our observation confirms that microbiota manipulation has the potential to influence the course of recurrent UTIs. Like Tariq et al, we hypothesize that the course of recurrent UTIs may be changed due to competition and enhanced colonization resistance after the introduction of the donor microbiota [12]. The genus *Escherichia/Shigella* was detected in low relative abundance (<.02%) by 16S microbiome analysis in patient feces post-FMT and *Klebsiella* could not be identified at all, possibly due to presence below the level of detection. High abundance of *Akkermansia* in 1 post-FMT sample might have been the result of broad-spectrum antibiotic use, though fluctuations in absence of antibiotic treatment have also been observed [19]. Antibiotic use post-FMT might also have influenced the restored state of microbiome colonization resistance, allowing for the return of MDRO UTIs.

FMT as a treatment strategy for intestinal eradication of MDROs in pediatric patients has not been previously described in the literature. Here, feces from an adult donor was used. At present, we have no data on whether using feces from a pediatric or adult donor leads to more favorable results. Likewise, the optimal route of FMT administration for this indication is currently unknown.

Previous reports and FDA warnings underline that screening of feces donors via risk assessments and fecal and blood analyses are important to prevent infectious complications [13–15]. The FDA reports focus on MDROs and enteropathogens; however, the decision on which pathogens to screen for is challenging, since translocation of antibiotic-susceptible bacterial gut commensals (including uropathogens) that may be present in both patient and donor may cause infections under specific patient conditions. Not only the presence but also the abundance of certain gut bacteria may be of importance [20]. Furthermore, although many PUFs are described, a clear molecular definition is lacking [18, 21]. Many Enterobacterales contain PUFs, sometimes more abundantly in strains not associated with UTI [18]. Since donor feces screening currently does not include screening for antibiotic-susceptible *E. coli* and other Enterobacterales, our observation should stimulate more intensive surveillance of post-FMT infections. The exclusion of donor stool based on the mere presence of (antibiotic-susceptible) *E. coli* is likely not feasible, as we anticipate that many donations would be excluded, with a subsequent impact on donor feces availability and economic feasibility of donor stool programs. The consequences for donor feces screening should be the topic of further studies to enhance FMT safety. Ultimately, standardized preparation of live biotherapeutic products may overcome many of these safety issues.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. M. T., E. J. K., T. G. J. M., A. B., and J. P. conceived the study. K. E. V. and J. P. drafted the manuscript. All authors were involved in data acquisition, analysis, or interpretation, and all authors critically reviewed, revised, and approved the manuscript.

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Ethics statement. This study was approved by the Medical Ethics Review Committee of Leiden University Medical Center (P15.154).

Data availability. Raw sequence data of the bacterial isolates described in the article can be found in the European Nucleotide Archive (project accession number PRJEB53460).

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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