Faecal microbiota replacement to eradicate antimicrobial resistant bacteria in the intestinal tract - a systematic review

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REVIEW

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Faecal microbiota replacement to eradicate antimicrobial resistant bacteria in the intestinal tract – a systematic review

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Purpose of review
Antimicrobial resistance is a rising threat to global health and is associated with increased mortality. Intestinal colonisation with multidrug-resistant organisms (MDRO) can precede invasive infection and facilitates spread within communities and hospitals. Novel decolonisation strategies, such as faecal microbiota transplantation (FMT), are being explored. The purpose of this review is to provide an update on how the field of FMT for MDRO decolonisation has developed during the past year and to assess the efficacy of FMT for intestinal MDRO decolonisation.

Recent findings
Since 2020, seven highly heterogenous, small, nonrandomised cohort studies and five case reports have been published. In line with previous literature, decolonisation rates ranged from 20 to 90% between studies and were slightly higher for carbapenem-resistant *Enterobacteriaceae* than vancomycin-resistant *Enterococcus*. Despite moderate decolonisation rates in two studies, a reduction in MDRO bloodstream and urinary tract infections was observed.

Summary and implications
Although a number of smaller cohort studies show some effect of FMT for MDRO decolonisation, questions remain regarding the true efficacy of FMT (taking spontaneous decolonisation into account), the optimal route of administration, the role of antibiotics pre and post-FMT and the efficacy in different patient populations. The observed decrease in MDRO infections post-FMT warrants further research.

Keywords
antimicrobial resistance, decolonisation, faecal microbiota replacement, multidrug-resistant organisms

INTRODUCTION

Antimicrobial resistance (AMR) is a rising and significant threat to global health [1]. In addition to the considerable economic burden, AMR is associated with increased morbidity and mortality [2]. In Europe, more than half of *Escherichia coli* isolates are resistant to at least one antimicrobial group and 7.9% of *Klebsiella pneumoniae* isolates are carbapenem resistant. Moreover, there is a worrisome increase in vancomycin-resistant *Enterococcus* (VRE) (18.3%) and infections with extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-E) [3,4]. Intestinal colonisation with multidrug-resistant organisms (MDRO) facilitates spread of MDRO within communities and hospitals. In both immunocompetent and immunocompromised hosts, gut colonisation can result in invasive infections, with high morbidity and mortality [5,6]. In a retrospective, single-centre study including 107 patients undergoing allogeneic stem cell transplantation (allo-SCT), 31% of patients were colonised with at least one MDRO. Compared to noncolonised patients, colonised patients more frequently experienced bacteraemia post-SCT (48% versus 24%) and

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KEY POINTS

- Due to increasing incidence of gut colonisation and subsequent development of infections with antibiotic resistant bacteria novel gut decolonisation strategies must be explored.
- Based on a limited number of studies, faecal microbiota transplantation (FMT) seems efficacious in eradicating antimicrobial resistant bacteria from the intestinal tract, though decolonisation rates vary between studies.
- When evaluating the effect of FMT, spontaneous decolonisation must be taken into account.
- The optimal route of administration, the role of pre and postantibiotic use, and the efficacy in different patient populations remains to be elucidated.
- Despite modest decolonisation rates, FMT may reduce the number of MDRO infections.

had a significantly worse two-year overall survival (34% versus 74%), with infection being the leading cause of death [7]. To prevent infections with MDRO, strategies to combat MDRO colonisation must be explored. The current ESCMID guideline does not recommend the use of nonabsorbable antibiotics for MDRO decolonisation, as the available evidence on its efficacy is insufficient [8]. More importantly, nonabsorbable antibiotics can contribute to selection of AMR bacteria with subsequent spread to the environment and other individuals [9].

Faecal microbiota transplantation (FMT) has been shown to be an effective treatment for patients with recurrent *Clostridioides difficile* infection (rCDI), a condition that is characterised by an antibiotic-induced disruption of commensal gut microbiota, i.e. dysbiosis [10]. Compared to healthy stool donors, rCDI patients have decreased microbiota diversity and increased numbers of antibiotic resistant genes. In these patients, FMT increases microbiota diversity, while decreasing the number of antibiotic resistance genes [11,12]. Contrary to rCDI, less is known about the degree of dysbiosis in individuals with MDRO colonisation, though some studies report decreased species richness in this population as well [13,14]. Several small studies, including one randomised controlled trial (RCT) [15▪▪], have explored whether FMT is an effective modality to decolonise patients with MDRO, as summarised by several recent reviews [16–18]. These reviews conclude that FMT is a promising treatment strategy for MDRO decolonisation, although the RCT by Huttner *et al.* [15▪▪] did not find a significant difference, but was terminated early. Conclusions are hampered by the major heterogeneity of studies regarding definition of (de)-colonisation, type of MDRO, route of administration, number of transplantations, periprocedural treatment with antibiotics, and duration of follow-up.

The objective of this review is to provide an update on how the field of FMT for MDRO decolonisation has developed during the past year, by highlighting recently published and ongoing studies, ultimately to assess whether FMT is an effective treatment strategy for intestinal MDRO decolonisation. Adding to the recent overview provided by Dharmaratne *et al.* [18], this review includes several newer studies, as well as studies with paediatric patients.

METHODS

This systematic review was conducted in accordance with the *Preferred Reporting Items for Systematic reviews and Meta-analyses* (PRISMA) 2020 guidelines [19]. Details of the protocol for this systematic review were registered in PROSPERO [20].

Eligibility criteria

We included all studies investigating the efficacy of FMT for intestinal MDRO decolonisation. This included clinical trials, cohort studies and case reports in adult and paediatric patients with intestinal MDRO colonisation, including carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem resistant nonfermenters (*Pseudomonas* and *Acinetobacter* spp.), VRE and ESBL-E, confirmed by at least one positive stool sample or rectal/perianal swab. Studies involving immunocompromised patients were eligible for inclusion. We excluded studies only investigating patients colonised with both *C. difficile* and MDRO, since extreme dysbiosis would be likely in this population. For our intervention (FMT) we considered all routes of administration: oral (capsule), nasogastric/duodenal, via colonoscopy or enema. We applied no restrictions to pretreatment (antibiotics, proton pump inhibitor (PPI) and bowel lavage), stool volume, fresh or frozen stool, donor relationship or number of transplantations. Studies only investigating other microbiota-altering treatments, such as probiotics and nonabsorbable antibiotics, were ineligible.

To be included, a study had to report the number of decolonised patients, confirmed by at least one stool sample or rectal/perianal swab post-FMT. Studies reporting the number of MDRO infections post-FMT, e.g. in patients with recurrent urinary tract infections, were only included if they also reported intestinal (de)colonisation. We also included unpublished manuscripts, conference abstracts and ongoing trials. To avoid language bias, studies published in non-English language journals were eligible for inclusion if one of the

team members could read the foreign language (French, Spanish, German and Dutch). All study settings (community, outpatient and inpatient) were allowed. We excluded studies published before 2020, since a recent meta-analysis has been performed with studies published before 2020 [18]. Finally, we excluded murine (or other animal) studies, reviews and meta-analyses.

Search strategy

Multiple electronic databases were searched on May 19th 2021; these included PubMed, Embase, Web of Science, the Cochrane Library, and Academic Search Premier. The search strategy, based on a PICO-style approach, was constructed by librarian specialised in literature searches and is provided in Supplement 1, http://links.lww.com/COG/A40. Next, a 'snowball' search was performed to identify additional studies by searching reference lists of study reports included in this systematic review or earlier reviews on the same topic. For ongoing trials clinicaltrials.gov was searched July 1st 2021, using the following keywords: 'FMT' and 'resistance'. No filters regarding start date were applied, as we did not want to miss ongoing trials that had started before 2020. The entire search was updated in August 2021.

Data extraction and analysis

After removal of duplications in EndNote, references were imported into Covidence software. Title/abstract and full-text screening was performed independently by two reviewers (M.P.B., M.M.C.L.). In case of disagreement, a third researcher was consulted (E.J.K.). A data extraction form was designed, after which one reviewer (M.P.B.) carried out the data extraction using Covidence. For each study, the following data were collected: study design, eligibility criteria, population characteristics, number of participants, type of pathogen, definition of (de)colonisation, detection technique, FMT route of administration, pretreatment, stool volume and type, donor type, decolonisation rate, MDRO infection rate, microbiota composition and duration of follow-up. The Newcastle Ottawa Scale, addressing three specific domains (i.e. selection, comparability and outcome), was used for assessing risk of bias in cohort studies [21]. Risk of bias was assessed by one reviewer (M.P.B.), but in case of uncertainty, a second reviewer was consulted (M.M.C.L). A meta-analysis was not undertaken due to significant heterogeneity regarding study design, population and intervention, and a paucity of included studies. A narrative summary of the data is provided below.

RESULTS

Study selection process

The study selection process is summarised in a PRISMA flowchart (Fig. 1). Most records that were excluded during title and abstract screening involved patients with rCDI. During full-text screening, 35 reports were excluded that either did not include our target population, e.g. patients not colonised with MDRO and receiving FMT for different indications, or did not report intestinal decolonisation rate, e.g. investigating post-FMT faecal composition or decolonisation of extra-intestinal sites instead. Finally, a total of 36 studies were included: seven cohort studies [22,23▪,24▪,25▪▪,26–28], five case reports [29–33], and 24 ongoing trials.

Study characteristics

A complete overview of the included cohort studies and case reports is provided in Table 1, and ongoing trials are summarised in Table 2 (supplement, http://links.lww.com/COG/A41). A total of 254 patients were assessed in the included cohort studies and case reports, with only one study investigating paediatric patients [27]. Eight studies included immunocompromised patients, mostly undergoing allo-SCT [23▪,24▪,27,29–33], and three studies included a total of 14 patients with concurrent rCDI [24▪,26,28]. Although most studies required one positive stool culture or rectal/perianal swab for the definition of colonisation, decolonisation was often confirmed by serial cultures or swabs. Most patients were colonised with CRE ($n = 119$), followed by VRE ($n = 61$), both CRE and VRE ($n = 21$), ESBL-E ($n = 14$), and multidrug resistant *Pseudomonas aeruginosa* ($n = 1$). Ghani *et al.* [24▪] did not specify the type of MDRO for their control group. To the best of our knowledge, the study by Wang *et al.* [33] is the first study investigating the efficacy of FMT for gut eradication of a hypervirulent *K. pneumoniae* strain.

Faecal microbiota transplantation procedure

The primary route of administration for FMT was upper endoscopy; a minority of studies used capsules, enemas or colonoscopy. Whereas stool volume varied (from 25 to 100 g), all stool samples were obtained from healthy, unrelated donors, and were mostly frozen. One study [27] pretreated patients with nonabsorbable antibiotics (oral colistin), and in seven studies patients had used antibiotics in the week prior to FMT [24▪,25▪▪,26,28,29,31,33]. Patients were pretreated with PPI in seven studies, and bowel lavage in six studies. Moreover, the

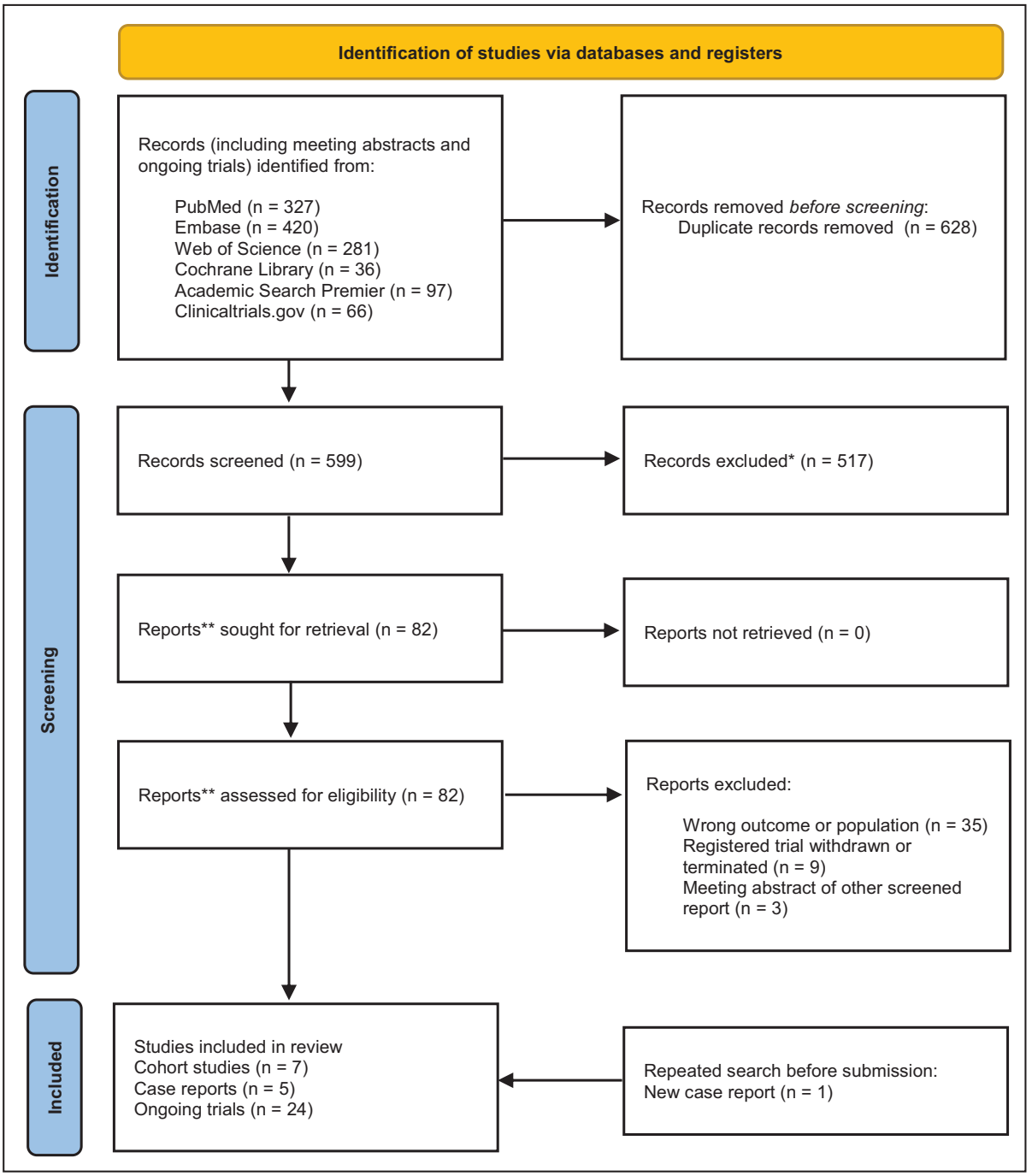

FIGURE 1. PRISMA flowchart of study selection process ∗Large number of records involved patients with recurrent *C. difficile* ∗∗In case of ongoing trials, we assessed the study protocol for eligibility.

number of transplantations varied, with six studies performing multiple transplantations per patient.

Faecal microbiota transplantation efficacy: decolonisation and infection rate

In the seven included cohort studies investigating any MDRO, decolonisation rates ranged from 20 to 90% for patients treated with FMT and 11 to 66% for controls. Duration of follow-up varied from 1 to 24 months. The largest between group difference was seen in the prospective cohort study by Lee *et al.* [22], i.e. a decolonisation rate of 71.4% versus 11.1% for FMT patients and controls respectively. Of note, duration of follow-up was only 3 months, whereas spontaneous decolonisation usually occurs at a later time point [9]. In the largest study performed thus far [25▪▪], decolonisation rates were

Table 1. Overview of included cohort studies and case reports

First author and year	Study design	Population	Number of participants	Number of culture/ PCR to define (de)colonisation	Type of pathogen[a]	FMT procedure[b]	Pretreatment	Antibiotic use post-FMT	Decolonisation rate	Number of MDRO infections post-FMT
Lee 2020 Korea [22]	Prospective cohort study with control group	Adult patients with CRE or VRE colonisation Median age, gender, immune status not reported	Total ($n=38$) FMT ($n=21$) Control ($n=17$)	Colonisation: 2 Decolonisation: NR	FMT cohort: CRE ($n=13$, not further specified), VRE ($n=5$), CRE and VRE ($n=3$) Controls: CRE ($n=7$), VRE ($n=10$)	NR	NR	NR	FMT: 8/20 (40%) at 1 month, 10/14 (71.4%) at 3 months Controls: 0/14 (0%) at 1 month, 1/9 (11.1%) at 3 months	NR
Bar-Yoseph 2020 Israel [23▪]	Prospective cohort study with control group	Adult patients with CRE colonisation Median age: 62 years Male gender: 53% Immunocompromised: 20.5%	Total ($n=39$) FMT ($n=15$) Control ($n=24$)	Colonisation: 1 Decolonisation: 3	FMT cohort: *Klebsiella pneumoniae* ($n=7$), *Enterobacter spp.* ($n=3$), *E. coli* ($n=2$), *Serratia marcescens* ($n=2$), Klebsiella oxytoca ($n=1$) Controls: *Klebsiella pneumoniae* ($n=19$), *Enterobacter spp.* ($n=2$), *E. coli* ($n=3$), *Citrobacter freundii* ($n=1$)	Oral (15 capsules per day for 2 consecutive days) Stool: 25–30 gram, frozen, unrelated donor	AB: no BL: no PPI: yes	FMT cohort: 5/15 (33.3%) Controls: 21/24 (87.5%)	FMT: 9/15 (60%) at 1 month, 8/12 (66.7%) at 6 months Controls: 10/24 (41.7%) at 1 month, 7/13 (53.8%) at 6 months	FMT: 0/15 Controls: 9/24 (37.5%)
Ghani 2020 United Kingdom [24▪]	Prospective cohort study with control group	Group 1: Haematology patients (mostly allo-HSCT) with CRE, VRE or ESBL colonisation Group 2: Patients with MDRO-mediated rUTI, mostly renal transplant recipients, no current infection Controls: similar patients but not undergoing FMT Median age 62.5 years Male gender 55% Immunocompromised: 76% rCDI ($n=4$)	Total ($n=60$) Group 1 ($n=11$) Group 2 ($n=9$) Control ($n=40$)	NR (just 'serial rectal swabs')	Group 1: CRE ($n=8$, including *E. coli*, *Citrobacter freundii* and *Klebsiella spp.*) VRE ($n=3$) or ESBL *E. coli* ($n=2$) Group 2: ESBL ($n=9$): *E. coli* ($n=7$), *Klebsiella pneumoniae* ($n=2$)	Upper endoscopy/naso-duodenal tube Stool: 50 gram, frozen, unrelated donor, 1–2 FMTs per patient	AB: discontinued 24h prior BL: yes PPI: yes	Yes, almost all patients, no absolute number (or specific antibiotic) is reported	7/17 (41%) of group 1 and 2 patients were decolonised (follow-up range 6 weeks - 24 months), NR for control group	Significant reduction in BSI (absolute number NR) and MDRO UTIs (pre-FMT median $=4\pm2$ episodes, post-FMT median $=1\pm2$ episodes) in group 1 and 2 compared to controls.
Seong 2020 Korea [25▪▪]	Prospective cohort study with control group	Adult patients with CRE or VRE colonisation Median age: 69 years Male gender: 53% Immunocompromised: none	Total ($n=83$) FMT ($n=35$) Control ($n=48$)	Colonisation: 1 Decolonisation: 2	FMT cohort: VRE 19/35 (54.3%), CRE 4/35 (11.4%), both 12/35 (34.3%) Controls: VRE 24/48 (50%), CRE 20/48 (41.7%), both 4/48 (8.3%)	At the discretion of the physician: upper endoscopy, oral or colonoscopy Stool: 100 gram, frozen, unrelated donor, 1 FMT per patient	AB: 45% in the week prior BL: yes if colonoscopy PPI: yes if upper endoscopy	19/35 (54.3%) in the week post-FMT	FMT: 65.7% at 6 months, 68.6% at 12 months Controls: 25.0% at 6 months, 27.1% at 12 months	NR
Lee 2021 Korea [26]	Prospective cohort study without control group	Adult patients with CRE or VRE colonisation Median age: 75 years Male gender: 30% Immunocompromised: NR rCDI ($n=2$)	$N=10$	Colonisation: NR Decolonisation: 3	*Klebsiella pneumoniae*, carbapenemase producing ($n=8$), VRE and *Klebsiella pneumoniae* ($n=2$)	Colonoscopy ($n=9$), upper endoscopy ($n=7$), 20 capsules ($n=1$) Stool: volume NR, frozen, unrelated donor, 1–3 FMTs per patient	AB: discontinued 48h prior BL: yes PPI: no	NR	4/10 at 1 month, 5/10 at 3 months and 9/10 at 5 months after initial FMT	NR

Table 1 (*Continued*)

First author and year	Study design	Population	Number of participants	Number of culture/PCR to define (de)colonisation	Type of pathogen[a]	FMT procedure[b]	Pretreatment	Antibiotic use post-FMT	Decolonisation rate	Number of MDRO infections post-FMT
Merli 2020 Italy [27]	Prospective cohort study without control group	Paediatric patients scheduled to undergo allo-HSCT, some having a history of systemic infections with MDRO Median age: 11 years Male gender 80% Immunocompromised: 100%	*N*=5	NR (just 'weekly rectal swabs)	Carbapenemase resistant: *E. coli* (*n*=3), *Klebsiella pneumoniae* (*n*=2), *Klebsiella oxytoca* (*n*=1), *Klebsiella ornithinolytica* (*n*=1), *Enterobacter cloacae* (*n*=1), *Pseudomonas aeruginosa* (*n*=1)	Upper endoscopy/naso-duodenal tube Stool: 100–240 mL, frozen (80%), unrelated donor, 1 FMT per patient	AB: yes, 80% received oral colistin for 3 days BL: no PPI: no	Yes, broad-spectrum antibiotic prophylaxis with piperacillin/tazobactam when neutrophils <500/µl or fever	4/5 (80%) at 1 week, 1/5 (20%) at 1 month	1 episode in 1 patient
Silva 2020 Portugal [28]	Retrospective cohort study	Adult patients with CRE colonisation Median age: 66 years Male gender: 38.4% Immunocompromised: none rCDI (*n*=8)	*N*=13	Colonisation: 1 Decolonisation: 3	CRE, not further specified	Upper endoscopy/naso-duodenal tube Stool: 50 mL, fresh, unrelated donor, number of FMTs NR	AB: only for rCDI patients (until the day before FMT) BL: yes PPI: yes	No	Total: 10/13 (77%) Without rCDI (CRE carriers only): 4/5 (80%), median time to decolonisation 16 weeks	0
Biernat 2020 Poland [29]	Case report	Both patients underwent allo-HSCT (one for AML, one for osteomyelofibrosis) Median age: 28.5 years Male (both patients) Immunocompromised: 100%	*N*=2	Colonisation: 1 Decolonisation: 1	Case 1: ESBL *E. coli* and ESBL *Klebsiella pneumoniae* Case 2: ESBL *Enterobacter cloacae*	Upper endoscopy/naso-duodenal tube Stool: 100 gram, fresh, unrelated donor, 3–4 FMTs per patient	AB: stopped prior to FMT (but recent broad spectrum treatment) BL: no PPI: yes	Yes	Case 1: Eradication of ESBL *E. coli* after first FMT and eradication of ESBL *Klebsiella* after third FMT. Acquired VRE after second FMT, eradicated after third. Colonised with MDR *Acinetobacter baumannii* after third FMT Case 2: Eradication of ESBL *E. cloacae* after first FMT, acquired VRE and ESBL *E. coli* after second and third FMT, eradicated after fourth FMT	1/2 Case 1 died due to *Acinetobac. baumannii* BSI
Bilinski 2020 Poland [30]	Case report	Adult with AML undergoing allo-HSCT Age: 36 years Male Immunocompromised: yes	*N*=1	Colonisation: 1 Decolonisation: 3	CRE (*Klebsiella pneumoniae*, NDM-1)	Upper endoscopy/naso-duodenal tube Stool: 100 gram, fresh, unrelated donor, 2 FMTs	AB: no BL: yes PPI: yes	Yes, metronidazole after first FMT	1/1 at 2 weeks but reappeared after chemotherapy and antibiotic prophylaxis. After a second FMT the patient remained decolonised at 6 months	0

Table 1 (*Continued*)

First author and year	Study design	Population	Number of participants	Number of culture/ PCR to define (de)colonisation	Type of pathogen[a]	FMT procedure[b]	Pretreatment	Antibiotic use post-FMT	Decolonisation rate	Number of MDRO infections post-FMT
Keen 2020 United States [31]	Case report	Patient with rUTI due to ESBL *Klebsiella pneumoniae*. History of kidney and liver transplantation Age: 62 years Female Immuncompromised: yes	$N=1$	Colonisation: 1 Decolonisation: NR (but patient was tested multiple times)	ESBL *Klebsiella pneumoniae*	Enema Stool: single 150 mL suspension (> 10^7 organisms per mL), frozen, unrelated donor, 1 FMT	AB: suppressive ertapenem until 2 days prior to FMT BL: no PPI: no	Yes, oral amoxicillin 6 weeks post-FMT, then intravenous vancomycin, piperacillin/ tazobactam 8 weeks post-FMT and amoxicillin/ clavulanate, followed by cefepime and metronidazole 10 weeks post-FMT	0/1 at 1 month and 4 months post-FMT	2
Su 2021 China [32]	Case report	Patient with AML undergoing allo-HSCT, colonised with CRE prior to conditioning therapy, identified on routine rectal screening. Age: 45 years Male Immunocompromised: yes	$N=1$	Colonisation: 1 Decolonisation: NR (but patient was tested seven times)	Carbapenem resistant *Klebsiella pneumoniae*	Upper endoscopy/naso-duodenal tube Stool: volume NR, frozen, unrelated donor, 2 courses with 17 day interval (three procedures per course)	AB: no BL: no PPI: no	No	1/1 (stool cultures were CRE negative at 1 week, 1 month, 2 months, 3 months, 6 months, 11 months, and 26 months)	0
Wang 2021 China [33]	Case report	Renal transplant patient with CRE bacteraemia and surgical site infection Age: 37 years Female Immunocompromised: yes	$N=1$	Colonisation: 2 Decolonisation: 1	Carbapenem resistant and hypervirulent *Klebsiella pneumoniae*	Upper endoscopy/naso-duodenal tube Stool: volume NR, fresh/ frozen NR, unrelated donor, 1 FMT	AB: meropenem, tigecycline, fosfomycin discontinued 24h prior to FMT BL: yes PPI: yes	No	1/1 at 1 week	0

[a]May surpass total number of patients as some patients were colonised with multiple MDROs.
[b]May surpass total number of patients as some patients had multiple FMTs with different procedures.
AB, antibiotics; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; BL, bowel lavage; BSI, bloodstream infection; CRE, carbapenemase resistant *Enterobacteriaceae*; ESBL, extended spectrum beta-lactamase; FMT, faecal microbiota transplantation; GVDH, graft-versus-host disease; MDRO, multidrug resistant organism; NDM-1, New Delhi Metallo-beta-lactamase – 1; NR, not reported; PPI, proton pump inhibitor; rCDI, recurrent *Clostridioides difficile* infection; rUTI, recurrent urinary tract infection; VRE, vancomycin resistant *Enterococcus*.

65.7% (FMT) versus 25.0% (controls) at 6 months, and remained similar at 12 months (68.6% versus 27.1% for FMT patients and controls, respectively).

Four of seven cohort studies included both CRE and VRE patients. Of these, two reported decolonisation rates for CRE and VRE patients separately [22,25▪▪]. In the study by Lee *et al.* [22] CRE decolonisation rate at 3 months was 88.9% (8/9 patients) for the FMT group and 25% (1/4 patients) for the control group. For VRE patients, decolonisation was only reported for 1 month post-FMT, being 60% (3/5 patients) for the FMT group and 0% (number of patients not specified) for the control group. In the study by Seong *et al.* [25▪▪], the 12-month decolonisation rate for CRE patients was 75% (3/4 patients) and 45% (9/20 patients) for the FMT and control group respectively. For VRE patients, a 12-month decolonisation rate of 52.6% (10/19 patients) for the FMT group and 12.5% (3/12 patients) for the control group was observed.

In the study by Merli *et al.* [27], decolonisation was achieved for four out of five paediatric recipients after 1 week, but all four patients were recolonised after 1 month. All patients received antibiotic prophylaxis after a minimum of 3 days post-FMT, as part of the conditioning regimen for allo-SCT. Recolonisation also occurred during antibiotic prophylaxis (for allo-SCT) in an adult patient. [30] Silva *et al.* [28], Su *et al.* [32] and Wang *et al.* [33] were the only studies in which patients did not receive antibiotics after FMT. Prolonged decolonisation was achieved in four out of five CRE patients in the first study, and in both patients in the case reports.

The occurrence of MDRO infections was reported in four out of seven cohort studies. In the two studies with a control group [23▪,24▪], MDRO infections were less frequent in the intervention group. Although Bar-Yoseph *et al.* [23▪] showed a modest decolonisation rate 6 months post-FMT (66.7%), no MDRO infections occurred in the FMT group. In contrast, 37.5% of patients in the control group experienced MDRO infections. A similar effect was reported by Ghani *et al.* [24▪], where only 41% of patients achieved decolonisation, but there was a significant reduction in bloodstream infections (BSI) (no haematology patient developed bacteraemia with their pre-FMT MDRO) and MDRO UTIs (pre-FMT median $= 4 \pm 2$ episodes, post-FMT median $= 1 \pm 2$ episodes), compared to controls.

Microbiota composition pre- and post-faecal microbiota transplantation

Three case reports [31–33] and two cohort studies [25▪▪,27] reported pre-FMT microbiota composition of patients with MDRO colonisation. Dysbiosis was seen in all patients of the case reports, with *Proteobacteria* making up more than a third of their gut microbiota, most likely due to prolonged broad-spectrum antimicrobial therapy prior to FMT. Low species richness was also seen in several patients in the study by Merli *et al.* [27], with one patient having a microbiota profile that was almost exclusively comprised of *Enterobacteriaceae* (97%). Moreover, Seong *et al.* [25▪▪] showed that patients colonised with VRE had higher counts of *Proteobacteria* en *Verrucomicrobia* than healthy stool donors. Seven studies reported faecal microbiota composition after FMT [23▪,25▪▪,26,27,31–33]. Bar-Yoseph [23▪] showed that post-FMT stool samples of responders, i.e. successfully decolonised patients, resembled those of donors, which was not seen for nonresponders. While abundance of *Enterobacteriaceae* decreased in post-FMT stool samples of responders, it increased for nonresponders. After FMT, significantly higher counts of *Bifidobacterium bifidum* were observed in samples of responders, compared to nonresponders. Lee *et al.* [26] showed greater microbiota diversity post-FMT, with a significantly increased abundance of *Bacteroidetes*, which was also observed in three case reports [31–33].

Ongoing trials

Currently, there are 24 ongoing trials investigating FMT for MDRO decolonisation, including 13 RCTs and 11 prospective cohort studies. The largest RCT (NCT04431934) is aiming to enrol 437 patients and is expected to be completed in December 2022. Very few studies have posted preliminary results, as shown in Table 2 (supplement, http://links.lww.com/COG/A41).

Risk of bias assessment

A summary of the risk of bias assessments for the included cohort studies is presented in Table 3 (supplement, http://links.lww.com/COG/A42). Overall, there were concerns about risk of bias for two out of seven cohort studies [22,24▪], mainly due to drop-outs (without description of those lost), and inadequate descriptions of the study population and outcomes.

DISCUSSION

In this narrative review, we provide an overview of recent studies investigating the efficacy of FMT for MDRO decolonisation. Only a few studies have addressed this question since 2020. In line with earlier reviews on the same topic [16,17,34,35], decolonisation rates varied greatly. Although only

two studies reported decolonisation rates for CRE and VRE separately and sample sizes were small, decolonisation rates were higher for CRE patients, with a large effect size compared to controls. To date, only one RCT investigating the efficacy of FMT for MDRO decolonisation has been published [15▪▪]. In this study, 39 immunocompetent ESBL-E or CRE carriers were randomised to either no intervention or a 5 days course of oral colistin and neomycin followed by FMT. After 35–48 days, there was no significant difference regarding decolonisation rate between the two groups (41% versus 29% for FMT patients and controls respectively). However, the study was limited by not reaching the calculated sample size, using different routes of administration (nasogastric tube and capsules) and pretreating patients with antibiotics in the intervention arm. Furthermore, control subjects were not treated with antibiotics, further complicating assessment of the true efficacy of FMT. A previous review by Yoon *et al.* [16] showed that post-FMT antibiotic use led to lower decolonisation rates. Although we could not draw any firm conclusions from our included studies, we did observe that recolonisation and a high number of MDRO infections occurred in patients that had received antibiotics post-FMT. This could be explained by the finding that post-FMT antibiotic use can blunt FMT engraftment, as shown by metagenomic analysis in another study [23▪]. Another phenomenon that needs to be taken into consideration when interpreting results is spontaneous decolonisation. A systematic review and meta-analysis by Bar-Yoseph *et al.* [9] showed that, in healthcare settings, ESBL-E and CRE colonisation rates spontaneously decreased from 80.2% and 73.9% at 1 month to 35.7% and 34.6% at 12 months respectively. In another systematic review including thirteen studies ($n = 1936$ patients) 80% of VRE patients were decolonised after 40 weeks, however not all studies confirmed decolonisation with three separate swabs [36]. These findings raise the possibility that decolonisation may be falsely attributed to FMT and underline the necessity of a control group when trying to establish the true efficacy of FMT for MDRO decolonisation. Despite this fact, only four of our included studies had a control group, considerably limiting the evidence included in our review. Notably, only two other controlled studies have been conducted prior to 2020 [15▪▪,37].

Intriguingly, while decolonisation rates in two of the larger included cohort studies were moderate, a major reduction in MDRO infections was observed [23▪,38]. In another prospective cohort study assessing the incidence of BSI in rCDI patients treated with either FMT or antibiotics, FMT patients had significantly fewer BSI than patients treated with antibiotics (4% versus 26%) [39]. The authors hypothesise that FMT may have aided in increasing colonisation resistance by restoring a disturbed microbiota. This may be accompanied by decreasing intestinal permeability (by treating CDI) and thus preventing translocation of Gram negative bacteria into the bloodstream. Other possible explanations include that FMT can reduce inflammation (and thereby translocation) as is observed in patients with inflammatory bowel disease or graft-versus-host disease, similar to patients in the study by Ghani *et al.* [38,40,41]. Lastly, even though FMT might not have eradicated the MDRO from the gut completely, it may have reduced the abundance of *Enterobacteriaceae*, and thereby reduced the likelihood of BSI.

Next to the low number of controlled studies, the evidence included in our review is limited by small samples sizes. Two studies reported dropouts, but did not provide a description of those lost. In addition, most studies defined colonisation as one positive stool culture (or PCR) or rectal/perianal swab, whereas colonisation is usually defined as at least two consecutive (positive) samples with the most recent confirmation one week prior to FMT. We chose not to exclude studies that only used one culture or PCR to define colonisation, since this would have significantly reduced the number of eligible studies. Moreover, we observed considerable heterogeneity between studies regarding study population (e.g. including immunocompromised patients), type of pathogens, FMT procedure and post-FMT antibiotic use. Therefore, we need to exercise caution in interpreting the results mentioned in Table 1. Since eight studies included immunocompromised patients, one might question the generalisability of the results. Although based on small numbers, the systematic review by Yoon *et al.* [16]. showed higher decolonisation rates for immunocompromised patients, compared to immunocompetent patients. For rCDI, FMT is as effective in immunocompromised patients as in immunocompetent patients [42]. Nevertheless, invasive MDRO infections are a considerable problem in immunocompromised patients, highlighting the importance of researching the role of FMT in this specific population.

Our review process had some methodological limitations. Although title/abstract and full-text screening were done by two reviewers independently, data extraction and risk of bias assessment was done by one reviewer. However, a second reviewer was always consulted in case of doubt. In case of missing data, we did not contact study authors. Strengths of our review include our comprehensive search strategy, including many databases,

searching for meeting abstracts, and repeating the search before submission of our manuscript.

Future research should include sufficiently powered RCTs with an adequate duration of follow-up to account for spontaneous decolonisation. The protocol for FMT should be standardised with one or more treatments, including the use of different donors to study donor effects. It is possible that different strategies should be applied to CRE and VRE gut eradication. Moreover, more stringent definitions of (de)colonisation should be applied and different pre- and posttreatments and routes of administration should be compared to optimise efficacy. Next to decolonisation, the number of MDRO infections post-FMT should be assessed. As shown in Table 2 (supplement, http://links.lww.com/COG/A41), several large RCTs, including both immunocompromised and immunocompetent patients, are currently recruiting. At least one RCT (NCT04188743) is using a more stringent definition of colonisation, requiring at least two positive rectal swabs prior to FMT. The same RCT is comparing the efficacy of donor stool to autologous FMT. Another RCT (NCT04181112) is pretreating one group with antibiotics, while not pretreating the other group. Different routes of administration are being investigated, though they are not being compared head-to-head within a single upcoming trial.

CONCLUSION

Since 2020, only a handful of smaller, noncontrolled studies investigating the efficacy of FMT for MDRO decolonisation have been published. Although a number of these cohort studies show some effect of FMT for MDRO decolonisation, questions remain regarding the true efficacy of FMT (taking spontaneous decolonisation into account), the optimal route of administration, the role of pre- and post-FMT antibiotic use, and the efficacy in different patient populations. Interestingly, despite modest decolonisation rates, FMT reduced the number of MDRO infections, a finding warranting further exploration.

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Conflicts of interest

There are no conflicts of interest.

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