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Original article

Oral decontamination with colistin plus neomycin in solid organ transplant recipients colonized by multidrug-resistant *Enterobacterales:* a multicentre, randomized, controlled, open-label, parallel-group clinical trial

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ABSTRACT

Objectives: To evaluate the efficacy of oral colistin-neomycin in preventing multidrug-resistant *Enterobacterales* (MDR-E) infections in solid organ transplant (SOT) recipients.
Methods: Multicentre, open-label, parallel-group, controlled trial with balanced (1:1) randomization in five transplant units. SOT recipients were screened for MDR-E intestinal colonization (extended-spectrum β-lactamase or carbapenemase producing) before transplantation and +7 and + 14 days after transplantation and assigned 1:1 to receive treatment with colistin sulfate plus neomycin sulfate for 14 days (decolonization treatment (DT) group) or no treatment (no decolonization treatment (NDT) group). The primary outcome was diagnosis of an MDR-E infection. Safety outcomes were appearance of adverse effects, mainly diarrhoea, rash, nausea and vomiting. Patients were monitored weekly until 30 days after treatment. Intention-to-treat analysis was performed.
Results: MDR-E rectal colonization was assessed in 768 SOT recipients; 105 colonized patients were included in the clinical trial, 53 receiving DT and 52 NDT. No significant decrease in the risk of infection by MDR-E was observed in the DT group (9.4%, 5/53) compared to the NDT group (13.5%, 7/52) (relative risk 0.70; 95% confidence interval 0.24–2.08; p 0.517). Four patients (5.6%), three (5.6%) in the DT group and one (1.9%) in the NDT group, developed colistin resistance. Twelve patients (22.7%) in the DT group

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had diarrhoea, eight related to treatment (15.0%); one patient (1.8%) developed skin rash and another (1.8%) nausea and vomiting. Two patients (3.8%) in the NDT group developed diarrhoea.
Conclusions: DT does not reduce MDR-E infections in SOT. Colistin resistance and adverse effects such as diarrhoea are a potential issue that must be taken seriously. **Maria Carmen Fariñas, Clin Microbiol Infect 2021;■:1**

Introduction

Patients receiving solid organ transplants (SOT) are at risk of developing infections by multidrug-resistant Gram-negative bacilli, mainly in the first month after transplantation [1–10]. Multidrug-resistant *Enterobacterales* (MDR-E) which produce extended-spectrum β-lactamase (ESBL) and/or carbapenemase or over-production of intrinsic chromosomal AmpC β-lactamases account for more than one third of infections in SOT recipients [1,2,6].

Faecal colonization by MDR-E has been described as an important risk factor for infection by the same strains in different types of patients as well in SOT recipients [1,2,7,11–19]. Furthermore, because the bowel is considered a key reservoir of MDR-E, decolonization treatment (DT) using oral nonabsorbable antibiotics has been tested as a means of controlling transmission and infection by these organisms. DT has been associated with eradication rates ranging from 42% to 68% in randomized controlled clinical trials [20,21]. However, doubts have been raised about the effectiveness of DT as a result of high recolonization rates and the risk of selecting for drug-resistant pathogens [14,15,17,22].

The aim of this study was to investigate the efficacy of nonabsorbable antibiotics in reducing MDR-E infections in SOT recipients in a clinical trial setting.

Methods

Trial design and setting

This trial was a multicentre, open-label, parallel-group, controlled trial with balanced (1:1) randomization conducted in five transplantation units in Spain and is part of a larger national cohort study (ENTHERE) [23,24]. The participating hospitals were: the Coordinating Center, Hospital Universitario Marqués de Valdecilla (Santander); Hospital Universitario de Cruces (Bilbao); Hospital Clinic Universitari (Barcelona); Hospital General Universitario Gregorio Marañón (Madrid); and Hospital Universitario Ramón y Cajal (Madrid). Isolation measures are provided in the Supplementary Material. The study was conducted in accordance with the Declaration of Helsinki and registered in the EudraCT clinical trials registry (2013-004838-15). The study protocol was reviewed and approved by the institutional ethics committee at the five participating hospitals in line with local regulations. All patients provided two written informed consent documents agreeing to participate in the cohort study and the clinical trial.

Participants

Eligible participants were all adults 18 years or older undergoing liver, kidney or combined liver/kidney and kidney/pancreas transplantation between 29 August 2014 and 31 March 2018 who tested positive for MDR-E in the rectal swab taken within 48 hours before transplantation. MDR-E were defined for this study as strains producing one or more ESBL, plasmid-mediated or derepressed AmpC or carbapenemases. During the trial, the patient recruitment rate was lower than expected because of a lower incidence of colonization by pretransplantation MDR-E. The monitoring committee recommended modifying the eligibility criteria to include patients with first positive swabs on days +7 and + 14 after transplantation. The protocol was amended, approved by the ethics committee and modified in the clinical trial registry.

Patients with active MDR-E infection and those treated 1 month before transplantation with active antibiotics against MDR-E were excluded. Other exclusion criteria were: contraindications to the use of the study drugs, enrolment in previous studies and resistance of MDR-E strains to colistin (defined as MIC >2 mg/L).

Randomization

A computer-generated randomization list with a constant block size of ten was administered by an independent epidemiologist who was unaware of the study. The random sequence was generated at the coordinating centre.

Interventions

Patients randomized to the treatment arm received selective intestinal decolonization with oral colistin sulfate (50 mg equivalent to 42 mg colistin base or 1.26 million units 4 times a day) (Laboratorios-Desarrollos-Farmaceuticos, Bajo Aragón, Defabar, Aragon, Spain) and oral neomycin sulfate (250 mg equivalent to 178 mg neomycin base 4 times a day) (Laboratorios-Salvat, Esplugues de Llobregat, Barcelona, Spain) for 14 days. DT administration and compliance monitoring are shown in the Supplementary Material. Patients in the control group did not receive oral antibiotics (no DT (NDT) group).

Follow-up

Patients were followed up with active screening for faecal MDR-E and clinical assessment. Monitoring was performed weekly from the time patients were included in the study until 30 days after randomization.

Outcomes

The primary outcome was development of MDR-E infections during the 30 days after treatment. Secondary outcomes included: intestinal colonization by MDR-E and change in colistin MICs between baseline and the final visit. Safety outcomes were appearance of adverse side effects mainly diarrhoea, rash, nausea and vomiting. Infections were defined according to US Centers for Disease Control and Prevention criteria [25]. Intestinal colonization was defined as the isolation of MDR-E in a rectal swab. Microbiologic success of DT was defined as the absence of MDR-E, when the final rectal swab was negative in at least three follow-up smears.

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Microbiologic methods

Rectal samples were obtained by swabbing and then cultured as described previously [23,24]. All isolates underwent susceptibility testing for 24 antimicrobials by standardized broth microdilution according to Clinical and Laboratory Standards Institute guidelines [26]. Standard PCR was used to amplify several genes encoding extended-spectrum β-lactamases (*bla*TEM, *bla*SHV and *bla*CTXM) and carbapenemases (*bla*KPC, *bla*VIM, *bla*IMP, *bla*NDM and *bla*OXA-48), and multiplex PCR was performed to detect plasmid-mediated AmpC (*bla*CIT, *bla*FOX, *bla*MOX, *bla*DHA, *bla*ACC and *bla*EBC). Clonal relatedness between isolates obtained in the same patient was assessed by repetitive element sequence–based PCR and pulsed-field gel electrophoresis.

Sample size

The sample size was estimated assuming a risk of infection of 30% in MDR-E–colonized patients; it was hypothesized that decolonization should achieve an absolute reduction by 20% to be clinically useful. Using a two-tailed alpha risk of 0.05 and a beta risk of 0.2, 83 patients in each study arm were needed with an anticipated dropout rate of 10%. The sample size was recalculated *post hoc* targeting a risk reduction of at least 25%, necessitating 53 patients per group, due to reports on emergence of colistin resistance [27,28].

Post hoc analysis

Although it was not included in the clinical trial registry description, patients were also followed for 1 year as part of the scheduled follow-up described in the methodology of the ENTHERE cohort study (unpublished data) in which the clinical trial was nested. Data were collected on infections diagnosed during 1 year after transplantation, and a rectal sample was taken via swabbing at the end of 1-year follow-up.

Statistical analysis

Statistical analysis was performed using intention-to-treat (ITT) and per-protocol (PP) approaches. The ITT population included all randomized patients; PP population included all patients who fulfilled the eligibility criteria and received the intervention. Subgroup analyses were performed according to the type of SOT. For analytical purposes, kidney/pancreas and kidney/liver transplants were included in the kidney and liver groups respectively. Outcome analyses planned for the subgroup analysis were the same as for the overall sample.

Proportions of patients were compared between groups with the Mantel-Haenszel chi-square test or the Fisher exact test, as appropriate. Relative risks (RR) and their 95% confidence intervals (CIs) were calculated. A p value of <0.05 was considered statistically significant. Statistical analysis was performed by SPSS 19.0 and Stata 11.0 software.

Results

Inclusion of participants

The study flowchart is shown in Fig. 1. During the study period, 768 patients were screened, of whom 105 were randomized, 53 to the DT group and 52 to the NDT group.

Baseline data

The study groups showed similar baseline clinical and demographic characteristics with no statistically significant differences in age, type of transplants included, comorbidities or risk factors for infection (Table 1).

Table 2 shows MDR-E strains isolated in the baseline rectal swab. ESBL-producing bacteria were the most frequently isolated microorganisms in both DT and NDT groups, representing 59.6% (65/109) of the total MDR-E isolates. Overall, 21.1% (23/109) of the strains were carbapenemase producers, most of which were *Klebsiella pneumoniae* (20/109, 18.3%) which also produced ESBLs (18/109, 16.5%). No differences were found between the two study groups.

Outcomes

Posttransplantation infections by MDR-E 30 days after treatment

No significant decrease in the risk of infection by MDR-E was observed in the DT group (9.4%, 5/53) compared to NDT group (13.5%, 7/52) (RR 0.70; 95% CI 0.24–2.08; p 0.517) in the ITT analysis (Table 3). Results were unchanged in the PP analysis (5/49 vs. 7/50; RR 0.73; 95% CI 0.25–2.14; p 0.563).

In the subgroup analysis by transplant type, four patients with liver transplantation had MDR-E infections: ITT analysis, one (4.4%) of 23 patients in the DT group and three (15.8%) of 19 in the NDT group (RR 0.28; 95% CI 0.03–2.44; p 0.313), and PP analysis, one of 23 vs. three of 18 (RR 0.26; 95% CI 0.03–2.30; p 0.303). Eight patients with kidney transplants had MDR-E infections: ITT analysis, four (13.3%) of 30 in the DT group and four (12.1%) of 33 in the NDT group (RR 1.10; 95% CI 0.30–4.01; p 1.00), and PP analysis, four of 26 vs. four of 32 (RR 1.20; 95% CI 0.33–4.40; p 1.00) (Supplementary Table S1). The characteristics of the MDR-E isolates are described in Supplementary Table S2.

Rectal colonization 30 days after treatment

In the ITT analysis, the colonization rate at 30 days after treatment was lower in the DT group (29/53, 54.7%) than in the NDT group (38/52, 73.1%), although the difference was not statistically significant (RR 0.75; 95% CI 0.56–1.01; p 0.050).

Colistin resistance

Four patients (all liver transplant recipients), three (6.1%) of 49 in the DT group and one (2.0%) of 50 in the NDT group, developed colistin resistance during the study (MIC values increased from <0.125 mg/L to 32 and 128 mg/L) (PP analysis: RR 2.94; 95% CI 0.32–27.36; p 0.618) (Table 3). None developed any type of infections during follow-up. All 11 isolates of colistin-resistant *K. pneumoniae* in all four patients were tested for plasmid-encoded *mcr-1* genes for colistin resistance, which were not detected in any of the isolates.

Adverse events related to treatment

Fourteen patients (26.4%) in the DT group and two (3.8%) in the NDT group had adverse events. In the DT group, 12 patients (22.7%) had diarrhoea, eight related to treatment (15.0%), and treatment was discontinued in five (9.4%); one patient (1.8%) developed skin rash and another one (1.8%) had nausea and vomiting, and both discontinued treatment. Both patients in the NDT group developed diarrhoea.

Post hoc analysis of 1-year follow-up

A total of 103 (98.1%) of 105 patients included in the clinical trial were followed for 1 year. Overall, 64 (61.0%) of 105 patients

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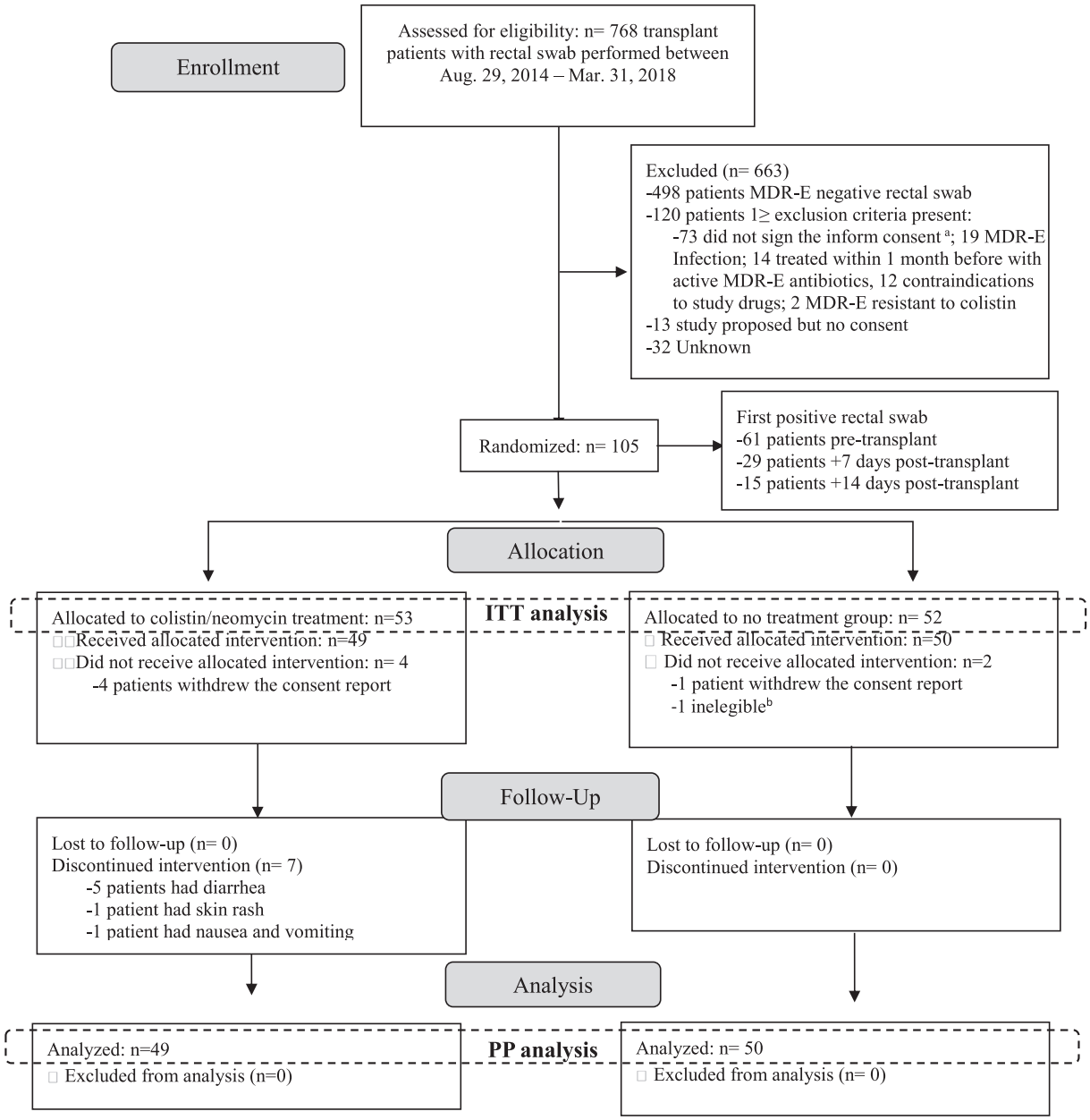

MDR-E, multidrug-resistant *Enterobacterales*; ITT analysis, intention-to-treat analysis; PP analysis, per-protocol analysis.
[a] Patients verbally agreed to participate but finally did not sign the informed consent.
[b] Inelegible: a second laboratory report was issued 24 hours later, stating that a second MDR-E isolated from the baseline swab was resistant to colistin

Fig. 1. Trial design. MDR-E, multidrug-resistant *Enterobacterales*; ITT analysis, intention-to-treat analysis; PP analysis, per-protocol analysis. [a]Patients verbally agreed to participate but did not provide written informed consent. [b]For those ineligible, a second laboratory report was issued 24 hours later stating that a second MDR-E isolated from baseline swab was resistant to colistin.

presented an infection of any type between inclusion in the clinical trial and the 1-year follow-up. The percentage of patients with infection in the NDT group was higher (65.4%, 34/52) than in the DT group (56.6%, 30/53), although the difference was not statistically significant (p 0.357) (Supplementary Table S3).

In the subgroup analysis by transplant type, there was no significant difference in the risk of infection among DT and NDT groups except for urinary infections in liver transplants (p 0.034) (Supplementary Table S4).

A rectal sample was obtained via swabbing from 75 patients (72.8%), 40 in the DT group and 35 in the NDT group. Swabs were positive for MDR-E in 15.0% (6/40) of patients in the DT group versus 25.7% (9/35) in the NDT group. The RR of decolonization at 1 year was 1.42 (95% CI 0.78–2.57).

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Table 1
Baseline characteristics by group

Characteristic	DT group ($N = 53$)	NDT group ($N = 52$)	p
Male	38 (71.7)	38 (73.1)	1.00
Age, y, mean (SD)	56.3 (11.0)	57.0 (12.6)	0.756
Type of transplant			0.230
Liver	23 (43.4)	16 (36.5)	
Kidney	29 (54.7)	32 (61.5)	
Kidney/pancreas	1 (1.9)	1 (1.9)	
Liver/kidney	0	3 (5.8)	
First positive rectal swab			
Before transplantation	29 (54.7)	32 (61.5)	
Day +7 after transplantation	13 (24.5)	16 (30.8)	
Day +14 after transplantation	11 (20.8)	4 (7.7)	0.156
Comorbidities			
Charlson comorbidity index >2	26 (49.1)	29 (55.8)	0.491
McCabe-Jackson index			
Nonfatal	29 (54.7)	25 (48.1)	
Ultimately fatal	24 (45.3)	27 (51.9)	0.560
Obesity	9 (17.3)	11 (21.6)	0.626
Ex-alcoholic	15 (29.4)	10 (19.6)	0.290
Smoking			
Current smoker	9 (17.3)	7 (13.7)	
Former smoker	13 (25.0)	16 (31.4)	0.734
Myocardial infarct	2 (3.8)	2 (3.8)	1.000
Congestive heart failure	3 (5.7)	3 (5.8)	1.000
Peripheral artery disease	6 (11.3)	4 (7.7)	0.741
Cerebrovascular disease	1 (1.9)	2 (3.8)	0.618
Chronic pulmonary disease	3 (5.7)	6 (11.5)	0.319
Connective tissue disease	3 (5.7)	0	0.243
Peptic ulcer	3 (5.7)	6 (11.5)	0.319
Diabetes mellitus	7 (13.2)	4 (7.7)	0.526
Moderate/severe renal disease	29 (54.7)	36 (69.2)	0.160
Moderate/severe liver disease	23 (43.4)	20 (38.5)	0.693
Solid neoplasm (no metastasis)	15 (28.3)	16 (30.8)	0.833
HCV infection	0	1 (1.9)	0.495
Risk factors for infection			
Invasive procedures (1 month before)	22 (42.3)	20 (39.2)	0.842
Dialysis catheters	18 (34.0)	17 (32.7)	0.892
Cardiac catheterization	1 (1.9)	1 (1.9)	0.970
Urinary catheterization	2 (3.8)	1 (1.9)	0.564
Gastroscopy	1 (1.9)	1 (1.9)	0.970
Hospital admission (1 year before)	22 (43.1)	21 (40.4)	0.843
Prior surgical procedure	8 (15.4)	5 (9.6)	0.555
Prior ICU	2 (3.9)	3 (5.8)	1.00
Infections (2 months before)	3 (6.0)	3 (5.8)	1.00
Prior (1 month) antibiotic treatment	3 (6.0)	2 (3.8)	1.00

Data are presented as *n* (%) unless otherwise indicated. DT, decolonization-colistin/neomycin treatment; ICU, intensive care unit; NDT, no decolonization treatment.Groups were compared by two-sided chi-square or Fisher exact p test.

Discussion

Rectal colonization by MDR-E has been described as a major risk factor for infection by the colonizing bacteria in different types of patients, and eradication of these colonizers has been used as a preventive strategy. To our knowledge, this is the first report of a randomized controlled trial examining an oral colistin and neomycin decolonization regimen for rectal MDR-E carriers and its impact on the development of infections in patients undergoing liver and kidney transplantation.

Alevizakos et al. [14] showed in a meta-analysis an extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) rectal colonization rate of 17% among liver transplant recipients and 24% among kidney transplant recipients. Carbapenemase-producing *Enterobacterales* (CPE) colonization varies between 2.5% in liver recipients and 10.8% in kidney recipients [15]. Freire et al. [19] in a prospective cohort study found that before liver transplantation, 18% of patients screened positive for carbapenem-resistant *Enterobacterales* (CRE) carriage in surveillance cultures. However, after liver transplantation, 31% of patients had positive CRE surveillance cultures at the time of hospital discharge. In our study the overall prevalence of rectal colonization by ESBL-E or CRE was 35.1% with no differences between participant hospitals.

The eradication of colonizing microorganisms has been attempted with several strategies and in various groups of patients in different settings [14–19]. A double-blind, placebo-controlled, randomized study conducted by Huttner et al. [20] in patients with various comorbidities examined the impact of oral neomycin and colistin on intestinal ESBL-E carriage detected by rectal swab. The authors demonstrated a temporary rectal decolonizing effect of oral antibiotics. Saidel-Odes et al. [21] have shown that a colistin-based regimen could be a suitable decolonization therapy for transplant recipients or immunocompromised patients pending chemotherapy with carbapenem-resistant *K. pneumoniae* colonization. In our study colonization rate at 30 days after treatment was lower in the DT group than in the NDT group, although without reaching statistical significance.

Giannella et al. [17] showed that CPE colonization at liver transplantation or acquired after liver transplantation were the strongest predictors of CPE infection. In our study we found that patients who received DT became infected at a lower rate than untreated patients, although these differences were not statistically

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Table 2
Multidrug-resistant *Enterobacterales* species in baseline rectal swab

Characteristic	DT group ($N = 55$ isolates)		NDT group ($N = 54$ isolates)		p
	Liver transplant	Kidney transplant	Liver transplant	Kidney transplant	
Total isolates	24 (43.64)	31 (56.36)	19 (35.18)	35 (64.81)	
Escherichia coli	11 (20.00)	12 (21.82)	10 (18.52)	18 (33.33)	0.291
ESBLs	9	11	10	16	
AmpC	1	1	0	2	
Carbapenemase	1	0	0	0	
Klebsiella pneumoniae	10 (18.18)	11 (20.00)	5 (9.26)	11 (20.37)	0.343
ESBLs	8	3	3	3	
Carbapenemase	0	1	0	1	
ESBLs + carbapenemase	2	7	2	7	
Citrobacter freundii	2 (3.64)	4 (7.27)	2 (3.70)	4 (7.41)	0.973
ESBLs	0	0	0	2	
AmpC	2	4	1	2	
Carbapenemase	0	0	1	0	
Enterobacter cloacae	1 (1.82)	3 (5.45)	1 (1.85)	1 (1.85)	0.410
AmpC	1	3	1	0	
Carbapenemase	0	0	0	1	
Enterobacter aerogenes	0	1 (1.82)	0	1 (1.85)	0.969
AmpC	0	1	0	1	
Morganella morganii	0	0	1 (1.85)	0	0.304
AmpC	0	0	1	0	

Data are presented as *n* (%). AmpC, AmpC β-lactamase; DT, decolonization-colistin/neomycin treatment; ESBL, extended-spectrum β-lactamase; NDT, nondecolonization treatment.
Baseline rectal swab refers to first positive rectal swab when the patient was included in clinical trial (before transplantation, +7 and + 14 days after transplantation). One liver and one kidney transplant recipient in the DT group and two kidney transplant recipients in the NDT group had two multidrug-resistant *Enterobacterales* isolated (*Klebsiella pneumoniae* and *Escherichia coli*).
Groups were compared by two-sided chi-square or Fisher exact p test.

Table 3
Outcomes in study population at 30 days after treatment

Characteristic	DT group ($N = 53$)	NDT group ($N = 52$)	RR (95% CI)	p
Patients with infections by MDR-E	5 (9.43)	7 (13.46)	0.70 (0.24–2.07)	0.517
Total number of infections by MDR-E	7 (13.21)[a]	9 (17.31)[b]		
Urinary	4 (7.56)	7 (13.46)	0.56 (0.17–1.80)	0.359
Abdominal	1 (1.89)	0	—	1.000
Bacteraemia	0	1 (1.92)	—	1.000
Surgical site infection	2 (3.77)	0	—	0.495
Skin and soft tissue infection	0	1 (1.92)	—	1.000
Rectal colonization 30 days after treatment	29 (54.72)	38 (73.08)	0.75 (0.56–1.01)	0.050
Colistin resistance	3 (5.66)	1 (1.92)	2.94 (0.32–27.39)	0.618
Adverse events related to treatment	14 (26.42)	2 (3.85)	6.87 (1.64–28.74)	0.001
Diarrhoea	12 (22.64)	2 (3.85)	5.89 (1.38–25.03)	0.005
Skin rash	1 (1.89)	0	—	1.000
Nausea and vomiting	1 (1.89)	0	—	1.000

Data are presented as *n* (%) unless otherwise indicated. CI, confidence interval; DT, decolonization-colistin/neomycin treatment; MDR-E, multidrug-resistant Enterobacterales; NDT, nondecolonization treatment; RR, risk ratio.
Intention-to-treat analysis. Groups were compared using two-sided chi-square or Fisher exact p test.
[a] Two patients had two different infections.
[b] One patient had two different infections; another patient had two equal infections.

significant. This was the case for both MDR-E infections and any other type of infection. When we performed subgroup analysis by type of transplantation, fewer patients among the liver recipients who received DT developed infection of any kind. However, no significant differences were observed in these patients with respect to MDR-E infections. ESBL and carbapenemase-producing *K. pneumoniae* from a urinary focus was the most frequently isolated microorganism. One in ten patients developed infection by the same baseline colonizing microorganism at the end of clinical trial.

A major concern related to decolonization with oral antibiotics is resistance, as it could be associated with further development of antimicrobial resistance to the drugs used [14,15,17,22,27,28]. Colistin resistance in the rectal flora was detected in three liver recipients in the DT group and in one liver recipient in the NDT group, none of whom developed MDR-E infection. Determination of plasmid-encoded colistin resistance genes *mcr*-1 by amplification was negative in all colistin-resistant isolates. No colistin resistance was found in kidney recipients. The main adverse effect associated with DT was diarrhoea, observed in almost 22% of treated patients, leading to discontinuation in almost 10%. There is no doubt that the administration of antibiotics disturbs the microbiome and the long-term health implications are not yet well understood [29].

Limitations and strengths

One of the limitations of our study is the absence of a blinding procedure. This was considered unnecessary because the outcomes were objective measurements not influenced by the assessment of the patient or the researcher collecting the information.

The other issue is that rectal swabs and not faecal samples were used to assess colonization. The sensitivity of swabs for detecting resistant pathogens present in small amounts is lower than that of faecal samples; nevertheless, there is evidence that rectal swabs are

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more sensitive than other anatomic sites for detecting MDR-E and have been proposed as the most appropriate specimens for detecting gastrointestinal carriage when a stool specimen is not considered feasible [30]. One major limitation of our study is that it was underpowered for the primary outcome. Finally, we included a subgroup analysis by transplant type, and although we recognize the lack of power for these analyses, we believe that they could add relevant information on the different types of MDR-E infections that are associated with the procedure. Our study has several strengths, notably its randomized design and the multicentre setting.

Conclusions

A 14-day regimen of oral colistin and neomycin does not reduce MDR-E infections. In addition, concerns about adverse effects such as diarrhoea and the development of colistin resistance should be taken seriously. We do not recommend decolonization using our regimen in routine clinical practice. More multicentre studies in SOT patients with larger sample sizes are needed.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.12.016.

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