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1 **Fecal microbiota transplant: A novel biological approach to extensively**  
2 **drug-resistant organism-related non-relapse mortality.**

3 Andrew J Innes<sup>1,2</sup>, Benjamin H Mullish<sup>3</sup>, Fiona Fernando<sup>2</sup>, George Adams<sup>2</sup>, Julian R  
4 Marchesi<sup>3,4</sup>, Jane F Apperley<sup>1,2</sup>, Eimear Brannigan<sup>5</sup>, Frances Davies<sup>5</sup> and Jiri Pavlů<sup>1,2</sup>

5

6 <sup>1</sup> Centre for Hematology, Faculty of Medicine, Imperial College London, Hammersmith Hospital  
7 Campus, Du Cane Road, London, W12 0NN

8 <sup>2</sup> Department of Hematology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du  
9 Cane Road, London, W12 0HS

10 <sup>3</sup> Division of Digestive Diseases, Department of Surgery and Cancer, Faculty of Medicine, Imperial  
11 College London, St Mary's Hospital Campus, South Wharf Road, Paddington, London, W2 1NY, UK

12 <sup>4</sup> Division of Organisms and Environment, School of Biosciences, Cardiff University, Cardiff, UK

13 <sup>5</sup> Department of Infectious diseases and Immunity, Imperial College Healthcare NHS Trust,  
14 Hammersmith Hospital, Du Cane Road, London, W12 0HS

15 **Running Title:** FMT: A biological approach to XDRO

16

17 **Key Words:** Hematopoietic cell transplantation, non-relapse mortality, supportive care, extreme drug  
18 resistant bacteria, multi-drug resistant bacteria, carbapenemase-producing Enterobacteriaceae  
19 (CPE)

20

21 **Corresponding author:**

22 Jiri Pavlů  
23 Imperial College NHS Trust  
24 Hammersmith Hospital  
25 Du Cane Road  
26 London, W12 0NN  
27 Tel 0203 313 8117  
28 Fax 0203 313 3965  
29 jiri.pavlu@nhs.net

30

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35 **Summary**

36 Extensively drug-resistant organisms (XDRO) are a global threat to health. Colonisation with XDRO  
37 prior to hematopoietic cell transplantation (HCT) frequently results in delayed delivery of  
38 antimicrobials to which the organisms are susceptible and significantly increases non-relapse  
39 mortality. Their inherent resistance to available antimicrobial agents coupled with a preponderance  
40 to evolve further resistance makes biological approaches attractive. Suppression of pathogenic  
41 organisms by fecal microbiome transplantation has previously been demonstrated, and here we  
42 detail use of this approach to successfully suppress XDRO prior to HCT that permitted an uneventful  
43 transplant course in an otherwise high-risk situation.

44 Non-relapse mortality (NRM) of allogeneic hematopoietic cell transplantation (HCT) has  
45 progressively fallen over the last four decades. Better supportive care, particularly in managing  
46 infection has significantly contributed to the improved safety over that period. However,  
47 antimicrobial resistance poses a significant global threat to health (1), and the emergence of  
48 extensively drug-resistant organisms (XDRO) within HCT units now poses a direct threat to transplant  
49 recipients (2). Gut colonisation with XDRO has been associated with an increased NRM (3) and  
50 infections with XDRO during neutropenic periods are complex to manage and associated with a high  
51 mortality (2). Innovative approaches in preventing and managing them are therefore necessary to  
52 avoid reversing much of the progress made in limiting NRM over the last 4 decades.

53 A 63-year-old man presented to our institution with a new diagnosis of Philadelphia positive acute  
54 lymphoblastic leukemia and received treatment following the UKALLXII trial schedule (4). He  
55 achieved complete remission after induction chemotherapy together with imatinib. Following  
56 intensification chemotherapy and continuous imatinib, allogeneic HCT was recommended to  
57 consolidate his therapy. His treatment course was complicated by two separate episodes of  
58 extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* bloodstream infections, two  
59 episodes of *Clostridium difficile* infection (CDI), and central line-related methicillin sensitive  
60 *Staphylococcus aureus* bacteremia. Each infection was successfully treated with antimicrobials, but  
61 he was subsequently found to be colonised with a highly-resistant *ges-5* carbapenemase-producing  
62 Enterobacteriaceae (CPE), *Klebsiella oxytoca*, on routine rectal screening (table 1).

63 While gut colonisation with XDRO does not pose any significant risk *per se*, these organisms can  
64 cause opportunistic infection during periods of prolonged neutropenia. Rates of spontaneous  
65 clearance of these organism from colonised individuals are low, even in immunocompetent hosts,  
66 ranging from 7-30% (5,6). Treatment options for elimination of XDRO from their site of origin within  
67 the intestine are limited; non-absorbable antimicrobial agents often lead to only transient  
68 suppression (5), and may precipitate the development of further resistance. Given the success of  
69 donor fecal microbiota transplant (FMT) in the management of recurrent/refractory CDI (7), and the  
70 apparently acceptable safety profile when used for CDI in the HCT setting (9), there is considerable  
71 interest in the potential role of FMT in gut decontamination prior to HCT. Recipients of FMT for CDI  
72 have been shown to have fewer antibiotic-resistant organisms within their gut microbiota following  
73 transplantation (10) and there are emerging clinical reports of successful use of FMT in gut  
74 decontamination of a variety of XDRO (including ESBL and CPE) (11), even in the setting of  
75 haematological disorders (8). Therefore after discussion, this patient was offered FMT prior to

76 allogeneic HCT in an attempt to eradicate the XDRO and *C. difficile* from its intestinal niche, with the  
77 aim of minimising his HCT NRM.

78 Following informed consent, the patient received gut preparation with four days of oral vancomycin  
79 and neomycin, both 500mg four times daily. Antibiotics were stopped 24 hours prior to FMT  
80 delivery, and preparation was completed with iso-osmotic bowel purgatives (Kleen Prep). The  
81 unrelated donor stool was pre-screened, and negative for *C. difficile* PCR and toxin, as well as for  
82 XDRO; other routine donor screening for transmissible infection was also negative (12). Preparation  
83 of the transplant occurred immediately after stool donation under strict anaerobic conditions, using  
84 an adapted version of a previously-described protocol (13) and stored at -80°C until required. The  
85 FMT product comprised a thawed slurry of around 100ml homogenised stool preserved in a mixture  
86 of glycerol and phosphate buffered saline (15:85, v/v) and was delivered via nasogastric tube.  
87 Fasting was instituted six hours prior to receipt of the FMT, and treatment with a proton-pump  
88 inhibitor (omeprazole) and pro-kinetic (metoclopramide) were administered one hour prior to FMT  
89 delivery. The patient was allowed to eat and drink normally one-hour post-administration. Following  
90 the procedure, he experienced mild nausea, loose stool and abdominal discomfort, which all  
91 resolved after 24 hours without any specific intervention. Repeat rectal screening 7 days following  
92 the FMT showed continued carriage of the ESBL *E. coli* but no evidence of *ges-5 K. oxytoca* CPE or *C.*  
93 *difficile*. By day 16 after FMT neither the CPE nor ESBL were detected on rectal screening swabs  
94 (Table 1).

95 Two weeks after FMT, the patient underwent a fludarabine (30mg/m<sup>2</sup> D-7 to -3) and melphalan  
96 (140mg/m<sup>2</sup> day -2) conditioned reduced intensity sibling allogeneic HCT, with standard cyclosporine  
97 and methotrexate graft-versus-host disease (GvHD) prophylaxis. The transplant course was  
98 complicated by one episode of neutropenic fevers on day +5, with isolation of a fully-sensitive  
99 *Enterococcus faecalis* from blood cultures (table 1). Empirical treatment with piperacillin-tazobactam  
100 (4.5g three times daily), amikacin (15mg/kg once daily), teicoplanin (12mg/kg twice daily for three  
101 doses, followed by 12mg/kg once daily) as per local policy with addition of colistin (3 million units  
102 twice daily) resulted in prompt resolution of fever within 24 hours, and following isolation of the  
103 sensitive organism antimicrobials were de-escalated to piperacillin-tazobactam and teicoplanin. A  
104 second episode of neutropenic fever developed on day +10, and responded to a change in  
105 antimicrobials from piperacillin-tazobactam to meropenem (1g three times daily), and cultures  
106 remained sterile. Neutrophil engraftment was achieved on day +25 and the patient was discharged  
107 from hospital on day +29. At day +100 he was well, with no evidence of leukemia, GvHD or XDRO by  
108 rectal screening. At 12-months post-transplant the patient remains well and in remission.

109 Carbapenemase-producing micro-organisms are now endemic in a number of countries (1,14) and  
110 the preponderance of these organism to extend their resistance spectrums is now contributing to  
111 the emergence of strains resistance to our last resorts antimicrobials (15). A paucity in novel  
112 antimicrobials means that current approaches are restricted to minimising the risk of XDRO  
113 colonisation by antimicrobial stewardship and infection control, as well as managing clinical infection  
114 with complex, and often more toxic, antimicrobial schedules. Novel strategies are therefore  
115 required, and biological approaches would seem most favourable given the weaknesses of our  
116 current pharmacological armoury. Resident gut commensals are adapted to the intestinal  
117 microenvironment and have developed complex ecological networks upon which they have  
118 subsequently become interdependent. Pathogens are equally reliant on their microenvironment,  
119 and competition for critical nutrients, alteration of pH or oxygen tension, and production of toxic  
120 metabolites are all mechanisms by which healthy commensals are capable of suppressing pathogens  
121 (16). While FMT has been reported in decontamination of XDRO in immunocompromised (17)  
122 patients and those with blood disorders before (8) here we detail our use of this biological approach  
123 in the suppression of XDROs in order to minimise NRM prior to allogeneic HCT. Our experience  
124 supports the use of FMT in this setting as safe and tolerable, and warrants further study of efficacy in  
125 a randomised fashion. The suppression of XDRO by FMT pre-HCT is particularly pertinent because  
126 rather than simply identifying an addition risk factor for NRM, the presence of XDROs should be  
127 considered a potentially modifiable risk factor, and this distinction is exceptionally important in risk  
128 stratification.

129

130

131 **Legend**

132 Table 1. Microbiological sample results/Timeline. *E.Coli*, *Escherichia coli*, *K. Oxytoca*, *Klebsiella*  
133 *Oxytoca*, *S. aureus*, *staphylococcus aureus*, *E. Faecalis*, *Enterococcus faecalis*, R, resistant, S,  
134 susceptible, I, intermediate, C. difficile, *Clostridium difficile*, PCR, Polymerase chain reaction, HCT,  
135 hematopoietic cell transplantation, XRDO, extensively drug-resistant organism.

136

137 References

- 138 1. Cantón R, Akova M, Carmeli Y, Giske C, Glupczynski Y, Gniadkowski M, et al. Rapid evolution  
139 and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin Microbiol Infect.*  
140 2012;18:413–31.
- 141 2. Satlin MJ, Cohen N, Ma KC, Chen L, Kreiswirth BN, Walsh TJ, et al. Bacteremia due to  
142 carbapenem-resistant Enterobacteriaceae in neutropenic patients with hematologic  
143 malignancies. *J Infect.* 2016;73:336–45.
- 144 3. Bilinski J, Robak K, Peric Z, Marchel H, Karakulska-Prystupiak E, Halaburda K, et al. Impact of  
145 Gut Colonization by Antibiotic-Resistant Bacteria on the Outcomes of Allogeneic  
146 Hematopoietic Stem Cell Transplantation: A Retrospective, Single-Center Study. *Biol Blood*  
147 *Marrow Transplant.* Elsevier Inc; 2016;22(6):1087–93.
- 148 4. Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR, et al. UKALLXII/ECOG2993:  
149 addition of imatinib to a standard treatment regimen enhances long-term outcomes in  
150 Philadelphia positive acute lymphoblastic leukemia. *Blood.* 2014 Feb 6;123(6):843–50.
- 151 5. Huttner B, Haustein T, Uçkay I, Renzi G, Stewardson A, Schaerrer D, et al. Decolonization of  
152 intestinal carriage of extended-spectrum B-lactamase-producing Enterobacteriaceae with  
153 oral colistin and neomycin: A randomized, double-blind, placebo-controlled trial. *J Antimicrob*  
154 *Chemother.* 2013;68(10):2375–82.
- 155 6. Oren I, Sprecher H, Finkelstein R, Hadad S, Neuberger A, Hussein K, et al. Eradication of  
156 carbapenem-resistant Enterobacteriaceae gastrointestinal colonization with nonabsorbable  
157 oral antibiotic treatment: A prospective controlled trial. *Am J Infect Control.* Elsevier Inc;  
158 2013;41(12):1167–72.
- 159 7. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal  
160 Infusion of Donor Feces for Recurrent *Clostridium difficile*. *N Engl J Med.* Massachusetts  
161 Medical Society; 2013 Jan 16;368(5):407–15.
- 162 8. Bilinski J, Grzesiowski P, Sorensen N, Madry K, Muszynski J, Robak K, et al. Fecal Microbiota  
163 Transplantation in Patients with Blood Disorders Inhibits Gut Colonization with Antibiotic-  
164 Resistant Bacteria: Results of a Prospective, Single-Center Study. *Clin Infect Dis.* 2017;[epub  
165 ahea:1–28.
- 166 9. Webb BJ, Brunner A, Ford CD, Gazdik MA, Petersen FB, Hoda D. Fecal microbiota

- 167 transplantation for recurrent *Clostridium difficile* infection in hematopoietic stem cell  
168 transplant recipients. *Transpl Infect Dis*. 2016;18(4):628–33.
- 169 10. Millan B, Park H, Hotte N, Mathieu O, Burguiere P, Tompkins TA, et al. Fecal Microbial  
170 Transplants Reduce Antibiotic-resistant Genes in Patients with Recurrent *Clostridium difficile*  
171 Infection. *Clin Infect Dis*. 2016;62(12):1479–86.
- 172 11. Manges AR, Steiner TS, Wright AJ, Manges AR, Steiner TS, Fecal AJW. Fecal microbiota  
173 transplantation for the intestinal decolonization of extensively antimicrobial- resistant  
174 opportunistic pathogens : a review. *Infect Dis (Auckl)*. 2016;48(2016):587–92.
- 175 12. Mullish BH, Marchesi JR, Thursz MR, Williams HRT. Review Microbiome manipulation with  
176 faecal microbiome transplantation as a therapeutic strategy in *Clostridium difficile* infection.  
177 *QJM*. 2015;108:355–9.
- 178 13. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized Frozen Preparation for  
179 Transplantation of Fecal Microbiota for Recurrent *Clostridium difficile* Infection. *Am J*  
180 *Gastroenterol*. Nature Publishing Group; 2012;107(5):761–7.
- 181 14. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase producing  
182 *Enterobacteriaceae*. *Emerg Infect Dis*. 2011;17(10):1791–8.
- 183 15. Liu Y-Y, Wang Y, Walsh TR, Yi L-X, Zhang R, Spencer J, et al. Emergence of plasmid-mediated  
184 colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological  
185 and molecular biological study. *Lancet Infect Dis*. 2016 Feb;16(2):161–8.
- 186 16. Kamada N, Chen GY, Inohara N, Núñez G. Control of pathogens and pathobionts by the gut  
187 microbiota. *Nat Immunol*. 2013;14(7):685–90.
- 188 17. Biliński J, Grzesiowski P, Muszyński J, Wróblewska M, Mądry K, Robak K, et al. Fecal  
189 Microbiota Transplantation Inhibits Multidrug-Resistant Gut Pathogens: Preliminary Report  
190 Performed in an Immunocompromised Host. *Archivum Immunologiae et Therapiae*  
191 *Experimentalis*. 2016. p. 255–8.

192

193 **Contributions:** AJI, BHM, FD, JRM, EM, JFA and JP conceived and implemented the treatment  
194 strategy and prepared the manuscript. BHM performed the procedure with the assistance of FF and  
195 GA, and the advice of JRM. All authors reviewed and revised the manuscript before approving the  
196 final draft.

Days post FMT	-224	-209	-203	-177	-168	-164	-30	-30	-30	-	0	14	16	16	16	19	23	29	36
Sample source	Blood cultures x 2	Stool	Blood cultures x 2	Stool	Rectal screen	Rectal screen	Blood cultures & line tip	Rectal screen x 2	Rectal screen x 2	Rectal screen x 2	Rectal screen	Reduced intensity sibling HCT	Rectal screen	Rectal screen	Rectal screen	Blood cultures	Rectal screen	Rectal screen	Rectal screen
Organism	<i>E. coli</i>		<i>E. coli</i>		<i>K. oxytoca</i> GES-5	<i>K. oxytoca</i> GES-5	<i>S. aureus</i>	<i>E. coli</i>	<i>E. coli</i>	<i>E. coli</i>	<i>E. coli</i>		No XDRO identified	No XDRO identified	No XDRO identified	<i>E. faecalis</i>	No XDRO identified	No XDRO identified	No XDRO identified
Amikacin	S		S		S	S	-	S	S	S	S					-			
Amoxicillin	R		R		R	R	-	R	R	R	R					S			
Aztreonam	R		R		R	R	-	R	R	R	R					-			
Cefoxitin	R		R		R	R	-	R	R	R	R					-			
Ceftazidime	R		R		R	R	-	R	R	R	R					-			
Ceftriazone	R		R		R	R	-	R	R	R	R					-			
Cefuroxime	R		R		R	R	-	R	R	R	R					-			
Ciprofloxacin	R		R		R	R	S	R	R	R	R					-			
Co-Amoxiclav	R		R		R	R	-	R	R	R	R					-			
Collistin	S		S		S	S	-	S	S	S	S					-			
Ertapenem	S		S		R	R	-	S	S	S	S					-			
Gentamicin	R		R		R	R	S	R	R	R	R					-			
Meropenem	S		S		I	I	-	S	S	S	S					-			
Piperacillin-tazobactam	I		I		R	R	-	R	R	R	R					-			
Temocillin	R		R		R	R	-	R	R	R	R					-			
Tigecycline	S		S		S	S	-	S	S	S	S					-			
Tobramycin	R		R		R	R	-	R	R	R	R					-			
Trimethoprim	R		R		R	R	S	R	R	R	R					-			
Clindamycin	-		-		-	-	S	-	-	-	-					-			
Erythromycin	-		-		-	-	S	-	-	-	-					-			
Flucloxacillin	-		-		-	-	S	-	-	-	-					-			
Fusidic acid	-		-		-	-	S	-	-	-	-					-			
Oxacillin	-		-		-	-	S	-	-	-	-					-			
Penicillin	-		-		-	-	R	-	-	-	-					-			
Rifampicin	-		-		-	-	S	-	-	-	-					-			
Teicoplanin	-		-		-	-	S	-	-	-	-					S			
Tetracycline	-		-		-	-	S	-	-	-	-					-			
Vancomycin	-		-		-	-	S	-	-	-	-					S			