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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^{1,2}, Benjamin H Mullish³, Fiona Fernando², George Adams², Julian R
4 Marchesi^{3,4}, Jane F Apperley^{1,2}, Eimear Brannigan⁵, Frances Davies⁵ and Jiri Pavlů^{1,2}

5

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

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

10 ³ 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 ⁴ Division of Organisms and Environment, School of Biosciences, Cardiff University, Cardiff, UK

13 ⁵ 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/m² D-7 to -3) and melphalan
96 (140mg/m² 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.

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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	-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	Faecal microbiota transplant	Rectal screen	Reduced intensity sibling HCT	Rectal screen	Rectal screen	Stool	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	<i>C. difficile</i> PCR negative	<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					