

## LETTERS TO THE EDITOR

## Fecal Microbiota Transplant for Multidrug-Resistant Organism Decolonization Administered During Septic Shock

*To the Editor*—Antibiotic resistance (AR) is a growing crisis fueled by globalization and widespread antibiotic use.<sup>1</sup> The development of new antibiotics has not matched the emergence of MDROs,<sup>2</sup> making it further necessary to explore other avenues to combat this issue. Fecal microbiota transplantation (FMT) is one such option that needs further exploration in the acute-care setting in cases with therapeutic limitations associated with AR such as the following.

A 57-year-old man who suffered a traumatic brain injury in China was transferred to Emory University Hospital after spending several months in an intensive care unit (ICU). In China, he underwent decompressive craniectomy and clot evacuation followed by tracheostomy, percutaneous endoscopic gastrostomy (PEG)–tube placement, and chronic indwelling urinary catheter placement. The hospitalization was complicated by pneumonia with a sputum culture that grew *Klebsiella pneumoniae* documented to only be sensitive to tigecycline. He was treated with meropenem, which was continued upon transfer to our hospital to treat hospital-acquired pneumonia as well as a newly diagnosed catheter-associated urinary tract infection. In total, he received ~5 weeks of broad-spectrum antibiotics. He did well without antibiotics for a 3-week period before developing a fever and leukocytosis.

Repeat urine culture at Emory University Hospital grew carbapenemase-producing *Klebsiella pneumoniae* per the modified Hodge test resistant to all tested antibiotics. Infectious diseases personnel were consulted. Antimicrobial susceptibility testing (AST) was performed using the Micro-Scan WalkAway-96 plus system and the Neg Breakpoint Combo Panel 44 (Siemens Healthcare Diagnostics, Deerfield, IL). Given the AST profile, E-tests (bioMérieux, Durham, NC) were performed for ceftolozane-tazobactam, ceftazidime-avibactam, colistin, and fosfomycin. Therapy with fosfomycin (3 g via PEG tube) was initiated because the patient was stable and had no renal failure.

Given the recurrence of MDRO infection, FMT was offered as a means to reduce MDRO colonization to prevent future such infections,<sup>3,4</sup> and initial permission from the FDA for an emergency investigational drug (eIND) was pursued. The following day, the patient further decompensated and required ventilator support. E-tests for his urine isolate showed an elevated minimum inhibitory concentration (MIC) to fosfomycin, resistance to ceftolozane-tazobactam, and susceptibility to ceftazidime-avibactam (Table 1). Confirmatory AST was performed using reference broth microdilution at the Centers for

Disease Control and Prevention, and polymerase chain reaction (PCR) identified the isolate to harbor *bla*<sub>KPC</sub> (Table 1). As a result, fosfomycin was stopped and intravenous (IV) ceftazidime-avibactam (2.5 g every 12 hours) and IV colistin (5 mg/kg loading dose followed by 1.25 mg/kg every 6 hours) was started. Respiratory culture from bronchoalveolar lavage grew carbapenem-resistant *K. pneumoniae* and *Pseudomonas aeruginosa*; inhaled colistin (150 mg every 12 hours) was added. On day 2 of his ICU stay, upon FDA approval of eIND application, FMT was performed via PEG tube (18 French halyard gastrostomy tube).<sup>5</sup> Due to ileus noted on imaging, stool was administered slowly; 20 cm<sup>3</sup> of stool was administered at 09:25 AM over 5 minutes followed by an additional 10 cm<sup>3</sup> in bolus form at 10:00 AM. During administration, vital signs and ventilator requirements remained stable with no signs of aspiration noted. Unfortunately, the patient continued to be febrile and hypoxic despite subsequent escalation in the ventilator settings. Given ongoing clinical deterioration, care was deescalated and FMT was stopped. The patient died at 17:42; no autopsy was requested.

In this case, we illustrate the growing global problem of AR and propose that FMT may have a role for patients with MDRO infections. The patient likely initially became colonized with KPC while hospitalized in China; the intestine in particular is a major site of *Klebsiella pneumoniae* colonization/carriage in ICU patients.<sup>6</sup> Broad-spectrum antibiotic usage exacerbates antibiotic resistance, and alteration in the intestinal microbiome is thought to be a key step in acquiring the composite of AR genes that have been labeled the resistome.<sup>7,8</sup> After initial treatment with meropenem in China, he continued on this antibiotic for subsequent hospital-acquired infections. Given determinants of AR may persist in intestinal flora for extended periods of time,<sup>7</sup> we suspect that this patient's microbiome did not recover before further pressure from broad-spectrum antibiotic use, resulting in the persistence of resistant strains of *Klebsiella pneumoniae*.<sup>9</sup> In hindsight, the best opportunity to restore intestinal flora and reduce antibiotic-resistant microbiome burden may have been the period after the course of meropenem was completed before subsequent decompensation.

Fecal microbiota transplantation has become a well-established modality to treat recurrent *Clostridium difficile* infection (RCDI).<sup>8,10</sup> This therapy is thought to improve microbial diversity through direct transfer of screened fecal material from donor to recipient. While FMT has been proposed as a tool to reduce MDRO colonization in research settings, it has not yet been established as a treatment option for urgent intestinal microbiome restoration. However, FDA approval of an investigational new drug (IND) application is required for clinical or research use for applications other than RCDI.<sup>5</sup> In this case, given the family's willingness to attempt FMT and subsequent approval of the eIND from the

TABLE 1. *Klebsiella pneumoniae* Isolates Susceptibility Test Results

Antimicrobial Drug(s)	Urine Isolate (Tested at Emory)		BAL Isolate (Tested at Emory)		Urine Isolate (Tested at CDC)	
	Interp	MIC (µg/mL)	Interp	MIC (µg/mL)	Interp	MIC (µg/mL)
Amikacin	R	>32	S	≤16	R	>64
Ampicillin	R	>16	R	>16	R	>32
Ampicillin-sulbactam	R	>16/8	R	>16/8	R	>32/16
Aztreonam	R	>16	R	>16	R	>64
Cefazolin	R	>16	R	>16	R	>8
Cefepime	R	>16	R	>16	R	>32
Cefoxitin	R	>16	R	>16	R	>16
Ceftazidime	R	>16	R	>16	R	>128
Ceftazidime-avibactam <sup>a</sup>	S	4/4			S	4/4
Ceftolozane-tazobactam	R	32/4			R	>16/4
Ceftriaxone	R	>32	R	>32	R	>32
Cefuroxime	R	>16	R	>16		
Chloramphenicol					I	16
Colistin	WT	0.125		0.125	WT	0.5
Doripenem					R	>8
Fosfomycin		>1024				
Gentamicin	R	>8	S	≤4	R	>16
Levofloxacin	R	>4	R	>4	R	>8
Meropenem	R	>8	R	>8	R	>8
Minocycline					R	>16
Nitrofurantoin	R	>64				
Piperacillin-tazobactam	R	>64/4	R	>64/4	R	>128/4
Tetracycline	R	>8			R	>32
Tigecycline <sup>a</sup>			I	4	S	2
Tobramycin	R	>8	S	≤4	R	>16
Trimethoprim-sulfamethoxazole	R	>2/38	R	>2/38	R	>8/152
Cefotaxime	R	>32	R	>32	R	>64
Ciprofloxacin	R	>2	R	>2	R	>8
Ertapenem	R	>4	R	>4	R	>8
Imipenem	R	>8	R	>8	R	64
Piperacillin	R	>64	R	>64		

NOTE. BAL, bronchoalveolar lavage; CDC, Centers for Disease Control and Prevention; Interp, interpretation; MIC, minimum inhibitory concentration; R, resistant; S, susceptible; I, intermediate; WT, wild-type; FDA, Food and Drug Administration; CLSI, Clinical and Laboratory Standards Institute.

<sup>a</sup>FDA breakpoints used for ceftazidime-avibactam and tigecycline; all other drugs were interpreted according to CLSI criteria.

FDA, FMT was performed. With the patient in septic shock, FMT was attempted as the slim benefit of an unknown mechanism outweighed the minimal risk associated with the procedure.

We anticipate that as difficult cases such as this become increasingly frequent, there may be a role for FMT in the acute-care setting, especially for intra-abdominal infections. Rather than requiring emergent approval for FMT, incorporating protocols detailing FMT into the inpatient standard of care for MDRO colonization may result in a more expedient implementation before it is potentially too late and the patient develops new and potentially more life-threatening infections.

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## REFERENCES

1. World Health Organization. *WHO publishes list of bacteria for which new antibiotics are urgently needed*. Geneva, Switzerland: World Health Organization; 2017.
2. Martens E, Demain AL. The antibiotic resistance crisis, with a focus on the United States. *J Antibiot (Tokyo)* 2017;70:520–526.
3. Bilinski J, Grzesiowski P, Sorensen N, et al. Fecal microbiota transplantation in patients with blood disorders inhibits gut colonization with antibiotic-resistant bacteria: results of a prospective, single-center study. *Clin Infect Dis* 2017;65:364–370.
4. Dubberke ER, Mullane KM, Gerding DN, et al. Clearance of vancomycin-resistant enterococcus concomitant with administration of a microbiota-based drug targeted at recurrent *Clostridium difficile* infection. *Open Forum Infect Dis* 2016;3:ofw133.
5. Woodworth MH, Neish EM, Miller NS, et al. Laboratory testing of donors and stool samples for fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *J Clin Microbiol* 2017;55:1002–1010.
6. Gorrie CL, Mirceta M, Wick RR, et al. Gastrointestinal carriage is a major reservoir of *K. pneumoniae* infection in intensive care patients. *Clin Infect Dis* 2017;65:208–215.
7. Forslund K, Sunagawa S, Kultima JR, et al. Country-specific antibiotic use practices impact the human gut resistome. *Genome Res* 2013;23:1163–1169.
8. Millan B, Laffin M, Madsen K. Fecal Microbiota transplantation: beyond *Clostridium difficile*. *Curr Infect Dis Rep* 2017;19:31.
9. Lawley TD, Clare S, Walker AW, et al. Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. *PLoS Pathog* 2012;8:e1002995.
10. Bakken JS, Borody T, Brandt LJ, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011;9:1044–1049.

## Dissemination of *Staphylococcus epidermidis* ST22 With Stable, High-Level Resistance to Linezolid and Tedizolid in the Greek-Turkish Region (2008–2016)

*To the Editor*—Linezolid resistance is increasingly described among the 3 most prevalent clones of linezolid-resistant *Staphylococcus epidermidis* (LRSE) that are occasionally involved in large outbreaks: sequence type 2 (ST2), ST5, and ST22.<sup>1</sup> The resistant phenotype has been related to the occurrence of mutations in genes coding for the V domain of 23S rRNA and ribosomal proteins L3/L4 or *cfr* acquisition.<sup>1</sup> The LRSE-ST22 isolates have been associated with infection and colonization cases in Spain, France, Germany, and, particularly, Greece, and most of these LRSE-ST22 arise after treatment with linezolid.<sup>1–7</sup> In this study, we aimed to characterize the first methicillin- and linezolid-resistant *S. epidermidis* from a patient without previous linezolid

exposure in Turkey and to assess its genetic similarity to the close geographical *S. epidermidis* from Greece.

In October 2016, a hypertensive 70-year-old male attended the emergency service at a hospital in Rize, Turkey, and was hospitalized with syncope and poor general condition (day 1). He was hospitalized in the neurology ward, where his symptoms deteriorated. These symptoms included fever, stiff neck, and confusion, and a diagnosis of clinical meningitis was established. A cerebrospinal fluid sample was collected, which was negative on cultural and microscopic analyses. Antibiotic therapy on day 2 included ceftriaxone, netilmicin, and vancomycin. The patient's condition deteriorated, and he was transferred to intensive care with room and contact isolation. Multidrug-resistant (MDR) *S. epidermidis* exhibiting resistance to oxacillin and linezolid was identified in 2 blood samples collected on days 14 and 15. The patient died on day 16 from multiple organ failure. Only a previous hospitalization for blood pressure control was registered 2 years before in the same hospital. Linezolid was never given to the patient, and additional linezolid-resistant gram-positive isolates were not detected before this case or until December 2017.

An LRSE isolate was sent to our laboratory for further characterization. The susceptibility to linezolid and vancomycin was confirmed by broth microdilution, to daptomycin and tedizolid by Etest, and to other 12 antibiotics by disk diffusion.<sup>8</sup> Using PCR and type sequencing, we searched *cfr*, *cfr(B)*, *optrA*, *mecA*, *mecC* genes, mutations in the 23S-rRNA-V-domain, and genes coding for L3/L4/L22 ribosomal proteins. Clonality was evaluated using pulsed-field gel electrophoresis (PFGE) and multilocus type sequencing (MLST; www.pubmlst.org). Antibiotic resistance stability (linezolid/tedizolid) was assessed after 100 daily passages in antibiotic-free Mueller-Hinton agar. Linezolid dependence was evaluated because it is a possible factor contributing to the emergence of ST22-*S. epidermidis* in Greece.<sup>5</sup> The Turkish LRSE and 2 LRSE-ST22 isolates from a high number of patients under linezolid therapy in 2 Greek regions (Patris and Athens) during 2008–2012<sup>2,3</sup> were compared by performing additional experiments not available in those studies: PFGE, ribosomal protein mutations, minimum inhibitory concentration (MIC)-tedizolid.

The Turkish LRSE-ST22 expressed resistance to linezolid (MIC ≥256 mg/L), tedizolid (MIC >32 mg/L), vancomycin (MIC = 4 mg/L), cefoxitin (*mecA*), and 8 other antibiotics. Linezolid resistance was related to T2504A and C2534T mutations in the 23S-rRNA-V domain and to the amino acid changes L94V, G152D, D159Y in L3 and N158S in L4 proteins (*S. epidermidis* RP62A numbering). The *cfr*, *cfr(B)* and *optrA* genes were not detected. The high linezolid and tedizolid MIC values were stably maintained after 100 serial passages, suggesting the absence of a biological burden linked to the identified mutations in non-selective contexts. Linezolid dependence was not observed in the conditions tested (Figure S1), suggesting a variable phenotype potentially dependent on previous linezolid exposure, as has been described for some strains.<sup>5</sup> The 3 Greek and Turkish isolates presented the same ribosomal mutations, MIC values for linezolid and tedizolid, and the same pulsotype A (Figure S2; Table 1).<sup>4</sup>