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LETTER TO THE EDITOR

First Description of *mcr-1*-Mediated Colistin Resistance in Human Infections Caused by *Escherichia coli* in Latin America

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Yi-Yun Liu and colleagues recently reported the emergence of plasmid-mediated colistin resistance in China, raising great concern around the world (1–5). The *mcr-1* gene was originally detected in commensal *Escherichia coli* from pigs but was immediately associated with other *Enterobacteriaceae* species of farm animal, meat, and human origins (1–5). A previous study reported short-term intestinal colonization in travelers to South America, suggesting the presence of the *mcr-1* gene in the region (4). In this report, we describe the detection of *mcr-1* in *E. coli* isolates causing human infections in Argentina.

A selection of 87 colistin-resistant clinical isolates submitted to the National Reference Laboratory in Antimicrobial Resistance (NRLAR) from 2008 to January 2016 were screened for *mcr-1* by PCR and Sanger sequencing. The collection included 28 *E. coli* isolates, 19 *Klebsiella pneumoniae* isolates, 36 isolates of other members of the family *Enterobacteriaceae*, and 4 isolates of nonfermenter Gram-negative bacilli. The *mcr-1* gene was detected in nine *E. coli* isolates recovered from nine patients admitted to six hospitals in three cities (Table 1). The average age of the patients was 68.5 (range, 53 to 93) years, and six of them were male. In five patients, *mcr-1*-positive *E. coli* isolates were associated with severe infections (Table 1). All nine *E. coli* isolates were genetically unrelated, as assessed by XbaI pulsed-field gel electrophoresis. *mcr-1*-mediated colistin resistance was successfully transferred by conjugation to a laboratory *Salmonella* strain; no other resistance was cotransferred. Four of the nine *E. coli* isolates coproduced different CTX-M variants (Table 1).

Given reports indicating discrepancies in the determination of the MICs of polymyxins (6), we assessed phenotypic methodologies used to detect *mcr-1*-mediated colistin resistance, i.e., agar dilution according to CLSI guidelines and Etest (bioMérieux), Vitek2C (bioMérieux), the BD Phoenix System (Becton Dickinson), and Sensititre (TREK Diagnostic Systems), by following the manufacturers' recommendations. Colistin MICs were interpreted according to EUCAST (resistance, >2 μg/ml). The nine *mcr-1*-positive *E. coli* isolates were resistant to colistin by all of the MIC methodologies; the MICs ranged from 4 to 16 μg/ml (Table 1). For the remaining 78 *mcr-1*-negative, colistin-resistant *E. coli* isolates, the colistin MICs ranged from 8 to >64 μg/ml (agar dilution; data not shown). The polymyxin B MICs determined by agar dilution mimic those of colistin (8 to 16 μg/ml). Although the disk diffusion method (10-μg colistin disk) is not standardized for polymyxins, all nine *E. coli* isolates carrying the *mcr-1* gene displayed colistin inhibition zones of ≤11 mm. Nevertheless, molecular detection is the gold standard for *mcr-1* identification.

These isolates represent the first confirmed Latin American *mcr-1*-positive clinical isolates, highlighting the widespread potential of this mechanism. Until now, *mcr-1*-positive isolates have been found sporadically in humans and associated with invasive and noninvasive diseases (5). However, in our country, *mcr-1*-positive *E. coli* isolates were found mostly in invasive infections, suggesting fitness for the hospital environment. The isolates harboring the *mcr-1* gene were genetically unrelated, and the mechanism was horizontally transferable. The available MIC measurement methodologies consistently detected *mcr-1*-positive *E. coli* isolates. Since 2010, the epidemiology of our country has changed drastically, especially driven by the dissemination of *K. pneumoniae* carbapenemase-producing *K. pneumoniae* ST258, other members of the family *Enterobacteriaceae* (7), and also extremely drug-resistant *Acinetobacter baumannii*. This situation was caused by the massive use of polymyxins as part of double- or triple-combination therapy schemes for severe infections. According to the National Surveillance on Antimicrobial Resistance conducted by the WHONET-Argentina Network (90 laboratories), colistin resistance in *E. coli* increased from (total number of *E. coli* isolates) 0.4% in 2012 ($n = 13{,}221$), to 0.8% in 2014 ($n = 18{,}244$) ($P < 0.001$). During 2015, the National Strategy for the Control of Antimicrobial Resistance was implemented in our country. However, the current information about antimicrobial resistance in veterinary medicine, animal production, and food production is scarce. At the NRLAR, we issued a regional alert on 2 February 2016, warning about the emergence of *mcr-1*-mediated colistin resistance in clinical isolates from Argentina, and released guidelines for active surveillance by health care providers. By 9 March 2016, 10 additional colistin-resistant *E. coli* isolates from six new hospitals had been submitted to the NRLAR and confirmed as *mcr-1* positive. The finding of *mcr-1* in *E. coli* clinical isolates is probably the tip of the iceberg that is a big hidden health issue in South America.

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TABLE 1 Characteristics of *mcr-1*-harboring *E. coli* isolates

Characteristic	*E. coli* isolate:									*Salmonella* sp. strain TC-M19736
	M15049	M15224	M17059	M17056	M19241	M19242	M19441	M19736	M19855	
Isolation date	July 2012	Oct. 2012	Nov. 2013	Nov. 2013	Mar. 2015	Apr. 2015	July 2015	Nov. 2015	Jan. 2016	
Diagnostic/underlying disease of patient	Neurologic disease	Diabetes	Appendicitis	Urinary tract infection	Prostate cancer	Heart failure	Rheumatoid arthritis	Secondary peritonitis/ colon cancer	NA[a]	
Isolation site	Blood	Urine	Abdomen	Blood	Urine (catheter)	Urine (catheter)	Bone	Blood	Abscess	
Hospital	1	2	3	3	3	3	4	5	6	
MIC (μg/ml)[b] of:										
Colistin	8	16	8	8	8	8	8	8	8	16
Polymyxin B	8	16	16	8	8	8	8	8	8	16
Additional resistance(s)[c]	TET, TMS, CIP, FOS	AMP, FGC, NIT, MIN, TMS, CIP, FOS	AMP, AMS, FGC, ESC, GEN, MIN, CIP	AMP, CIP	CIP	AMP, AMS, FGC, ESC, TMS, GEN	AMP, AMS, FGC, ESC, CMP, GEN, MIN, CIP	AMP, AMS, CMP, CIP	AMP, AMS, FGC, ESC, GEN, MIN, CIP	None
ESBL[d] genes	None	None	CTX-M-14 group	None	None	CTX-M-2 group	CTX-M-15 group	None	CTX-M-14 group	

[a] NA, not available.

[b] Susceptibility to colistin and polymyxin B was evaluated by agar dilution.

[c] AMP, ampicillin; AMS, ampicillin-sulbactam; FGC, first-generation cephalosporins; ESC, extended-spectrum cephalosporins; TET, tetracycline; MIN, minocycline; TMS, trimethoprim-sulfamethoxazole; CIP, ciprofloxacin; FOS, fosfomycin; NIT, nitrofurantoin; GEN, gentamicin; CMP, chloramphenicol.

[d] ESBL, extended-spectrum β-lactamase.