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Brief Report

Carbapenemase-producing Enterobacteriaceae among pregnant women and newborns in Algeria: Prevalence, molecular characterization, maternal-neonatal transmission, and risk factors for carriage

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The diffusion of carbapenemase-producing Enterobacteriaceae (CPE) represents a worldwide public health problem. This study revealed that the prevalence of OXA-48–producing enterobacteria was 4.6% (19/414) and 1.6% (7/422) in mothers and newborns, respectively, from 2 maternity units in Algeria. Previous hospital admission was an independent factor associated with an increased risk of CPE carriage in the mothers ($P = .021$). The low birth weight was significantly associated with this carriage in the newborns ($P = .008$). The screening of these bacteria is essential to prevent the dissemination of CPE.

Mother-child maternity units are environments that should remain relatively free of multidrug-resistant bacteria because these units principally admit mothers to give birth. The presence of multidrug-resistant bacteria could represent a threat and could have an influence on the outcome of the newborn.[1] The spread of carbapenemase-producing Enterobacteriaceae (CPE) leading to extremely drug-resistant bacteria is a major concern worldwide, especially in endemic countries.[2,3] Data from children, especially newborns, are scarce, and failures in infection control practices can be responsible for the diffuse horizontal spread.[4,5]

METHODS

All mothers and their newborns managed in 2 maternity units in northern Algeria (Bejaia [Maternity A] and Tizi Ouzou [Maternity B]) were prospectively and randomly recruited: 357 mothers anzd 365 newborns aged <18 hours in Maternity A (January 1 to April 30, 2016) and 57 mother-newborn pairs in Maternity B (January 1 to April 30, 2017). Epidemiologic data were recorded for each mother and neonate. The screening of CPE carriage was taken by rectal (mothers and newborns) and vaginal (mothers) swabs. In parallel, a total of 505 environmental surface samples were obtained by swabbing surfaces.[6] Swabs were cultured in 1 mL of Trypticase Soy Broth (Fluka, St. Louis, MO) supplemented with ertapenem (0.5 mg/L) and vancomycin (32 mg/L) and incubated for 18 hours at 37°C. A 200-μL aliquot was plated onto MacConkey agar (Fluka) containing 0.5 mg/L of ertapenem and incubated 18 hours at 37°C. Bacterial identification was performed using the Vitek MS system (BioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibility was determined by the disk diffusion method according to guidelines from the European Committee on Antimicrobial Susceptibility Testing.[7] Minimum inhibitory concentration of colistin was determined using microbroth dilution (Umic; Biocentric, Bandol, France). The genotypic characterization of β-lactams resistance was determined by polymerase chain reaction (PCR) with specific primers and confirmed by sequencing the PCR products.[8] Plasmid-mediated resistance to aminoglycosides and quinolones was studied as described previously.[8] Plasmid incompatibility groups were determined using PCR-based replicon typing.[8] The genetic relationship between CPE strains was assessed by rep-PCR (DiversiLab; bioMérieux, Marcy l'Etoile, France). Isolates with identical strain patterns were considered indistinguishable if the similarity percentage was ≥95%.

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Table 1
Characteristics of OXA-48–producing Enterobacteriaceae strains isolated from mothers, newborns, and the maternity environment

Strain	Species	Resistance phenotype	Carbapenem MICs, mg/L	Sequence type	Plasmid type	β-lactamase and PMQR content	Origin
60	*Escherichia coli*	AMX, TIC, PIP, AMC, TZP, TCC	ETP (2), IPM (1), MEM (0.38)	ST833	IncL/M	bla_{OXA-48}	Mother, Maternity A
61	*E coli*	AMX, TIC, PIP, AMC, TZP, TCC, ETP	ETP (0.75), IPM (0.5), MEM (0.38)	ST833	IncL/M	bla_{OXA-48}	Mother, Maternity A
62	*E coli*	AMX, TIC, PIP, AMC, TZP, TCC, ETP	ETP (6), IPM (12), MEM (4)	ST833	IncL/M	bla_{OXA-48}	Mother, Maternity A
63	*Klebsiella pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, ETP, IPM	ETP (3), IPM (4), MEM (2)	ST13	IncL/M	bla_{OXA-48}	Newborn, Maternity A
64	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP	ETP (6), IPM (6), MEM (2)	ST13	IncL/M	bla_{OXA-48}	Newborn, Maternity A
65	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP	ETP (24), IPM (>32), MEM (4)	ST13	IncL/M	bla_{OXA-48}	Mother, Maternity A
84A	*E coli*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, OFX	ETP (1), IPM (1.5), MEM (0.5)	ST638	IncL/M, IncX2	bla_{OXA-48}, *qnrS*	Mother, Maternity A
84B	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP	ETP (0.5), IPM (0.75), MEM (0.38)	ST610	IncL/M	bla_{OXA-48}	Mother, Maternity A
85	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP	ETP (0.5), IPM (0.75), MEM (0.38)	ST45	IncL/M	bla_{OXA-48}	Newborn, Maternity A
111	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP,OFX, NA, CIP	ETP (1), IPM (2), MEM (0.5)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
112	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP,OFX, NA	ETP (1), IPM (1.5), MEM (0.5)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
114	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP,OFX, NA	ETP (2), IPM (3), MEM (1.5)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
116	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP,OFX, NA	ETP (1), IPM (3), MEM (0.75)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
118	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP,OFX, NA	ETP (1.5), IPM (3), MEM (1)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
117	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP,OFX, NA	ETP (1), IPM (2), MEM (0.75)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
131	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, FOS	ETP (1.5), IPM (0.75), MEM (0.5)	ST13	IncL/M	bla_{OXA-48}	Newborn, Maternity B
120	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, FOS	ETP (1.5), IPM (0.75), MEM (0.5)	ST13	IncL/M	bla_{OXA-48}	Mother, Maternity B
128	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, FOS	ETP (4), IPM (0.75), MEM (0.5)	ST13	IncL/M	bla_{OXA-48}	Newborn, Maternity B
130	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, FOS	ETP (0.5), IPM (0.75), MEM (0.5)	ST13	IncL/M	bla_{OXA-48}	Mother, Maternity B
129	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, FOS	ETP (1.5), IPM (1), MEM (0.75)	ST13	IncL/M	bla_{OXA-48}	Newborn, Maternity B
113	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP, MEM, OFX, NA	ETP (0.75), IPM (2), MEM (0.75)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
121	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP, OFX, NA	ETP (0.75), IPM (2), MEM (0.75)	ST1878	IncL/M	bla_{OXA-48}	Newborn, Maternity B
123	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ERT, MER, OFX, NA	ETP (2), IPM (3), MEM (1)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
124	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP, OFX, NA	ETP (0.75), IPM (2), MEM (0.75)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
125	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP, OFX, NA	ETP (0.75), IPM (2), MEM (0.5)	ST1878	IncL/M	bla_{OXA-48}	Mother, Maternity B
126	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, FOS	ETP (0.75), IPM (1), MEM (0.5)	ST13	IncL/M	bla_{OXA-48}	Mother, Maternity B
127	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, ETP, IPM, FOS	ETP (2), IPM (2), MEM (0.75)	ST13	IncL/M	bla_{OXA-48}	Mother, Maternity B
133	*K pneumoniae*	AMX, TIC, PIP, AMC, TZP, TCC, FOX, CAZ, CTX, ETP, OFX, NA	ETP (1.5), IPM (2), MEM (1)	ST1878	IncL/M	bla_{OXA-48}	Environment, Maternity B

MICs, minimum inhibitory concentrations; *PMQR*, plasmid-mediated quinolone resistance; *AMX*, amoxicillin; *TIC*, ticarcillin; *PIP*, piperacillin; *AMC*, amoxicillin/clavulanic acid; *TZP*, piperacillin/tazobactam; *TCC*, ticarcillin/clavulanic acid; *FOX*, cefoxitin; *OFX*, Ofloxacin; *CAZ*, ceftazidime; *CTX*, cefotaxime; *NA*, nalidixic acid; *CIP*, Ciprofloxacin; *FOS*, fosfomycin; *ETP*, ertapenem; *IPM*, imipenem; *MEM*, meropenem.

Multilocussequencetyping(MLST)analysiswasperformedusingthePasteurInstitute'sMLSTscheme(bigsdb.web.pasteur.fr).Statisticalanalyses wereperformedusingGraphPadPrism6(GraphPadSoftware,LaJolla,CA). $P<.05$wasconsideredastatisticallysignificantdifference.

RESULTS

A total of 414 mothers and 422 newborns were included. The main mother and newborn characteristics are given in Supplemental Table S1. Overall, 836 rectal swabs and 221 vaginal swabs were collected. A total of 28 CPE isolates were obtained from mothers (n = 19), with 2 different strains (84A and 84B) isolated from the same mother, newborns (n = 7), and the environment (n = 1). The overall prevalence of CPE was 4.6% (19/414) and 1.6% (7/422) in mothers and newborns, respectively. In mothers, the prevalence of vaginal carriage and rectal carriage was 0.9% (2/221) and 4.1% (17/414), respectively. In Maternity A, 9 CPE strains were isolated: 6 (*Escherichia coli* [n = 4]) and *Klebsiella pneumoniae* [n = 2]) were recovered from 6 mothers, isolated from rectal (n = 5) and vaginal (n = 1) sites, and 3 (*K pneumoniae* [n = 3]) from newborns. In Maternity B, 19 carbapenem-resistant *K pneumoniae* strains were isolated: 14 from 13 mothers, isolated from rectal (n = 12) and vaginal (n = 2) sites, 4 from newborns, and 1 from environmental sampling (a table surface) of the intensive care room. The antimicrobial susceptibilities of the CPE are shown in Table 1.

Microbiologic investigations showed that the 28 CPE harbored the bla_{OXA-48} gene localized on the IncL/M plasmid. One *E coli* isolate also contained the *qnrS* gene and harbored 2 plasmids belonging to the IncL/M and IncX2 groups (Table 1). For *K pneumoniae*, rep-PCR identified different profiles in the 2 maternity units corresponding to 3 clusters (Supplemental Fig S1). The strains mainly belonged to ST13 (n = 10) in the 2 maternity wards and ST1878 (n = 12) in Maternity B (Table 1). This last sequence type was isolated from mothers (n = 10), a newborn, and the table surface of the intensive care room, suggesting a local outbreak. For *E coli* strains, rep-PCR revealed that the 4 isolates belonged to 3 different profiles (Supplemental Fig S2) and belonged to ST638 and ST833 (Table 1).

Previous exposure to antimicrobial treatment during the preceding 3 months before admission (55.5% vs 34.6%; $P < .01$), previous hospital admission (55.5% vs 26%; $P < .01$), and no previous chronic diseases (5.5% vs 27.2%; $P < .01$) were significantly associated with women's CPE carriage (Table 2). The multivariate analysis identified previous hospital admission as an independent factor associated with an increased risk of CPE carriage in the mothers (odds ratio, 5.2; 95% confidence interval, 1.18-27.62; $P = .021$). Among the newborn CPE carriers, low birth weight was significantly associated with this carriage ($P < .01$) (Table 2). The carriage of the CPE isolates among newborns was independent of their mothers' carrier status (P = not significant). The carrier site in the mother (rectal or vaginal) did not affect the carriage of these strains among newborns (P = not significant).

DISCUSSION

In this study, we report the asymptomatic carriage of OXA-48–producing *E coli* and *K pneumoniae* isolates in mother-newborn pairs. No mother-to-newborn transmission of these isolates was observed as recently reported at birth in Italy with *K pneumoniae* carbapenemase–producing *K pneumoniae*.[9] We identified that previous hospital admission was the risk factor for CPE acquisition in the multivariate analysis. Prolonged hospital exposure and the use of antibiotics have been noted previously as risk factors for EPC acquisition.[10,11] Finally, in our study, low birth weight was significantly associated with CPE carriage in the newborn. This risk factor has not been described previously. We observed that no carriers were premature, suggesting that CPE had no direct role on a premature delivery and could not represent a high risk for infections encountered frequently in preterm newborns but could influence birth weight.

Table 2
Univariate analysis of risk factors for acquisition of carbapenemase-producing Enterobacteriaceae in mother-newborn pairs

	CPE+	CPE–	*P* value
Mothers			
Mean age (y) ± SD	31.6 ± 4.7	31.7 ± 5.3	.821
Mean number of ± SD	1.61 ±1.09	2.33 ± 2.02	.087
Antibiotic treatment for the past 3 mo			
Yes	10 (2.4%)	137 (33%)	
No	8 (1.9%)	259 (62.5%)	.08
Previous hospital admission			
Yes	10 (2.4%)	103 (24.8%)	
No	8 (1.9%)	293 (70.7%)	.012
Chronic disease			
Yes	1 (0.2%)	108 (26%)	
No	17 (4.1%)	288 (69.5%)	.052
Surgical intervention			
Yes	8 (1.9%)	128 (30.9%)	
No	10 (2.4%)	268 (64.7%)	.309
Newborns			
Sex			
Male	3 (42.9%)	226 (53.5%)	
Female	4 (57.1%)	189 (44.7%)	.707
Mode of delivery			
Natural	3 (42.9%)	219 (51.8%)	
Cesarean	4 (57.1%)	196 (46.4%)	.712
Mean birth weight (kg) ± SD	3.03 ± 0.62	4.37 ± 0.56	.012
Low birth weight, <2,500 g	3 (42.9%)	26 (6.3%)	.008

NOTE. Statistical analyses were performed using the χ^2 test or Fisher exact test to verify the significance between CPE+ and CPE– among mothers and newborns.
CPE+, carrier of carbapenemase-producing enterobacteria; *CPE–*, noncarrier of carbapenemase-producing enterobacteria; *SD*, standard deviation.

MLST analysis showed that the *K pneumoniae* ST1878 was isolated only in Maternity B from mothers, newborns, and surfaces of the hospital environment. Importantly, these isolates showed the same rep-PCR profile, suggesting a local outbreak. In addition, we noticed that all mothers carrying this clone were admitted in the same room and gave birth by cesarean section. Given the fact that our data do not support mother-newborn transmission and only 1 sample in 505 was positive for CPE, we suggest that the possible sources of this outbreak may be the hands of health care personnel. In addition, cross-transmission via health care workers' hands seems to be important in the spread of *K pneumoniae* strains.[12]

CONCLUSION

The findings of CPE as neonate-gut colonizers may have implications to prevent cross-transmission by these strains. When the evolution of antibiotic resistance is moving faster than the synthesis of new antimicrobials, focused interventions to reduce this cross-transmission in settings of high endemicity are required; these must absolutely include all wards.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajic.2018.07.009.

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