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RIsk factors for colistin-resistant Enterobacteriaceae in a low-endemicity setting for carbapenem resistance - a matched case-control study

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Background: Emergence of colistin-resistance has been related to its increased use in clinical settings, following the global spread of carbapenem-resistant Gram-negative bacteria. The use of colistin in animal production may constitute a further source for spread of resistant strains to humans. In Switzerland, carbapenem-resistance is still rare (under 0.5% for both *E. coli* and *K. pneumoniae*) and consecutive use of colistin low (0.01 defined daily doses [DDD]/1000 inhabitants/day in outpatient settings and 0.3 DDD/100 bed-days in hospitals). However, colistin is commonly used in livestock animals, mainly pigs. Given the importance of enhancing knowledge on the breach of this last resort antibiotic, we sought to determine risk factors for human colonization or infection with colistin-resistant *E. coli* and *K. pneumoniae* in a setting where colistin is mainly used for animal production.

Material/methods: We performed a case control study at the University Hopsital Basel, Switzerland – an 855- bed tertiary care centre. Patients with detection of colistin-resistant *E. coli* or *K. pneumoniae* isolated from any clinical sample submitted to the microbiology laboratory between 2011 and 2015 were included. For each case patient, three controls with detection of a colistin-susceptible strain of the identical genus of Enterobacteriaceae were selected. Matching was performed according to the site of isolation, ward type and date of admission. Pertinent clinical data was collected by medical chart review. Conditional univariable logistic regression was used to calculate odds ratios for colistin-resistance. All variables found to be significant in univariable analysis were included in the conditional multivariable regression model. P-values ≤0.05 were considered significant.

Results: Forty-two cases (33 with colistin-resistant *E. coli* and 9 with colistin-resistant *K. pneumoniae*) and 126 matched controls were identified. One of the colistin-resistant strains and none of the colistin susceptible strains were identified as carbapenem-resistant. Prior exposure to colistin was recorded in two cases and none of the controls. Baseline characteristics, comorbidities, prior exposure to different antibiotic classes and healthcare settings did not differ between cases and controls, except for prior exposure to carbapenems, sulfonamids and hospitalization abroad during the prior three months (table). In multivariable analyses, hospitalization abroad remained associated with colistin-resistance (OR 4.48, 95%CI 1.08-18.63, p=0.039).

Conclusions: In a low-endemicity setting for carbapenem-resistance, hospitalization abroad was the only risk factor for colonization or infection with colistin-resistant *E. coli* or *K. pneumoniae*, despite common use of colistin in animal production. Prior exposure to colistin was not related to detection of colistin-resistance, which mainly occurred in the absence of concurrent carbapenem-resistance.

	OR	**95%CI**	**p-value**
Age (years)	0.99	0.96-1.01	0.216
Prior hospitalization abroad	5.32	1.34-21.16	**0.018**
Charlson Comorbidity Index	1.05	0.83-1.33	0.692
Penicillins	0.54	0.20-1.44	0.221
Cephalosporins	0.72	0.25-2.04	0.537
Carbapenems	5.00	1.19-20.92	**0.028**
Quinolones	2.27	0.68-7.54	0.181

Sulfonamids	5.79	1.09-30.83	**0.039**
Aminoglycosides	3.00	0.19-47.96	0.437