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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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Introduction and Purpose

- Colistin-resistant Enterobacteriaceae are an emerging problem worldwide, especially because of the global spread of carbapenem-resistant Enterobacteriaceae resulting in increased use of this antibiotic of last resort.
- In November 2015, a new plasmid-related colistin-resistance mechanism called mcr-1 has been described, enabling horizontal gene transfer between bacteria of the same and different species (1), facilitating further spread.
- Carbapenem-resistance in Switzerland is still low, therefore use of colistin is still rare (0.01 defined daily doses [DDD]/1000 inhabitants/day in outpatient settings and 0.3 DDD/100 bed-days in hospitals (2)).
- However, colistin is used widely in veterinary medicine and it is hypothesized, that there might be a connection between colistin-resistant bacteria in animals and humans (1).
- The goal of this study was to assess clinical risk factors for colistin-resistant *E. coli* and *K. pneumoniae* in a low endemicity setting for carbapenem-resistant Enterobacteriaceae.

Methods

- Retrospective screening of samples for colistin-resistant *E. coli* and *K. pneumoniae* isolated from any clinical sample submitted to the microbiology laboratory from 01/2011 – 11/2015. Electronic and/or paper chart review for data collection.
- For each case patient, three controls with detection of a colistin-susceptible strain of the identical genus of Enterobacteriaceae was selected. Matching was performed according to site of isolation, ward type and date of isolation (Fig. 1).
- Patient's baseline characteristics and comorbidities were compared by applying the Mann-Whitney U test or Fisher's exact test.

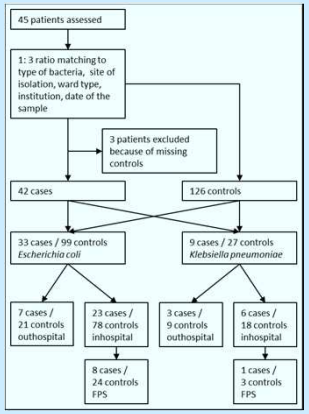

Figure 1: Flowchart; FPS = Felix Platter-Hospital

- Conditional univariable logistic regression was used to calculate odds ratios (OR) for colistin-resistance. All variables found to be significant in univariable analyses were included in the conditional multivariable regression model using stepwise forward and backward selection

Results

- Forty-two cases (33 with colistin-resistant *E. coli* and 9 with colistin-resistant *K. pneumoniae*) and 126 matched controls were identified.
- Age, gender and underlying diseases did not differ between cases and controls (Tab. 1).
- Susceptibility rates to quinolons, fosfomycin and tobramycin differed significantly between cases and controls (Fig. 2).
- Prior exposure to carbapenems as well as hospitalization and stay abroad were associated with colistin-resistance (Fig. 3).
- Only prior exposure to carbapenems was associated with colistin-resistance in multivariable analysis (OR 5.00, 95%CI 1.19-20.92, p=0.028).

	Cases (n = 42)		Controls (n = 126)		
	n	%	n	%	p-value
Age	70	61-84	78	67-84	0.210
Male gender	30	71.4	86	68.3	0.700
Charlson Comorbidity Index	2	1-4	2	1-3	0.831
Underlying disease					
Cardiac disease	14	33.3	52	41.3	0.362
Peripheral vas.disease	6	14.3	12	9.5	0.395
Cerebrovascular disease	4	9.5	20	15.9	0.446
Dementia	11	26.2	28	22.2	0.598
Chronic lung disease	10	23.8	19	15.1	0.195
Connective tissue disease	0	0.0	2	1.6	-
Peptic ulcer diasease	3	7.1	7	5.6	0.712
Hemiplegia	0	0.0	4	3.2	-
Chronic renal disease	13	30.9	43	34.1	0.705
Liver disease	2	4.8	4	3.2	-
Cancer without metastasis	4	9.5	12	9.5	1.000
Metastatic Cancer	3	7.1	10	7.9	1.000
Leukemia	1	2.4	9	7.1	-
Lymphoma	1	2.4	4	3.2	-
HIV	1	2.4	2	1.6	-
AIDS	0	0.0	2	1.6	-
Solid organ transplantation	3	7.1	3	2.4	-
HSCT	1	2.4	4	3.2	-
Surgery prior to Colistin	11	26.2	41	32.5	0.441

Table 1: Demographics and underlying diseases

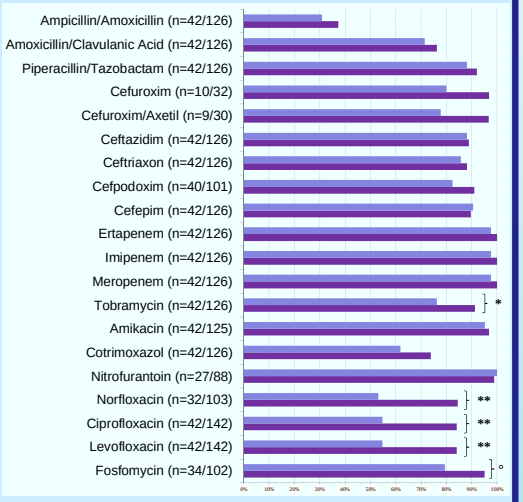

Figure 2: Antibiotic susceptibility testing of cases (light) and controls (dark).
P-values: * = 0.010, ** = <0.001, ° = 0.011

References

(1) Liu YY, Lancet Infect Dis, 2016 Feb;16(2):161-8. doi: 10.1016/S1473-3099(15)00424-7. Epub 2015 Nov 19
(2) Swiss Antibiotic Resistance Report 2016. FOPH publication number: 2016-OEG-3

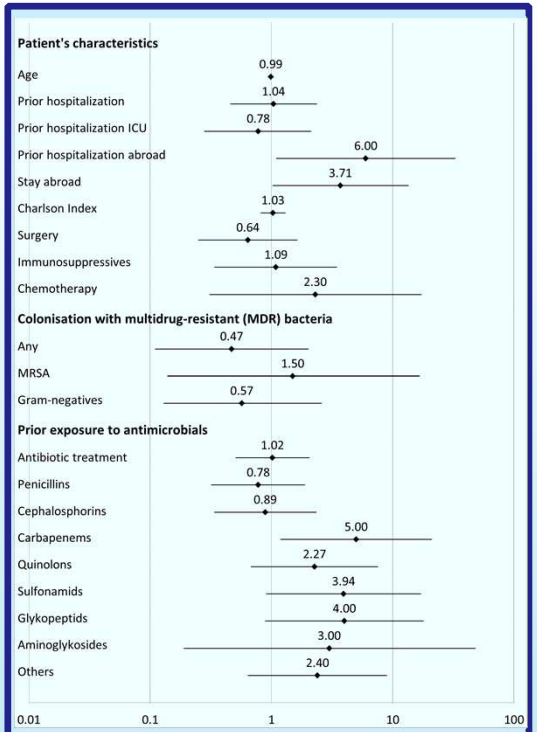

Figure 3: Risk factors for colistin-resistance, OR and 95% CI in a logarithmic scale (x-axis)

Conclusions

- In a low-endemicity setting for carbapenem-resistance with common use of colistin in animal production, prior exposure to carbapenems was the only risk factor for colonization or infection with colistin-resistant *E. coli* or *K. pneumoniae*.
- Prior exposure to colistin was low and not related to detection of colistin-resistance.
- Colistin-resistance mainly occurred in absence of concurrent carbapenem-resistance. The higher rate of quinolon- , fosfomycin - and tobramycin-resistance needs to be evaluated.