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Characterisation of hypervirulent *Klebsiella pneumoniae* strains causing blood stream infections or showing carbapenem resistance in Germany: a multi-centre study

A. Fischer [1], G. Valenza [1], D. Eisenberger [2], V. Lehner-Reindl [2], J. Jung [3], F. Johannes [4], N. Wantia [5], A. Serr [6], J. Liese [7], H. Rohde [8], M. Hogardt [9], A. Hamprecht [10], E.A. Idelevich [11], M. Weig [12], P. Dudler [2], J. Held [1]

[1]University Hospital Erlangen - Erlangen (Germany), [2]Bavarian State Office for Health and Food Safety - Erlangen (Germany), [3]University Hospital Munich (LMU) - Munich (Germany), [4]University of Würzburg - Würzburg (Germany), [5]University Hospital Munich (TU) - Munich (Germany), [6]University Hospital Freiburg - Freiburg (Germany), [7]University Hospital Tübingen - Tübingen (Germany), [8]University Hospital Hamburg - Hamburg (Germany), [9]University Hospital Frankfurt - Frankfurt (Germany), [10]University Hospital Oldenburg - Oldenburg (Germany), [11]University Hospital Greifswald - Greifswald (Germany), [12]University Hospital Göttingen - Göttingen (Germany)

Presenting author email: juergen.held@uk-erlangen.de

Background
Hypervirulent *Klebsiella pneumoniae* (hvKp) is an emerging pathotype that often infects healthy individuals and causes sever infections like organ abscesses. The objective of our study was to examine the epidemiology of hvKp isolates derived from blood cultures (BCI) or showing carbapenem-resistance (CRI) in Germany and to characterise the strains phenotypically and molecularly.

Methods
BCI and CRI were collected from 11 centres across Germany over a period of 6-12 months. The isolates were phenotypically characterised by string test and by agar dilution with 4 µg/ml tellurite. Furthermore, all isolates were molecularly tested for aerobactin, salmochelin, yersiniabactin, colibactin, and the regulators of capsule production rmpA and rmpA2 with the eazyplex®-hv-*K. pneumoniae* assay. The genomes of all strains in which the rmpA or rmpA2 gene was detected or which were positive in the string test were sequenced.

Results
576 BCI and 75 CRI were included in the study. A high Kleborate score of 3-5 was significantly more common in CRI (17.3%) compared to BCI (7.4%; p=0.008). The rmpA and/or rmpA2 gene was detected in 6.1% (BCI) and in 9.3 % (CRI). RmpA2 but not rmpA showed a trend to be more prevalent in CRI (p=0.067 and p=0.619, respectively). Interestingly, the string test and the rmpA/rmpA2-genes were both positive in 22 BCI, while in 33 isolates (48.5%) only the string test and in 13 isolates (19.1%) only the rmpA/rmpA2-genes were positive, suggesting additional regulators for capsule production. Tellurite resistance was more frequent in isolates with a Kleborate score of 3-5 but its specificity was not high enough to serve as a screening tool. The whole-genome sequenced BCI belonged to 50 different sequence types (ST). The most prevalent ST was 23 accounting for 10,2% of isolates. ST23, reported to be associated with hypervirulence, had a Kleborate score of 4-5 in 93.5% of our BCI.

Conclusions
Potentially hvKp are found in a considerable number of BCI and even more in CRI. It is important to implement surveillance measures to monitor the further spread of this pathotype.

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Outcomes and factors associated with mortality for *Enterococcus faecalis* and *Enterococcus faecium* bloodstream infections: a prospective multi-centre cohort study from the PROBAC project

F. Scharloo [1,2], F. Cogliati Dezza [3,2], I. López-Hernández [2], P.M. Martínez Pérez-Crespo [4], A.J. Goikoetxea [5], M.T. Pérez-Rodríguez [6], J. Fernández-Suárez [7], E. León Jiménez [4], M.Á. Morán Rodríguez [8], I. Fernández-Natal [9], J.M. Reguera-Iglesias [10], C. Natera-Kindelán [11], M.C. Fariñas [12], L. Boix-Palop [13], A. Jover-Sáenz [14], J.M. Sánchez-Calvo [15], L·E· López-Cortés [2], J. Rodríguez-Baño [2]

[1]Faculty of Medicine, University Medical Center Utrecht - Utrecht (Netherlands), [2]Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Sevilla. Departamento de Medicina, Universidad de Seville, Instituto de Biomedicina de Sevilla/CSIC, Seville, (Spain), and CIBERINFEC, Instituto de Salud Carlos III, Madrid - Seville (Spain), [3]Department of Public Health and Infectious Diseases, Sapienza University of Rome - Rome (Italy), [4]Unidad de Enfermedades Infecciosas y Microbiologìa, Hospital Universitario Nuestra Señora de Valme - Seville (Spain), [5]Unidad de Enfermedades Infecciosas, Hospital Universitario de Cruces - Bizkaia (Spain), [6]Unidad de Enfermedades Infecciosas, Departamento de Medicina Interna, Complexo Hospitalario Universitario de Vigo - Vigo (Spain), [7]Hospital Universitario Central de Asturias - Oviedo (Spain), [8]Unidad de Gestión Clínica de Enfermedades Infecciosas, Hospital Universitario de Burgos - Burgos (Spain), [9]Hospital Universitario de León, Complejo Asistencial Universitario de León - León (Spain), [10]Servicio de Enfermedades Infecciosas, Hospital Regional Universitario de Mallaga, IBIMA Mallaga - Mallaga (Spain), [11]Unidad de Enfermedades Infecciosas, Hospital Universitario Reina Sofia - Cordoba (Spain), [12]Unidad de Enfermedades Infecciosas, Hospital Universitario Marqueìs de Valdecilla, Universidad de Cantabria - Santander (Spain), [13]Infectious Diseases Department, Hospital Universitari Mútua Terrassa - Barcelona (Spain), [14]Unidad de Infección Nosocomial, Hospital Universitario Arnau de Vilanova - Lleida (Spain), [15]Unidad de Enfermedades Infecciosas y Microbiologia Clinica, Hospital Universitario - Jerez De La Frontera (Spain)

Presenting author email: f.scharloo@students.uu.nl

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Background
Enterococcal BSI represents significant morbidity and mortality, with fatality rates of approximately 20-30%. Infections by E. faecalis and E. faecium have microbiological and clinically differences. Moreover, several studies have demonstrated higher mortality rates in E. faecium BSI. This study aims to explore differences in mortality for E. faecalis and E. faecium BSI and identify prognostic factors associated with poor outcome.

Methods
The study is a post-hoc analysis of the PROBAC project, a national multicenter, observational, prospective cohort study conducted in 26 Spanish hospitals between October 2016 and March 2017. All patients with monomicrobial *E. faecalis* and *E. faecium* BSI were included (Figure 1). Multivariable logistic regression was performed to explore the association of species with all-cause mortality and to identify the prognostic factors in patients with *E. faecalis* BSI and *E. faecium* BSI.

Results

307 patients with monomicrobial enterococcal BSI were included, 186 (60.6%) by *E. faecalis* and 121 (39.4%) *E. faecium* . Median age was 71 (IQR 61–82), 65.2% was male. Population characteristics and univariate analysis of factors associated with mortality are shown in Table 1. All-cause mortality was 20.8% (64 patients). In a multivariable model (Table 2A), no difference in mortality for patients with BSI due to *E. faecium* versus *E. faecalis* was found (OR=1.04 (95%CI=0.54–1.97), p=0.914). Regarding *E. faecalis* BSI, Charlson Comorbidity Index ≥3 (OR=3.22 (1.16-8.94), p=0.025), congestive heart failure (OR 3.06 (1.23–7.59), p=0.016) and SOFA score ≥3 (OR 10.63 (3.96–28.6), p<0.001) were independent predictors of mortality (Table 2B). For *E. faecium* BSI, only SOFA score ≥3 (OR 3.25 (1.20–8.80), p=0.020), was an independent prognostic factor (Table 2C).

Conclusions

Enterococcal BSI was associated with significant mortality. This study was not able to show a difference in mortality between *E. faecalis* and *E. faecium* BSI. Furthermore, our results showed that clinical severity at BSI onset is associated with mortality in both *E. faecalis* BSI and *E. faecium* BSI. By contrast, the burden of comorbidity is only associated with prognosis of *E. faecalis* BSI.

Figure 1. Flowchart of study population

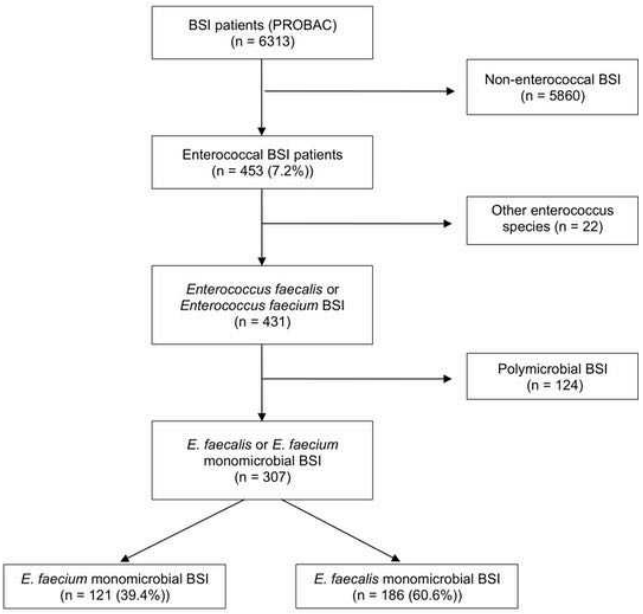

Table 1. General characteristics of enterococcal BSI population

	No. (%) of patients				
	BSI cases (n = 307)	Mortality with factor	Mortality without factor	RR (95% CI)	*p* value
Demographic					
Age ≥ 69 years	170 (55.4)	42/170 (24.7)	22/136 (16.2)	1.52 (0.98 - 2.43)	**0.039**
Male sex	199 (65.2)	44/199 (22.1)	19/106 (17.9)	1.23 (0.76 - 2.00)	0.390
Comorbidities					
Charlson comorbidity index (without age) ≥ 3	51 (16.6)	14/51 (27.5)	50/256 (19.5)	1.41 (0.84 - 2.34)	0.204
Congestive heart failure	63 (20.5)	20/63 (31.7)	44/244 (18.0)	1.76 (1.12 - 2.76)	**0.017**
Diabetes mellitus	74 (24.1)	20/74 (27.0)	44/233 (18.9)	1.43 (0.90 - 2.27)	0.133
Chronic renal insufficiency	49 (16.0)	16/49 (32.7)	48/258 (18.6)	1.75 (1.09 - 2.83)	**0.026**
Hepatic disease	32 (10.4)	12/32 (37.5)	52/276 (18.9)	1.98 (1.19 - 3.30)	**0.014**
Peptic ulcer disease	14 (4.6)	7/14 (50.0)	57/293 (19.5)	2.57 (1.45 - 4.57)	**0.013**
Solid tumor	81 (26.4)	23/81 (28.40	41/226 (18.1)	1.56 (1.01 - 2.44)	**0.051**
Hemiplegia	16 (5.2)	6/16 (37.5)	58/291 (19.9)	1.88 (0.96 - 3.69)	0.112
Immunosuppressive therapy	41 (45.9)	12/41 (29.3)	52/266 (19.5)	1.49 (0.88 - 2.56)	0.154
Urinary catheter	66 (21.5)	21/66 (31.8)	43/241 (17.8)	1.78 (1.14 - 2.79)	**0.013**
Antibiotic use in past month	126 (41.0)	33/126 (26.2)	31/181 (17.1)	1.53 (0.99 - 2.36)	**0.054**
Type of acquisition					
Hospital-acquired	155 (52.2)	37/155 (23.9)	26/142 (18.3)	1.30 (0.83 - 2.04)	0.242
Healthcare-associated	78 (26.3)	13/78 (16.7)	50/219 (22.8)	0.73 (0.42 - 1.27)	0.253
Community-acquired	64 (21.5)	13/64 (20.3)	50/233 (21.5)	0.95 (0.55 - 1.63)	0.842
Source of infection					
Biliary tract	36 (11.7)	8/36 (16.7)	58/271 (21.4)	0.78 (0.36 - 1.68)	0.511
Abdominal (non-biliary)	39 (12.7)	10/39 (25.6)	54/268 (20.1)	1.72 (0.71 - 2.28)	0.430
Catheter-related	21 (6.8)	6/21 (28.6)	58/286 (20.3)	1.41 (0.69 - 2.88)	0.403
Skin and soft tissue	5 (1.6)	2/5 (40.0)	62/302 (20.5)	1.95 (0.65 - 5.85)	0.280
Respiratory	10 (3.3)	3/10 (30.0)	61/297 (20.5)	1.46 (0.55 - 3.86)	0.440
Central nervous system	1 (0.3)	0 (0.0)	64/306 (20.9)	-	1.000
Endocarditis	25 (8.1)	5/25 (20.0)	59/282 (20.9)	0.96 (0.42 - 2.16)	0.913
Urinary tract	60 (19.5)	11/60 (18.3)	53/247 (21.5)	0.85 (0.48 - 1.53)	0.593
Other	3 (1.0)	0/0 (0.0)	64/304 (21.1)	-	1.000
Unknown	107 (34.9)	21/107 (19.6)	43/200 (21.5)	0.91 (0.57 - 1.46)	0.700
Etiology					
E. faecalis	186 (60.6)	38/186 (20.4)	26/121 (21.5)	0.95 (0.61 - 1.48)	0.824
E. faecium	121 (39.4)	26/121 (21.5)	38/186 (20.4)	1.05 (0.68 - 1.64)	0.824
Ampicillin resistance	101 (38.2)	22/101 (21.8)	31/163 (19.0)	1.45 (0.70 - 1.86)	0.586
Vancomycin resistance	8 (3.0)	1/8 (12.5)	53/255 (20.8)	0.60 (0.09 - 3.82)	1.000
Active empirical treatment	144 (46.9)	34/144 (23.6)	30/163 (18.4)	1.28 (0.83 - 1.98)	0.262
Clinical presentation					
Pitt score 3 or higher	75 (24.4)	29/75 (38.7)	35/232 (15.1)	2.56 (1.69- 3.89)	**0.001**
SOFA 3 or higher	125 (41.5)	43/125 (34.4)	16/176 (9.1)	3.79 (2.24 - 6.41)	**<0.001**
Outcome					
Recurrence of infection	16 (5.2)	2/16 (12.5)	62/291 (21.3)	0.59 (0.16 - 2.18)	0.399
All-cause mortality	64 (20.8)				
BSI-related mortality	35 (11.4)				

General characteristics of enterococcal BSI population and univariate analysis of factors associated with mortality.