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ORIGINAL ARTICLE

Subsequent infection with extended-spectrum β-lactamase-producing Enterobacteriaceae in patients with prior infection or fecal colonization

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Abstract

In clinical practice, there is a growing need to assess the impact of prior colonization or infection with extended-spectrum β-lactamase-producing Enterobacteriaceae (EPE) on new EPE infections. We have investigated the frequency of, and duration to, a subsequent EPE infection in patients with prior fecal carriage or infection with EPE. Culture data for 3272 EPE-positive patients in Western Sweden during 2004–2014 were evaluated. The median follow-up time was 3.7 years. The first recorded EPE-positive fecal screen, or clinical (urine, blood) culture, and subsequent EPE-positive clinical samples were analyzed, focusing on the first and last recurrence of EPE infection. ESBL *Escherichia coli* dominated (95%). Almost all (94%) patients initially positive in fecal screen ($n = 1436$) and 72 and 71% of those initially positive in urine ($n = 1717$) and blood ($n = 119$) had no further EPE clinical isolates. Subsequent EPE bacteremia was only detected in 0.7, 1.6, and 4.2% of the respective patient group. Recurrent EPE-positive urine cultures occurred in 27% (460/1717), most (75%) within 6 months, and rarely (13%) after 1 year. Repeated EPE-positive clinical samples were significantly ($p < 0.01$) more common in patients > 65 years and in men with ESBL *Klebsiella pneumoniae.* In our low-endemic setting, subsequent EPE infections in previously colonized patients were rare. On the other hand, in patients previously EPE-positive in urine or blood, subsequent EPE urinary tract infections were common, especially within 6 months and in patients > 65 years old.

Keywords Extended-spectrum β-lactamases (ESBL) · *E. coli* · *K. pneumoniae* · Fecal screening · Urinary tract infection · Bacteremia · Recurrent infection

Introduction

Multi-drug-resistant extended-spectrum β-lactamase-producing Enterobacteriaceae (EPE), which cause community- and hospital-acquired infections, in particular bloodstream and urinary tract infections (UTI), are a major health concern [1–3]. The most common ESBL-producing organisms causing disease are *Escherichia coli* (ESBL-*E.c*) and *Klebsiella pneumoniae* (ESBL-*K.p*). Severe infections with ESBL-producing organisms are associated with higher mortality and health care-related costs [4–6].

The empirical treatment of infections suspected to be due to enterobacteria in patients who have previously been colonized or have had a clinical infection with EPE is an important and growing clinical challenge. Numerous studies focus on possible risk factors including prior colonization for subsequent EPE infections, mostly bacteremia, in selected high-risk patient groups in hospital settings [7–11]. There is a growing need to assess the impact of the EPE carrier state and earlier EPE infection on new EPE infections in unselected patient groups [12]. This is important since several guidelines stimulate the use of broad-spectrum antibiotics such as the carbapenems for previously EPE-colonized and/or infected patients, and indiscriminate empiric carbapenem usage may drive resistance and select for carbapenem resistance [8, 13].

In this study, we have investigated the frequency of subsequent EPE-positive clinical cultures (urine or blood) obtained for diagnostic purposes in all patients in our database initially EPE-positive in a clinical culture or in fecal screening.

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Methods

Study setting

Clinical Microbiology, Sahlgrenska University Hospital, serves all health care of approximately 750,000 inhabitants in the greater Gothenburg area, Western Sweden, including a 2000-bed university hospital, a 200-bed tertiary hospital, 110 long-term-care facilities, and 75 outpatient clinics. The study period was set to 2004–2014. During this period, the number of blood cultures increased from 24,600 to 44,000 and urine cultures from 64,700 to 75,800 samples/year. By 2014, the bacteremia rate of EPE in *E. coli* was 6.6 and 4.4% in *K. pneumoniae*. The first ESBL-positive patient in our region was detected in late 2003.

A screening program for the carriage of multi-resistant Enterobacteriaceae has been ongoing since 2000. Patients hospitalized abroad at some point during the last 10 years are screened at admission. Most (97%) screen samples are fecal samples. Fecal sampling as well as the rate of EPE-positive screened patients increased during the study period, from 3425 to 21,982 samples/year and from 0.12 to 1.8% respectively.

Algorithm for database searching

The entire database was searched for all samples that were positive for EPE collected from patients in both the in- and outpatient setting, i.e., all screen samples and all diagnostic clinical samples. EPE of other species than *E. coli* and *K. pneumoniae* were excluded due to scarcity. For the same reason, we limited the analyses of clinical samples to blood and urine samples and for screen samples to fecal samples. Samples from wards with extended screening regimens or outbreaks were excluded.

The first EPE isolate (screen or clinical culture) and, thereafter, only EPE-positive clinical cultures were recorded. In case of multiple EPE-positive cultures obtained within a 7-day period, only one of them was included after prioritizing as follows: first the blood, then urine, and, lastly, the screen culture. Hereafter, the first and last subsequent clinical culture for each patient was selected for analysis. A minimum follow-up time of 1 year was required for every patient and the overall median follow-up time was 3.7 years. Presence of urine cultures positive for Enterobacteriaceae not producing ESBL (non-EPE) was investigated in patients with repeated ESBL-*E.c* bacteriuria during the period of their recurrences.

Culturing procedure

Species identification was determined according to routine clinical practice and antibiotic susceptibility determination according to EUCAST [14]. All cephalosporin-resistant isolates were tested for the ESBL-phenotype, using the double-disc diffusion test [15].

Statistical analysis

Data entry was carried out using Microsoft Excel and STATA 15.0. For categorical variables, the chi-squared test was used. A p value of < 0.05 was considered significant.

Results

Overall findings

We identified 3272 patients with at least one EPE-positive sample. In 1717 of these patients, the first isolate was detected in urine, in 119 in blood, and in 1436 patients by fecal screening (Fig. 1, Table 1). The screen-positive patients were younger, with only 16% being > 65 years old, as compared to 45% of those initially detected by a clinical sample. Most of the patients, that is, 94, 72, and 71%, who were EPE-positive in the screen, urine, and blood samples, respectively, had no subsequent positive clinical sample at all. Subsequent EPE-positive clinical samples were found significantly more often in patients with a previous clinical isolate than in those initially screen positive (28 versus 5.6%, $p < 0.0001$). A change of species from ESBL-*E.c* to ESBL-*K.p* or vice versa from the first to a subsequent positive culture was rarely (0.06%) encountered.

Patients initially positive in screen for fecal carriage of EPE

Only 80 of the 1436 screen positive patients had a subsequent positive clinical sample for EPE, mostly (71/80) ESBL-*E.c* and only 10 were positive in blood (Fig. 1). Eighteen patients were repeatedly EPE-positive. Although overall rare, significantly higher frequencies of subsequent EPE-positive clinical cultures were seen in the elderly and for patients who were initially screen-positive for ESBL-*K.p* (Tables 1 and 2).

The overall median times from the EPE-positive screen sample to the first or to the last detected clinical EPE isolate were 5.4 and 6.4 months respectively (Fig. 2, Table 1). Only 20 (1.4%) of the initially EPE-screen positive patients had a subsequent ESBL-positive clinical sample after 1 year.

Patients initially positive for EPE in clinical urine samples

Of the 1717 patients who were initially EPE-positive in a clinical urine sample, 28% had at least one and 13% had two or more (median 4, range 2–23) subsequent EPE-positive clinical cultures (Fig. 1). Only 28 (1.6%) patients

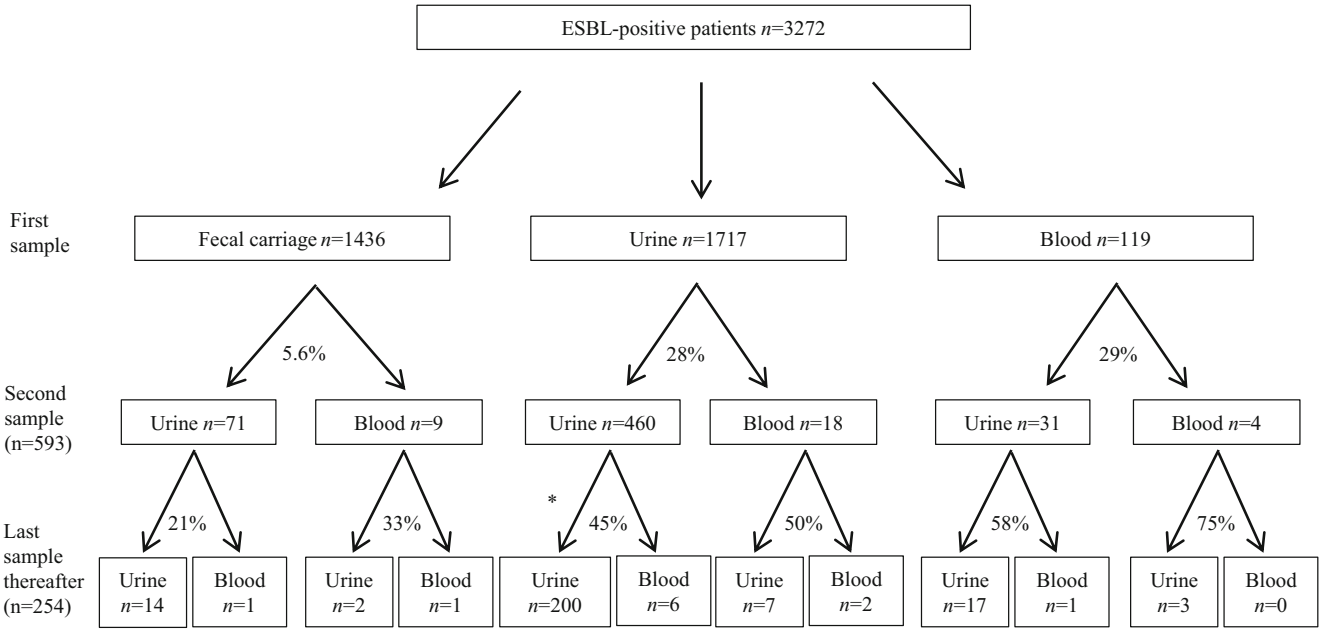

Fig. 1 Flowchart depicting the patients with at least one EPE-positive culture during the study period and, where applicable, the second and last registered EPE-positive clinical culture. Positive clinical samples between the first and last recurrences are not included, except for those cases in which there was an additional positive blood culture, i.e., four patients marked with an asterisk

were subsequently EPE-positive in the blood at some point with a median time from the first urine to the subsequent blood culture of 71 days (range 8–2474 days).

One and several subsequent EPE-positive clinical samples were detected significantly more frequently: (i) in elderly (> 65 years) patients, as compared to patients in the two younger age groups; (ii) in men compared to women; and (iii) in those who initially were positive in the urine for ESBL-*K.p* compared to ESBL-*E.c* (Table 1).

The overall median time was 1.9 months to the first and 5.3 months to the last subsequent EPE-positive clinical sample after the initial EPE bacteriuria episode, of which 34% were registered within 30 days and 75% within 6 months (Table 1). Sixty-three patients (13%) had their first recurrent EPE-positive culture registered after 1 year, two of these in blood.

For the 1614 patients who were initially positive for ESBL-*E.c* in the urine, 26% had at least one (15%) or several (11%) subsequent EPE-positive urine samples (Table 2). Recurrent EPE bacteriuria was observed most frequently in the elderly (35%). In the younger patients, recurrences were significantly more common in men than in women both for those < 18 years (39 vs 20%, $p < 0.05$) and for the 18–65 age group (26 vs 17%, $p < 0.001$). The median time to the first as well as to the last urine sample positive for ESBL-*E.c* was similar for both sexes (Fig. 3).

Patients positive for EPE in blood cultures

Only 119 patients were initially positive for EPE in the blood of which 29% had at least one and 18% had several subsequent clinical samples (Fig. 1). ESBL-*E.c* clearly dominated and a majority (67%) of the patients was elderly (Table 1). The overall median times to the subsequent EPE-positive clinical samples were short.

Considering all 157 patients with EPE-bacteremia at some point, irrespective of previous EPE-culture findings, 52 patients (33%) had at least one and 27 (17%) had several subsequent EPE-positive clinical samples. A concurrent EPE-positive urine and blood culture (within 7 days) indicating urinary focus was seen in 70 of these patients (45%). Repeatedly EPE-positive blood cultures were seen in 8% of the patients, one patient with ESBL-*K.p*, and 12 with ESBL-*E.c*. The overall median time from the EPE-bacteremia episode to the first and to the last subsequent clinical culture was a little less than 2 months (54 days, range 10–889 days) and 3 months (111 days, range 14–1291 days), respectively. Whereas all EPE-recurrences were seen within 9 months in those 18–65 years, subsequent EPE-positive clinical samples occurred, but were rare (0.06%) after 1 year in the elderly.

Discussion

We show that for patients with a history of EPE in a fecal screen, the frequency of subsequent EPE-positive clinical culture was very low, especially for cases of bacteremia. One year after the positive index screen culture, the frequency was close to zero. The literature is scarce, and although similar low frequencies have been noted for screen-positivity in non-selected

Table 1 Baseline characteristics

First EPE-positive sample for each patient	Number (%) of patients with ≥ 1 following sample[a]	Number (%) of patients with ≥ 2 following samples[a]	Median time (days) to 2nd sample (range)	Median time (days) to last sample (range)
Screen (*n* = 1436)	80 (5.6%)	18 (1.3%)	162 (9–1616)	193 (10–2005)
Age group				
< 18 years (*n* = 179)	3 (1.7%)	1 (0.6%)	136 (72–482)	268 (72–482)
18–65 years (*n* = 1024)	50 (4.9%)	9 (0.9%)	150 (10–1616)	182 (10–1616)
> 65 years (*n* = 233)	27 (12%)[b]**	8 (3.4%)[b]**	182 (9–1423)	218 (10–2005)
Gender				
Men (*n* = 581)	33 (5.7%)	8 (1.4%)	89 (9–1423)	149 (10–1423)
Women (*n* = 855)	47 (5.5%)	10 (1.2%)	236 (10–1616)	252 (10–2005)
Species				
E. coli (*n* = 1374)	71 (5.2%)	15 (1.1%)	182 (10–1616)	203 (10–2005)
K. pneumoniae (*n* = 62)	9 (15%)[c]**	3 (4.8%)[c]**	44 (9–483)	58 (15–678)
Urine (*n* = 1717)	478 (28%)	215 (13%)	57 (8–2783)	161 (8–3945)
Age group				
< 18 years (*n* = 186)	47 (25%)	16 (8,6%)	33 (8–2128)	140 (8–2271)
18–65 years (*n* = 784)	157 (20%)	61 (7.8%)	52 (8–2135)	113 (8–2135)
> 65 years (*n* = 747)	274 (37%)[b]**	138 (18%)[b]**	69 (8–2783)	184 (13–3945)
Gender				
Men (*n* = 441)	163 (37%)[c]**	86 (20%)[c]**	46 (8–1847)	142 (8–2474)
Women (*n* = 1276)	315 (25%)	129 (10%)	66 (8–2783)	163 (8–3945)
Species				
E. coli (*n* = 1614)	439 (27%)	192 (12%)	60 (8–2783)	163 (8–3945)
K. pneumoniae (*n* = 103)	39 (38%) [c]*	23 (22%)[c]**	46 (8–1847)	93 (13–2019)
Blood (*n* = 119)	35 (29%)	21 (18%)	52 (10–889)	116 (19–1291)
Age group				
< 18 years (*n* = 9)	3 (33%)	2 (22%)	75 (43–86)	110 (75–189)
18–65 years (*n* = 30)	5 (17%)	3 (10%)	32 (24–263)	56 (32–263)
> 65 years (*n* = 80)	27 (34%)	16 (20%)	52 (10–889)	139 (19–1291)
Gender				
Men (*n* = 65)	18 (28%)	11 (17%)	46 (10–889)	95 (20–1291)
Women (*n* = 54)	17 (31%)	10 (19%)	55 (19–263)	139 (19–1241)
Species				
E. coli (*n* = 108)	30 (28%)	20 (19%)	50 (10–889)	99 (19–1291)
K. pneumoniae (*n* = 11)	5 (45%)	1 (9%)	299 (12–342)	299 (21–342)

Distributions of age groups and gender for the patients, as well as the identified bacterial species related to the number of and median time to subsequent EPE-positive cultures in the blood or urine with respect to the initial detected positive sample

[a] Percentage of patients in left column

[b] Significance levels by age group compared to remaining population

[c] Significance levels compared to the other species or gender respectively

*$p < 0.05$, chi-squared test; **$p < 0.01$, chi-squared test

patient groups in other EPE-low-endemic settings, the impact of colonization on infection needs further attention [12, 16].

It has been proposed that selected patient groups could benefit from routine screening for EPE [9, 11, 17, 18]. In patients with hematological malignancies, fecal colonization has been shown to increase more than threefold the risk of bloodstream infections, probably due to the translocation of the bacterial flora from the intestinal lumen [18]. However, in other studies, the benefit of screening for EPE has been questioned [19]. In healthy Swedes colonized by EPE, the risk of EPE-bacteremia was estimated to be very low [20]. Here, we describe patients EPE-screen positive at hospital admission, and the frequency of subsequent EPE-positive clinical cultures was still very low. However, considering the present results, we cannot exclude that screening a subset of

Table 2 Distributions of gender and age groups for the patients with subsequent clinical EPE-positive samples, categorized by bacterial species and sample type

Sample type				ESBL-*E.coli* positive patients							ESBL-*K. pneumoniae*-positive patients						
				Men			Women			Total	Men			Women			Total
Initially screen positive				< 18	18–65	> 65	< 18	18–65	> 65		< 18	18–65	> 65	< 18	18–65	> 65	
First	Second	Last	*n*	90	327	125	79	665	88	1374	5	23	11	5	9	9	62
Screen				88	312	115	78	635	75	1303	5	20	8	5	7	8	53
Screen	Urine			1	8	8	1	24	9	51	0	2	1	0	2	0	5
	Blood			0	3	1	0	1	0	5	0	1	0	0	0	0	1
Screen	Urine	Urine		1	1	1	0	4	4	11	0	0	2	0	0	1	3
		Blood		0	1	0	0	0	0	1	0	0	0	0	0	0	0
	Blood	Urine		0	2	0	0	0	0	2	0	0	0	0	0	0	0
		Blood		0	0	0	0	1	0	1	0	0	0	0	0	0	0
Initially urine culture positive																	
First	Second	Last	*n*	39	141	207	142	607	478	1614	2	19	33	3	17	29	103
Urine				24	105	118	113	502	313	1175	1	10	20	1	10	22	64
Urine	Urine			11	18	39	19	71	81	239	0	1	5	1	3	5	15
	Blood			0	0	2	0	3	3	8	0	0	1	0	0	0	1
Urine	Urine	Urine		4	18	39	10	29	80	180	0	7	6	1	4	2	20
		Blood		0	0	5	0	0	0	5	0	0	1	0	0	0	1
	Blood	Urine		0	0	3	0	1	1	5	1	1	0	0	0	0	2
		Blood		0	0	1	0	1	0	2	0	0	0	0	0	0	0
Initially blood culture positive																	
First	Second	Last	*n*	4	14	39	4	15	32	108	0	0	8	1	1	1	11
Blood				3	12	28	2	13	20	78	0	0	4	1	0	1	6
Blood	Urine			0	0	4	1	1	4	10	0	0	3	0	0	0	3
	Blood			0	0	0	0	0	0	0	0	0	0	0	1	0	1
Blood	Urine	Urine		1	2	6	1	0	6	16	0	0	1	0	0	0	1
		Blood		0	0	0	0	0	1	1	0	0	0	0	0	0	0
	Blood	Urine		0	0	1	0	1	1	3	0	0	0	0	0	0	0
		Blood		0	0	0	0	0	0	0	0	0	0	0	0	0	0

patients may be beneficial, for instance those with high risk of recurrent UTI.

A matter of concern is that almost one third of the patients with EPE in a clinical diagnostic culture had at least one recurrence and of these almost 50% had several subsequent EPE-infections, mostly UTI. Most of the recurrences occurred within the first 6 months. Subsequent EPE-bacteremia was rare and for almost half of the patients with EPE-bacteremia the urinary tract was the likely focus. Recurrences were significantly more common in elderly patients, in men, and in patients with ESBL-*K.p*. Recurrence of ESBL-*K.p* also appeared significantly earlier than recurrence of ESBL-*E.c* and subsequent bacteremia rates were somewhat higher. These findings most likely reflect the fact that the prevalence of urological comorbidity is greater in these groups, bearing in mind that *K. pneumoniae* is a secondary UTI pathogen and was a rare finding.

We have not confirmed EPE-strain homology from the first to subsequent occasions. However, reinfection with a new EPE strain is less likely in our EPE low-endemic setting. Intermittent urinary samples with non-EPE uropathogens were seen occasionally in only 12% of the patients with recurrent EPE-bacteriuria (data not shown). In previous studies, high frequency of strain homologies has been revealed in recurrent UTI due to sensitive *E. coli* especially for recurrences within 1 year [21, 22]. It is likely that this is the case also for ESBL-*E.c*. We have preliminary data pointing in this direction but strain homology clearly needs further investigation not the least for emerging multidrug-resistant EPE-clones with known urovirulence, like *E. coli* O25b-ST131 [23].

We have refrained from comparing rates of recurrent UTI due to EPE with that of non-EPE, and we have not predicted risks in the absence of comparative data for previously non-infected patients. Rates due to sensitive *E. coli* have

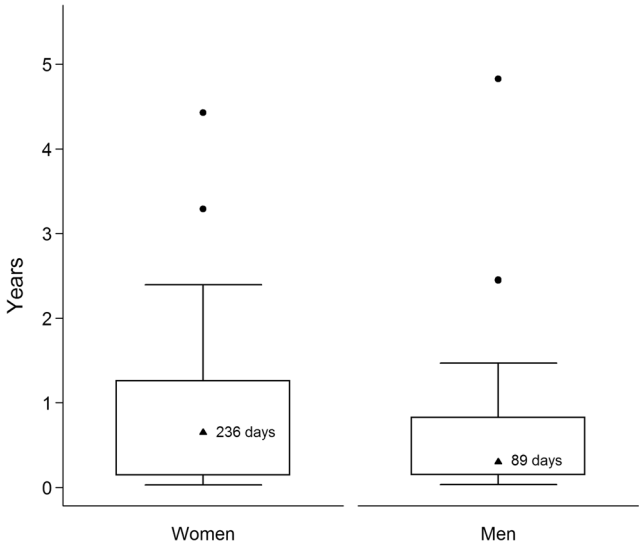

Fig. 2 Time from the first fecal EPE-positive screen to the last registered EPE-positive clinical sample in relation to patient gender. The box plot shows the median, indicated by a filled triangle, lower and upper quartiles, as well as the minimum and maximum numbers of days to the subsequent positive culture for 47 women and 33 men

previously been studied extensively and our rates for ESBL-*E.c* are comparative to these older studies [24–27].

The present investigation has limitations. In primary care in Sweden, urine sample cultivation is not generally recommended in sporadic UTI and follow-up urine cultures may have been performed despite not recommended. This has most likely influenced our dataset. We did not evaluate medical records, and therefore, we could not differentiate disease severity, for example pyelonephritis and cystitis from asymptomatic bacteriuria. Furthermore, known patient-related risk factors for EPE-colonization and clinical infection were not taken in consideration, which may have altered the results for the high-risk patient groups [7–11].

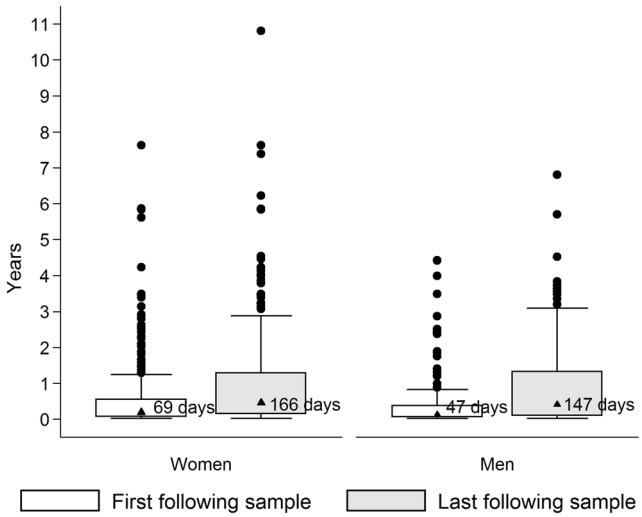

Fig. 3 Time from the first ESBL-*E. c*-positive urine culture to the last registered EPE-positive clinical sample in relation to patient gender. The box plot shows the median, indicated by a filled triangle, lower and upper quartiles, as well as the minimum and maximum numbers of days to the subsequent positive culture for 299 women and 140 men

The results may not be generalizable, particularly not to settings with higher ESBL prevalence. Nonetheless, a low risk of constant exposure to new EPE-strains is a prerequisite in understanding the natural history in patients with EPE-carriage or infection. The strength of our study is also that it covers all the patients with culture samples in a large geographic area including all types of health-care over a very long time.

In conclusion, the frequency of subsequent EPE-positive clinical samples in patients with earlier fecal colonization with ESBL-producing *E. coli* or *K. pneumoniae* was very low. However, a history of EPE in blood or urine cultures particularly in patients with recurrent UTI is a matter of concern, and subsequent EPE-infection is common, especially within 6 months and in patients > 65 years old. Further studies are needed to identify patient-related risk factors as well as bacterial characteristics influencing recurrence of EPE-infections.

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Compliance with ethical standards

This study was conducted in accordance with the Declaration of Helsinki and national and institutional regulations.

Ethical approval The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden (recordal: 170-17).

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent No informed consent was required.

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