International Journal of Antimicrobial Agents 53 (2019) 820–829

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Prediction of bloodstream infection caused by extended-spectrum β-lactamase-producing Enterobacterales in patients with suspected community-onset sepsis

Inga Fröding[a,b,*], John Karlsson Valik[c,d], Ludvig Bolinder[d], Pontus Nauclér[c,d], Christian G. Giske[a,b]

[a] Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden
[b] Department of Clinical Microbiology, Karolinska University Laboratory, Stockholm, Sweden
[c] Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[d] Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 26 November 2018
Accepted 9 February 2019

Editor: Dr. Jim Gray

Keywords:
Prediction
Bacteraemia
Community-onset infection
Enterobacterales
Risk factors

ABSTRACT

Objectives: In severe infections, time to appropriate therapy is decisive for survival. Patients with bloodstream infection caused by extended-spectrum β-lactamase-producing Enterobacterales (EPE-BSI) often receive inadequate empirical treatment. This study aimed to identify risk factors, to evaluate a previously suggested risk score and to suggest a new score for facilitating empirical treatment choice.

Methods: Predictors for EPE-BSI were assessed through a retrospective case–control design. The diagnostic performance of the two scores was evaluated. Included patients had blood cultures sampled at four EDs in Stockholm (2012–2015), were admitted, and received antibiotics with activity against Gram-negative bacilli.

Results: A total of 277 EPE-BSI cases and 400 controls were included. The strongest predictor of EPE-BSI was prior EPE-positive culture (cases 33% vs. controls 3%; multivariate (MV) OR = 19.1). Recent EPE-positivity within ≤3 months had a univariate OR of 32.8. Other major predictors were recent prostate biopsy (14% vs. 1%; MV OR = 22.2) and healthcare abroad (6% vs. 2%; MV OR = 3.9). Several previously suggested risk factors were not associated with EPE-BSI. The previously developed Utrecht score had a sensitivity of 54% and a specificity of 77%. The Stockholm score suggested herein (prior EPE-positive culture/prostate biopsy/healthcare abroad) showed comparable sensitivity (50%) but better specificity (96%). Prediction in patients lacking major predictors was difficult and caused high false-positive rates, which would cause unnecessary overtreatment.

Conclusions: Prior EPE-positive culture, especially recently sampled, prostate biopsy and healthcare abroad were the strongest risk factors for community-onset EPE-BSI in Stockholm. Local data are needed when evaluating risk-scoring models before implementation.

1. Introduction

Antimicrobial resistance in Gram-negative bacilli is an increasing problem worldwide. Enterobacterales resistant to third-generation cephalosporins (3GCs) are classified by the World Health Organization (WHO) as a critical priority pathogen and are a cause of increased healthcare costs and mortality [1,2]. Production of extended-spectrum β-lactamases (ESBLs) confers resistance to cephalosporins, which are the first-line empirical treatment for community-onset sepsis in many countries, including Sweden [3]. The rate of ESBL-producing Enterobacterales (EPE) is increasing worldwide at a rapid rate. ESBL production, and thus cefotaxime resistance, was found in 8% of *Escherichia coli* from bloodstream infections (BSIs) in Stockholm in 2017 according to data extracted from the laboratory information system of Karolinska University Laboratory (Stockholm, Sweden),

In severe infections, the time to appropriate antibiotic therapy is decisive for survival [4–6]. In the absence of point-of-care tests for detection of sepsis pathogens and resistance markers, empirical treatment is initiated before the infecting microorganism is known. Treatment decisions are based on patients' clinical presentation,

* Corresponding author. Present address: Department of Clinical Microbiology, Bacteriology F72, Karolinska University Laboratory, 141 86 Stockholm, Sweden. Tel.: +46 8 585 847 16.
E-mail address: inga.froding@sll.se (I. Fröding).

https://doi.org/10.1016/j.ijantimicag.2019.02.008
0924-8579/

history and severity of illness. BSIs caused by EPE (EPE-BSIs) are associated with a high risk of receiving inadequate empirical treatment, and these patients are at risk of higher mortality [7,8]. There is thus an increasing need to identify patients at risk for EPE-BSI on admission. Several studies suggest different scores to aid this decision [9–13]. Rottier et al. developed a prediction score for BSI caused by 3GC-resistant enterobacteria, herein referred to as the 'Utrecht score' [14]. The score consists of six variables assigned different points, however this complexity might limit practicality. Thus, a simpler screening system for EPE-BSI in patients with suspected sepsis would be beneficial.

In case–control studies, the choice of the source population is of great importance for the ability to generalise the results through prediction scores [8,14–16]. When utilising patients with BSI caused by a susceptible strain of the same species as controls [10,17,18], the results can only be applied in the setting with a species-identified positive blood culture, before susceptibility results are available. As a proxy for the suspicion of a severe Gram-negative infection, we used initiation of treatment with an agent with a Gram-negative spectrum and collection of blood culture [14].

The aim of this study was (i) to evaluate the performance of the Utrecht score as an aid for decisions on empirical therapy to cover EPE-BSIs in patients with suspected community-onset sepsis and (ii) to identify predictors for EPE-BSI useful for less complex screening tools. Furthermore, the impact of time since previous culture finding of EPE to predict future EPE-BSI was investigated.

2. Methods

2.1. Setting and patients

This study was performed as a retrospective case–control study in one secondary/tertiary-care university hospital (with two emergency departments (EDs)) as well as two secondary-care hospitals in Stockholm (Sweden), covering a population of 1.5 million people for secondary care.

Patients attending the EDs between 1 January 2012 and 31 December 2015 were included if they were aged ≥18 years, had a blood culture drawn, were admitted and had antibiotic treatment started ≤24 h with an agent with activity against Gram-negative bacteria (Fig. 1). Agents included broad-spectrum cephalosporins, piperacillin/tazobactam (PTZ), monobactams, carbapenems, aminoglycosides, fluoroquinolones, trimethoprim/sulfamethoxazole (SXT), tigecycline and colistin. Patients transferred from another hospital were excluded. Cases were patients with growth of an EPE in the blood culture, and repeated episodes were excluded. Controls ($n = 400$) were randomly selected and were matched for hospital and year of sampling.

Patients were identified through the laboratory information system at Karolinska University Laboratory. Potential cases and controls were subjected to retrospective chart review. The microbiological methods utilised by the routine laboratory are described in the Supplementary material.

2.2. Variables and definitions

Patient data recorded included: patient characteristics; microbiological cultures and antimicrobial susceptibility; Charlson co-morbidity index [19]; and severity of disease assessed by Sequential Organ Failure Assessment (SOFA) score [20,21]. Risk factors for EPE-BSI examined were based on suggestions in prior studies as well as local observations. Prior antibiotic use was analysed separately for each antibiotic group, as any antibiotic treatment and as a subgroup consisting of agents with an impact on the gut microbiota but limited activity against EPE, including aminopenicillins, cephalosporins, fluoroquinolones, trimethoprim and SXT (Supplementary Table S1) [22].

The Utrecht score is based on the sum of points (in parenthesis) given for certain risk factors: prior EPE-positive culture <1 year (100); suspected urinary tract infection (UTI) (50); suspected pneumonia (−50); immunocompromised (25); any use of antibiotics in prior 2 months (25); and age (1 point per year). Rottier et al. suggest a cut-off at ≥120 for identifying patients with a high risk for 3GC-resistant Enterobacterales (Supplementary Table S2) [14].

Empirical treatment was defined as agents given in the first 24 h. If several agents were given, the patient was classified as belonging to the agent/group with the least resistance among EPE isolates in the cases (Supplementary Table S3, susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint table valid at time of isolation [23]). The order of increasing resistance was: carbapenems; PTZ; aminoglycosides; fluoroquinolones/SXT; and cephalosporins. Empirical treatment generally recommended for patients with a high risk of EPE-BSI is a carbapenem or high-dose PTZ [24–28]. Combination treatment with amikacin is another alternative, but aminoglycosides have been questioned as monotherapy for systemic infections [29,30]. For these reasons, a carbapenem or PTZ was evaluated as the treatment of choice for a patient with a positive Stockholm or Utrecht score.

Treatment was considered appropriate when the EPE isolate was susceptible in vitro, except for PTZ 4 g every 6 h, which was considered appropriate both for susceptible and intermediate (new EUCAST definition from 2019: susceptible, increased exposure) strains.

2.3. Statistical analysis

Logistic regression was used to compute the odds ratio (OR) and 95% confidence interval (CI). All ORs were adjusted for hospital and year. Fifteen predictors were selected for further multivariate logistic regression analysis (for details see Supplementary material). Diagnostic performance of the Utrecht score compared with the presence of any of the three most important predictors identified through logistic regression, called the 'Stockholm score', was evaluated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The hypothetical impact on empirical treatment of the two scores compared with the actual empirical treatment the patients received was evaluated. Stata Statistical Software: Release 13 (StataCorp LP, College Station, TX) was used for statistical calculations.

3. Results

In total 277 cases of community-onset EPE-BSI fulfilled the inclusion criteria. The size of the study population was estimated at 46 723 episodes occurring in 2012–2015, giving an estimated prevalence of EPE-BSI of 0.59% in patients admitted to hospital with suspected infection where empirical coverage of Gram-negative bacilli was chosen (Fig. 1). Patient characteristics are shown in Table 1. Overall 7-day mortality was 5.1% for cases and 3.5% for controls.

3.1. Predictors for EPE-BSI

The 15 predictors selected for inclusion in the multivariate logistic regression model are indicated with an asterisk in Table 1, and the final model is shown in Table 2. The two strongest predictors were any prior EPE-positive culture and recent prostate biopsy. Further significant predictors were prior healthcare abroad, SOFA score ≥4, suspected UTI and age 40–69 years. Patients with suspected lower respiratory tract infection (LRTI) and skin

Table 1
Patient characteristics for cases with community-onset EPE-BSI and controls

Patient characteristics/predictors	Controls ($n = 400$) *n* (%)	EPE-BSI cases ($n = 277$) *n* (%)	OR (95% CI)[a]	*P*-value
Hospital code*				
1	200 (50)	153 (55)	1.0 (Ref.)	
2	100 (25)	72 (26)	0.9 (0.7–1.4)	0.739
3	100 (25)	52 (19)	0.7 (0.5–1)	**0.049**
Year*				
2012	100 (25)	53 (19)	1.0 (Ref.)	
2013	100 (25)	66 (24)	1.3 (0.8–2)	0.330
2014	100 (25)	80 (29)	1.5 (1–2.4)	0.061
2015	100 (25)	78 (28)	1.5 (1–2.3)	0.081
Age category*				
<40	43 (11)	9 (3)	1.0 (Ref.)	
40–49	26 (7)	20 (7)	3.6 (1.4–9.1)	**0.007**
50–59	37 (9)	41 (15)	5.1 (2.2–11.9)	**<0.001**
60–69	74 (19)	88 (32)	5.9 (2.7–13)	**<0.001**
70–79	107 (27)	59 (21)	2.7 (1.2–5.9)	**0.014**
≥80	113 (28)	60 (22)	2.7 (1.2–5.9)	**0.014**
Female*	175 (44)	97 (35)	0.7 (0.5–0.9)	**0.018**
Charlson category				
0–1	168 (42)	123 (44)	1.0 (Ref.)	
2–3	148 (37)	94 (34)	0.9 (0.6–1.2)	0.354
4–5	37 (9)	23 (8)	0.8 (0.5–1.5)	0.497
≥6	47 (12)	37 (13)	1 (0.6–1.6)	0.964
Haematological malignancy	27 (7)	21 (8)	1 (0.6–1.9)	0.964
Urological cancer	38 (10)	27 (10)	1 (0.6–1.7)	0.963
Other cancer	49 (12)	35 (13)	1 (0.6–1.6)	0.976
Any transplant	14 (4)	9 (3)	0.8 (0.3–1.9)	0.612
Immunocompromised[b,*]	88 (22)	51 (18)	0.7 (0.5–1.1)	0.099
Diabetes mellitus *	90 (23)	80 (29)	1.5 (1–2.1)	**0.042**
Chronic kidney dysfunction	53 (13)	34 (12)	0.9 (0.6–1.4)	0.657
Obstructive urinary tract disease*	96 (24)	124 (45)	2.6 (1.9–3.7)	**<0.001**
Prior endoscopy ≤30 days*	14 (4)	22 (8)	2.3 (1.1–4.6)	**0.020**
Prior surgery ≤30 days	33 (8)	21 (8)	0.9 (0.5–1.7)	0.844
Central venous line	34 (9)	31 (11)	1.3 (0.8–2.2)	0.368
Urinary catheterisation at admission *	65 (16)	79 (29)	2.1 (1.4–3)	**<0.001**
Prostate biopsy ≤30 days*	2 (1)	38 (14)	39.2 (9.2–166.5)	**<0.001**
Prior healthcare abroad ≤6 months*	6 (2)	18 (6)	4.4 (1.7–11.2)	**0.002**
Healthcare-associated[c,*]	207 (52)	191 (69)	2.1 (1.5–3)	**<0.001**
Any prior EPE-positive culture[d,*]	11 (3)	91 (33)	17 (8.8–32.6)	**<0.001**
No prior EPE-positive culture	389 (97)	186 (67)	1.0 (Ref.)	
EPE in prior clinical culture	10 (3)	81 (29)	16.6 (8.4–32.9)	**<0.001**
EPE in faecal screening culture	1 (0.3)	10 (4)	20.5 (2.6–162.2)	**0.004**
SOFA score*				
0–1	154 (39)	79 (29)	1.0 (Ref.)	
2–3	151 (38)	93 (34)	1.2 (0.8–1.8)	0.282
4–5	59 (15)	58 (21)	1.9 (1.2–3)	**0.007**
≥6	36 (9)	47 (17)	2.6 (1.6–4.4)	**<0.001**
Suspected diagnosis at admission*				
Unknown	130 (33)	70 (25)	1.0 (Ref.)	
Abdominal	35 (9)	17 (6)	0.9 (0.5–1.8)	0.801
LRTI	92 (23)	19 (7)	0.4 (0.2–0.7)	**0.002**
SSTI	21 (5)	2 (1)	0.2 (0.0–0.7)	**0.017**
UTI	104 (26)	166 (60)	3.3 (2.2–4.9)	**<0.001**
Other	18 (5)	3 (1)	0.3 (0.1–1.1)	0.074
Prior antibiotic treatment ≤3 months[e,*]				
No prior antibiotic	213 (53)	113 (41)	1.0 (Ref.)	
Microbiota impact agent [f]	131 (33)	123 (44)	1.7 (1.2–2.4)	**0.002**
Other antibiotic agent	56 (14)	41 (15)	1.4 (0.9–2.2)	0.167

EPE, extended-spectrum β-lactamase-producing Enterobacterales; BSI, bloodstream infection; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; LRTI, lower respiratory tract infection; SSTI, skin and soft-tissue infection; UTI, urinary tract infection.

* Predictors marked with an asterisk were selected for further multivariate logistic regression.

[a] Displayed ORs are adjusted for the matching variables hospital and year.

[b] Immunocompromised combines immunosuppressant use, neutropenia (at infection onset) and solid-organ transplantation.

[c] Healthcare-associated infection was defined as any patient coming from a long-term care facility centre, any intravenous administration, prostate biopsy or wound care ≤30 days, haemodialysis and ≥48 h hospitalisation during the last 90 days [31].

[d] Cultures sampled <8 days before blood cultures are not included.

[e] Antibiotic treatment duration >24 h, except for aminoglycosides for which single doses were also included.

[f] Selected antibiotics with assumed impact on the microbiota but limited activity against EPE, including cephalosporins, aminopenicillins, fluoroquinolones, trimethoprim and trimethoprim/sulfamethoxazole [22].

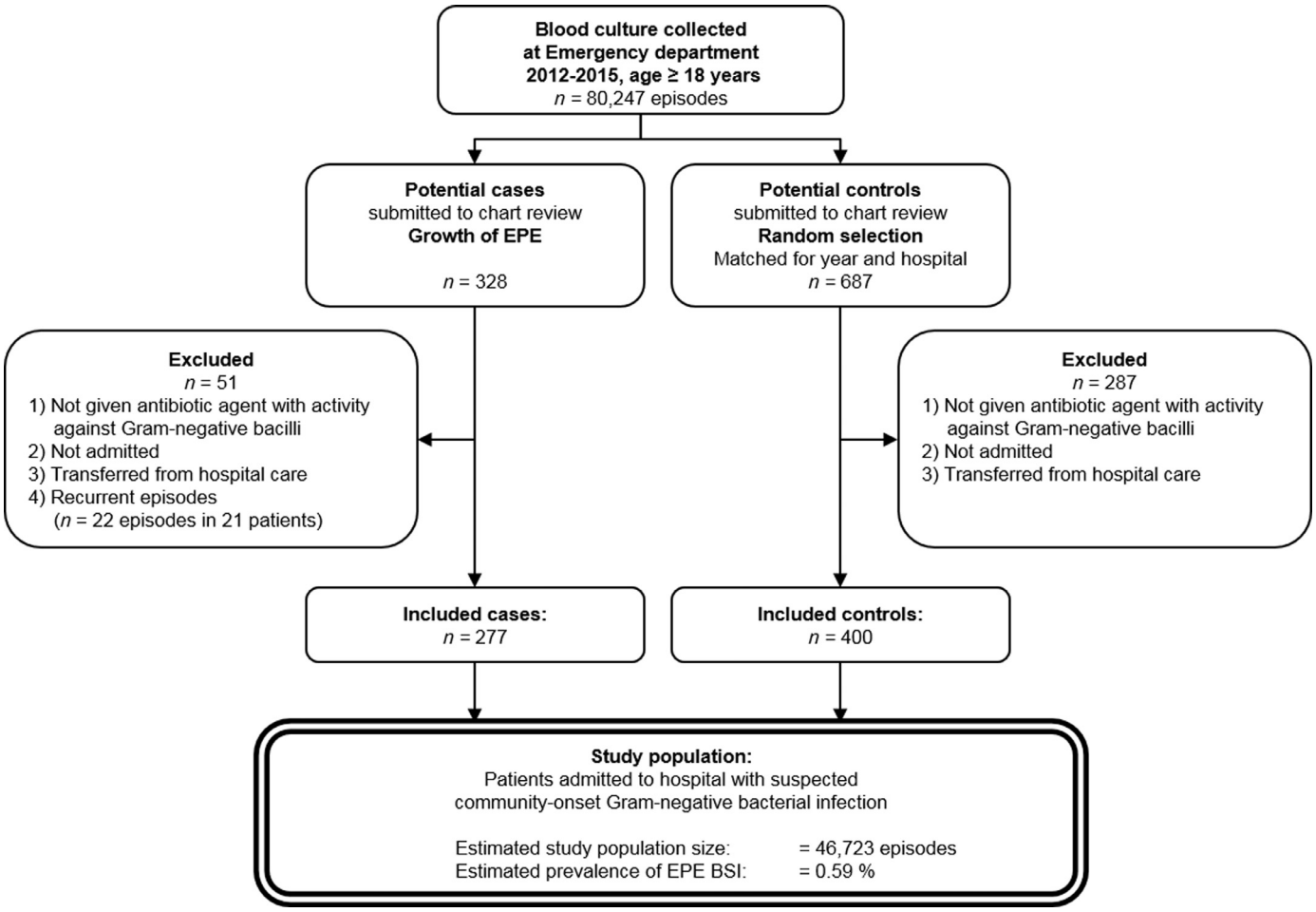

Fig. 1. Flowchart of study. EPE, extended-spectrum β-lactamase-producing Enterobacterales; BSI, bloodstream infection.

Table 2
Multivariate analysis of risk factors for community-onset EPE-BSI[a]

Risk factor	OR (95% CI)	*P*-value
Any prior EPE-positive culture [b]	19.1 (9.2–39.8)	**<0.001**
Prostate biopsy ≤30 days	22.2 (5.0–97.3)	**<0.001**
Prior healthcare abroad ≤6 months	3.9 (1.3–11.6)	**0.016**
Age category		
<40 years	1.0 (Ref.)	
40–49 years	3.0 (1.0–9.0)	**0.047**
50–59 years	2.8 (1.0–7.6)	**0.045**
60–69 years	3.3 (1.3–8.4)	**0.011**
70–79 years	1.6 (0.6–4.1)	0.317
≥80 years	1.6 (0.6–4.0)	0.352
Suspected diagnosis at admission		
Unknown	1.0 (Ref.)	
Abdominal	1.0 (0.5–2.1)	0.998
LRTI	0.4 (0.2–0.7)	**0.005**
SSTI	0.1 (0.0–0.7)	**0.015**
UTI	2.6 (1.6–4.3)	**<0.001**
Other	0.5 (0.1–2.2)	0.350
SOFA score		
0–1	1.0 (Ref.)	
2–3	1.5 (0.9–2.6)	0.086
4–5	2.1 (1.2–3.8)	**0.014**
≥6	4.0 (2.0–7.9)	**<0.001**

EPE, extended-spectrum β-lactamase-producing Enterobacterales; BSI, bloodstream infection; OR, odds ratio; CI, confidence interval; LRTI, lower respiratory tract infection; SSTI, skin and soft-tissue infection; UTI, urinary tract infection; SOFA, Sequential Organ Failure Assessment.

[a] Risk factors kept in the final model are shown. The matching variables hospital and year of admittance were also included in the model (data not shown).

[b] Cultures sampled <8 days before blood cultures are not included.

and soft-tissue infection (SSTI) had a lower risk for EPE-BSI than patients with other suspected sources of infection.

The source of culture and the time passed from the latest prior EPE-positive culture is shown in Fig. 2. Among the cases, 17.7% had a prior EPE-positive culture sampled between 8 days and 3 months earlier, in most cases urinary samples. This was the strongest predictor, with an OR of 32.8 (Table 3). The elevated risk for EPE-BSI with prior EPE-positive culture remained significant when >3 months had passed since sampling. The OR for having any EPE-positive clinical sample did not differ from having only EPE-positive faecal screening (Table 1).

3.2. Comparison of the Utrecht and Stockholm scores

Three strong and easily available predictors (prior EPE-positive culture, prior healthcare abroad and prior prostate biopsy) were combined to a simplified score referred to as the Stockholm score (Supplementary Table S2). The presence of any one of these factors implies an increased risk for EPE-BSI and patients should be considered for empirical treatment with EPE-active agents. The diagnostic specificity was higher for the Stockholm score (96%) than the Utrecht score (77%), with limited loss of sensitivity (50% and 54%, respectively) (Table 4; Supplementary Table S4).

A receiver operating characteristic (ROC) analysis of the Utrecht score examined the influence of the cut-off on diagnostic performance in the present data set. To reach a specificity comparable with the Stockholm score (96%), a cut-off at ≥164 points is needed, which resulted in a sensitivity of 29% for the Utrecht score in the

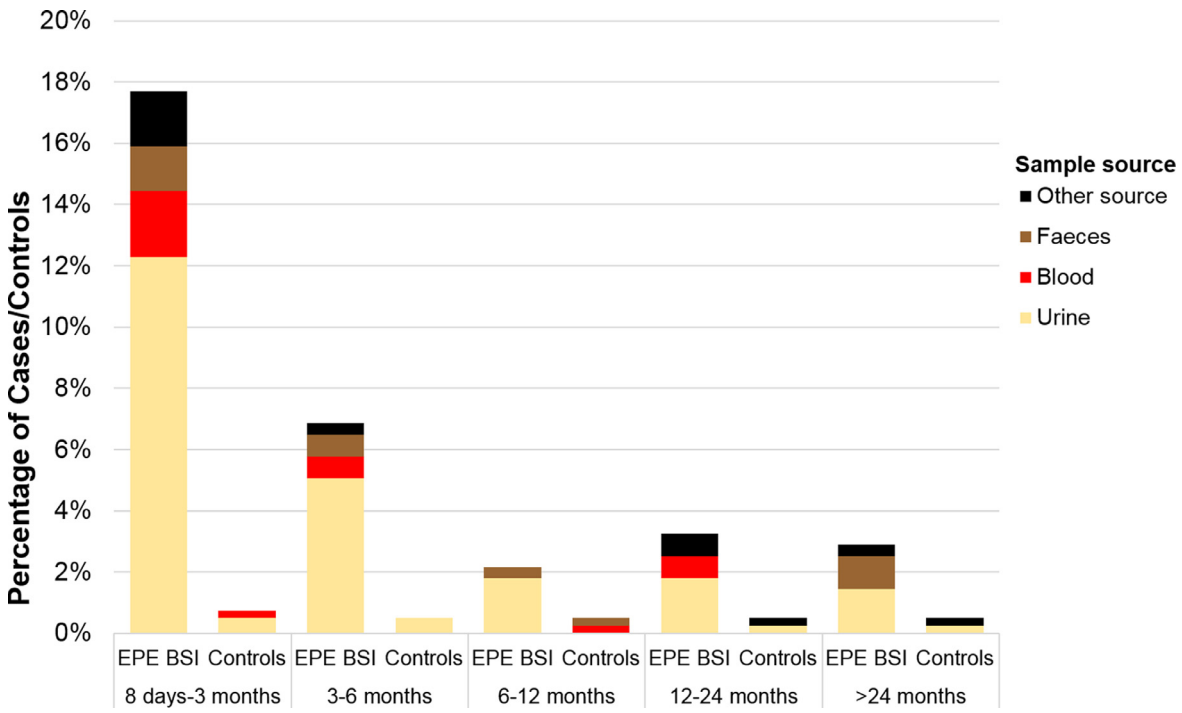

Fig. 2. Sample source of latest prior EPE-positive culture and time passed to current episode, showing percentage of EPE-BSI cases and controls. If the patient had a clinical sample, this sample was noted. If EPE was detected both in blood/urine/other at the latest prior time, it is noted as only blood. If the patient had no clinical sample, the latest prior faecal screening sample was noted. EPE, extended-spectrum β-lactamase-producing Enterobacterales; BSI, bloodstream infection.

Table 3
Time passed from latest prior extended-spectrum β-lactamase-producing Enterobacteriaceae (EPE)-positive culture to current episode

Time passed since latest prior EPE-positive culture	Controls ($n = 400$) n (%)	EPE-BSI cases ($n = 277$) n (%)	aOR (95% CI) [a]	*P*-value
No prior culture	389 (97.3)	186 (67.1)	1.0 (Ref.)	
>24 months	2 (0.5)	8 (2.9)	8.4 (1.7–40.3)	0.008
12–24 months	2 (0.5)	9 (3.2)	9.7 (2.1–45.5)	0.004
6–12 months	2 (0.5)	6 (2.2)	6.1 (1.2–30.5)	0.029
3–6 months	2 (0.5)	19 (6.9)	19.9 (4.6–86.7)	<0.001
8 days–3 months	3 (0.8)	49 (17.7)	32.8 (10.1–106.8)	<0.001

aOR, adjusted odds ratio; CI, confidence interval.
[a] aOR for each time period compared with having no prior culture with EPE. aORs are adjusted for matching variables.

current epidemiological setting. A cut-off at ≥126 points resulted in a sensitivity of 50% (comparable with the Stockholm score) and a specificity of 81%.

For the Stockholm score, ROC analysis was performed to assess the influence of the presence of more than one risk factor. However, simultaneous presence of two risk factors was uncommon, with a sensitivity of only 2.9%, but the specificity reached 99.8%. No included patients had all three risk factors.

Performance of the Stockholm score was highest in the subgroup of patients with suspected UTI, with an estimated PPV of 12.2% and NPV of 99.4%. EPE-BSI was uncommon in patients with LRTI and SSTI, and in these subgroups the PPV of the Stockholm score was as low as 1.7 for LRTI and 0.8 for SSTI.

3.3. Empirical treatment and benefit of application of scores

Fig. 3a,b shows the time to appropriate therapy for the cases, and Fig. 3c,d shows the time to first empirical therapy for controls (appropriateness was not assessed).

The impact of a hypothetical strict application of two regimens (meropenem 1 g every 8 h and PTZ 4 g every 6 h) was evaluated for score-positive patients. All score-positive patients would be given the agent in question, regardless of other factors influencing treatment choice. The number of patients who would have received appropriate treatment >24 h earlier had the score been applied at admission as well as the number of additional controls who would have been treated with the agent were assessed (Table 5).

In reality, meropenem was given to 25% of cases and 8% of controls as empirical treatment. If all patients with a positive Stockholm score (139 cases) had been given meropenem, the time to appropriate therapy would have decreased >24 h for 14% (40 cases), whilst an additional 3% of controls would have been given meropenem. This corresponds to 1518 patients in the estimated population of 46 723 patients with suspected Gram-negative infection. For the Utrecht score, meropenem would have had improved treatment for 19% of cases (53 cases) and would have resulted in giving meropenem to an additional 21% of controls (9578 patients).

PTZ was given to 20% of cases and 26% of controls. If PTZ 4 g every 6 h had been used as empirical treatment for all score-positive patients, the number of additional controls treated would have been the same as for meropenem, but fewer cases (11% for Stockholm and 13% for Utrecht) would have had >24 h improved treatment. However, for the cases who had an EPE-BSI that was caused by isolates resistant to PTZ but susceptible for the treatment they actually received (in most cases meropenem), application of this regimen would have been harmful. This was the case in 3% for the Stockholm score and 4% for the Utrecht score.

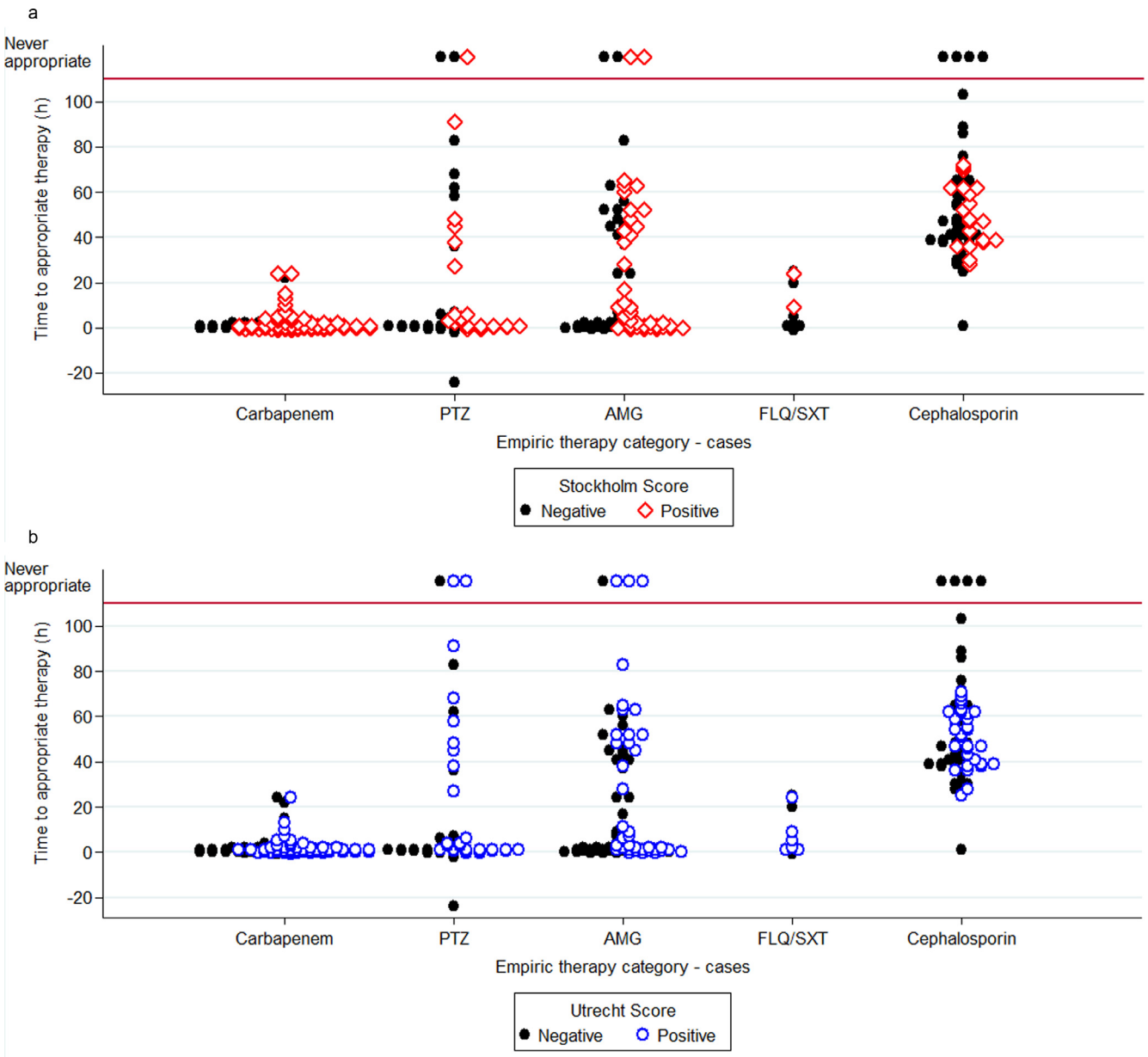

Fig. 3. Hypothetical impact of Stockholm and Utrecht scores on empirical therapy. The figures display which empirical therapy was given within 24 h. If several agents were given, the patient was classified as belonging to the agent/group with the least resistance among the EPE isolates in the cases (Supplementary Table S3). Black filled circles are patients with a negative score. (a,c) Red open diamonds indicate patients with a positive Stockholm score; (b,d) blue open circles indicate patients with a positive Utrecht score (≥120 points). (a,b) Time from blood culture to appropriate therapy for cases with EPE-BSI ($n = 277$). Cases who never received appropriate therapy are shown above the horizontal line. (c,d) Time from blood culture to first empirical therapy (appropriateness not assessed) for controls ($n = 400$). EPE, extended-spectrum β-lactamase-producing Enterobacterales; BSI, bloodstream infection; PTZ, piperacillin/tazobactam; AMG, aminoglycoside; FLQ, fluoroquinolone; SXT, trimethoprim/sulfamethoxazole.

3.4. Predictors for EPE-BSI in the subset of patients missed with the Stockholm score

A separate multivariate analysis was performed on the subset of patients without the three major predictors (prior EPE-positive culture, prior prostate biopsy or prior healthcare abroad) with the aim of finding a potential identification algorithm for patients who would be missed with the Stockholm score. The predictors kept in the final model in this subset included suspected UTI (OR = 3.5, 95% CI 2.3–5.5), any prior endoscopy (OR = 2.6, 95% CI 1.1–6.2), age category 60–69 years (OR = 2.9, 95% CI 1.1–7.9), SOFA score ≥6 (OR = 3.8, 95% CI 1.8–7.9) and prior treatment with a microbiota impact agent (OR = 1.9, 95% CI 1.2–3.0) (Supplementary Table S5). However, these predictors would be of little use in a score since ORs are relatively low and the risk factors were common in both groups. Of the EPE-BSI cases, 20% had none of the three major predictors and had not been hospitalised in the previous year.

4. Discussion

This study examined risk factors for community-onset EPE-BSI among patients presenting with suspected infection with Gram-negative bacilli in Stockholm in 2012–2015. The diagnostic performance and impact on empirical therapy of the implementation of two prediction scores was retrospectively assessed, namely the Utrecht score [14] and our proposed Stockholm score consisting of the three strongest predictors in the multivariate

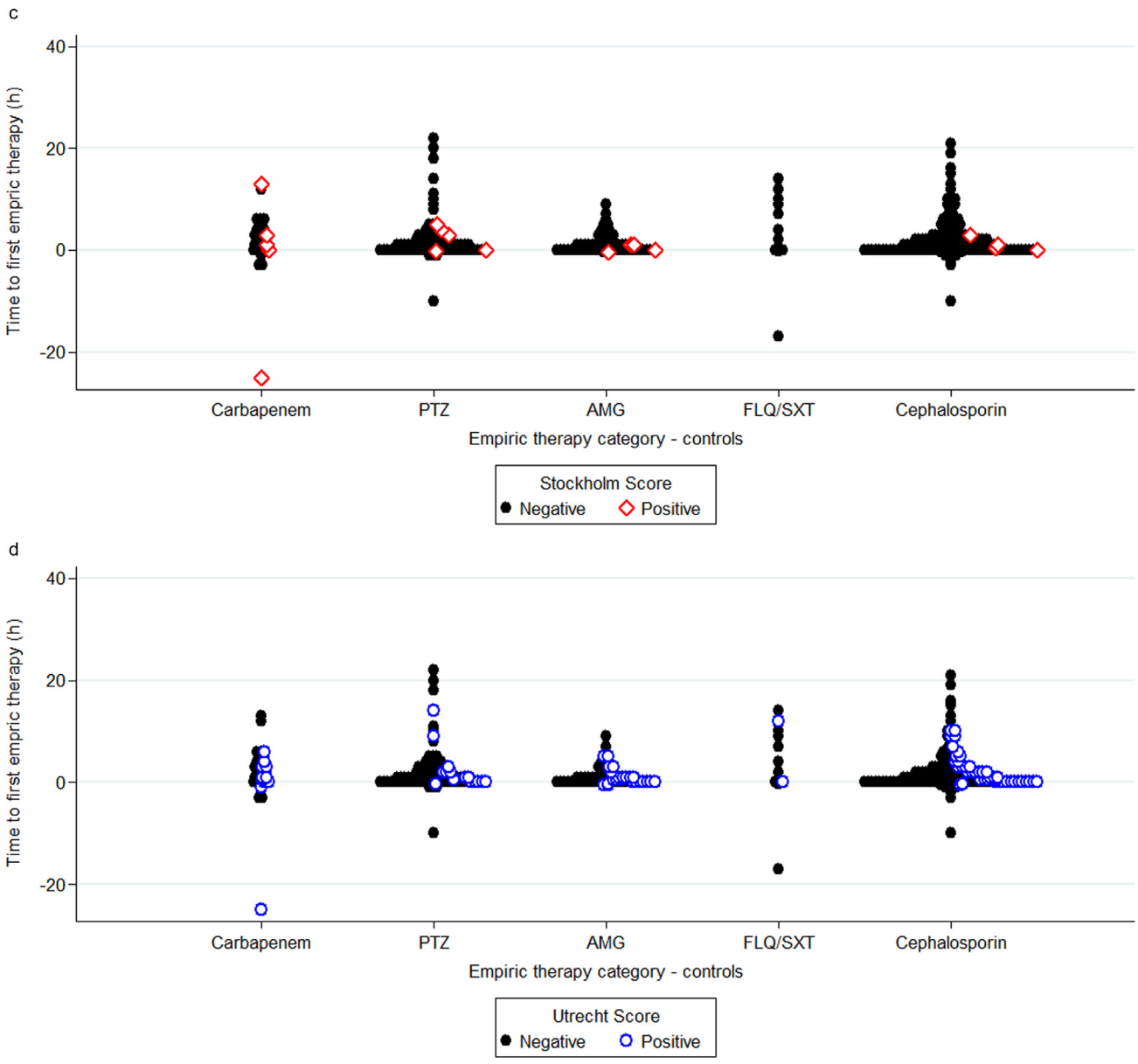

Fig. 3. Continued

analysis, i.e. history of any one of prior EPE-positive culture, healthcare abroad within 6 months or prostate biopsy within 1 month.

4.1. Predictors for EPE-BSI and the significance of recent EPE-positive culture

The strongest risk factor for EPE-BSI in this study was a prior culture positive for EPE. The significance of this risk factor in different settings is highly dependent on the epidemiological situation and sampling routines. Among *E. coli* from blood cultures sampled in 2012–2015 in all wards in the included Stockholm hospitals, the proportion of ESBL was 7–9%. It has been estimated that ca. 5% of the population in Sweden were colonised by EPE in 2012–2013 [32]. In 5% of prior EPE-positive patients the only sample source was a faecal screening sample, but there was no significant difference in risk between sample types (Fig. 2; Table 1).

Time from the latest prior EPE-positive culture was found to be important (Fig. 2; Table 3). A prior EPE-positive culture within the last 3 months before presenting at the ED with a suspected Gram-negative infection had an OR of 32.8 compared with no prior EPE culture. This means that a recent EPE culture must always be considered when choosing empirical therapy, but also that EPE cultures more distant in time should not be disregarded since the association remains significant. In another Swedish study, the only significant risk factor detected for EPE-BSI was a prior EPE-positive culture [18].

A high rate of EPE infections following prostate biopsy has been reported from several countries, including Sweden and the Netherlands [9,33]. Aly et al. showed a rapid increase in the proportion of EPE in Stockholm causing BSI after prostate biopsy between the years 2003–2010, when <1% of the *E. coli* produced an ESBL, and 2011–2012, when the proportion had increased to 20% [33]. Ciprofloxacin prophylaxis for the procedure has been suggested as the main reason for this increase in multiresistant bacteria, especially EPE. A possible explanation for this could be that ciprofloxacin prophylaxis exerts a selection pressure for the *E. coli* ST131 subclone H30-Rx (C2), which is strongly associated with

Table 4
Performance of the two scoring systems, the Utrecht score and the Stockholm score

	Sensitivity (%)	Specificity (%)	PPV[a]	NPV[a]
All patients				
Stockholm score	50	96	6.2	99.7
Utrecht score ≥120	54	77	1.4	99.6
Subgroups[b]				
Suspected UTI				
Stockholm score	58	94	12.2	99.4
Utrecht score ≥120	72	31	1.4	98.7
Suspected UTI or abdominal or unknown				
Stockholm score	51	95	7.9	99.6
Utrecht score ≥120	57	66	1.3	99.5
Sepsis (SOFA score ≥2)				
Stockholm score	51	96	7.3	99.6
Utrecht score ≥120	57	77	1.7	99.6

PPV, positive predictive value; NPV, negative predictive value; UTI, urinary tract infection; SOFA, Sequential Organ Failure Assessment.
[a] PPV and NPV are calculated on an estimated prevalence of 0.59% among all patients fulfilling inclusion criteria for the study population, i.e. blood culture taken at emergency department, admitted to hospital and treatment started ≤24 h with agent with activity against Gram-negative bacilli. The estimated size of the study population is 46 723.
[b] Population and prevalence in the subset of patients have been calculated on the distribution of suspected sources in the control group. For details on calculations and corresponding data on other suspected sources, see Supplementary Table S4.

Table 5
Impact of application of score on appropriateness of empirical treatment compared with empirical therapy given (cases, $n = 277$; controls, $n = 400$)

Regimen given to all score-positive patients	Cases (score-positive)			Controls
	Score positive	Regimen appropriate[a]	Regimen improves treatment[b]	Score-positive controls, treatment is changed[c]
	n (%)	*n* (%)	*n* (%)	*n* (%)
Meropenem 1 g q8h				
Stockholm score	139 (50)	139 (50)	40 (14)	13 (3)
Utrecht score ≥120	149 (54)	148 (53)	53 (19)	82 (21)
Piperacillin/tazobactam 4 g q6h				
Stockholm score	139 (50)	120 (43)	30 (11)	13 (3)
Utrecht score ≥120	149 (54)	121 (44)	37 (13)	78 (20)

q8h, every 8 h; q6h, every 6 h; EPE, extended-spectrum β-lactamase-producing Enterobacterales; BSI, bloodstream infection.
Hypothetical scenario where all patients with a positive score are given the same empirical treatment. Regimen 1, meropenem (MEM); regimen 2, piperacillin/tazobactam (PTZ). MEM 1 g q8h daily is considered appropriate for MER-susceptible isolates. PTZ 4 g q6h daily is considered appropriate both for PTZ-susceptible and PTZ-intermediate isolates.
[a] Use of score results in appropriate treatment. Cases with a positive score. EPE-BSI is caused by an isolate considered treatable with the agent in question.
[b] Regimen improves treatment. Cases with a positive score. EPE-BSI caused by an isolate treatable by the regimen in question but who actually did not receive appropriate treatment <24 h.
[c] Controls for whom the use of a score would result in changed treatment. Controls with a positive score who would receive the regimen but who actually did not receive the agent in question as empirical therapy.

fluoroquinolone resistance and the CTX-M-15 and CTX-M-9 ESBL types, which are common in Sweden [32,34].

Other significant risk factors were suspected UTI and severity of disease, which have been described in other studies [14,35,36]. The risk associated with age was not linear; rather, the 60–69 years age group had the highest risk compared with the <40 years age group. However, these predictors were too common in the control group for them to be included in a risk score. Inclusion of age would substantially decrease the specificity and thus cause overtreatment. Several other previously suggested risk factors were not significant in the multivariate analysis, such as immunosuppression, healthcare-associated infection and urinary catheterisation. This might be caused by the influence of local prevalence or hospital outbreaks. We also failed to show a significant influence of prior antibiotic treatment in our material even though this was analysed in detail. Only when studying the subgroup of patients without the three major predictors was prior use of antibiotics with an impact on the microbiota but with limited activity against EPE statistically significant.

4.2. Performance of risk scores and impact on empirical therapy

When applying the Utrecht score to the study population, lower specificity was obtained than by Rottier et al. [14] (77% vs. 87%) but similar sensitivity (54% in both). They suggested adapting the cut-off to other factors, such as severity of illness, thus increasing the sensitivity when necessary, which further complicates using that score. Adaptation of the cut-off did not result in a better performance of the Utrecht score than the Stockholm score.

We made minor adaptations to the Utrecht score. The Stockholm score predicts the risk for EPE-BSI, whilst the Utrecht score was developed for all 3GC-resistant Enterobacterales BSIs, regardless of the mechanism of resistance. For use of prior antibiotic treatment, antibiotic use within 3 months instead of 2 months was recorded. However, we believe that these adaptations have a limited impact on the performance of the scores. The Utrecht score cut-off at ≥120 means that any patient above the age of 45 years presenting with a UTI and treated with any antibiotic within the previous 2 months should be given a broad-spectrum antibiotic. In

the current study setting, this would generate excessive overuse. In patients with suspected UTI, the PPV of the Utrecht score was only 1.4% compared with 12.2% for the Stockholm score (Table 4).

The main finding of this study is recognising the importance of prior cultures, especially recent cultures ≤6 months, when choosing empirical therapy. Yet in this study, one-third of patients with prior EPE-BSI did not receive appropriate therapy within 12 h.

Two of the main components of the Stockholm score (prior EPE-positive culture and healthcare abroad within 6 months) are well-known risk factors for EPE, which many clinicians already take into consideration when choosing empirical therapy. Nevertheless, with application of the Stockholm score we noted that empirical therapy could be further improved regarding EPE-BSI without causing considerable overuse. The score is especially useful in patients with UTI, whilst the PPV is low in patients with SSTI and LRTI.

Prediction of EPE-BSI in patients without the presence of the major predictors is difficult. The severity and source of infection as well as prior antibiotic treatment influenced the risk, but the latter two were not useful tools for guiding empirical therapy as they were common in both groups.

A limitation of this study is its retrospective nature, which can cause information bias. Moreover, blinding of the chart review was not feasible. Data on healthcare abroad and prior antibiotic treatment might be incomplete. Selection of the control group inevitably includes some patients with community-acquired pneumonia and SSTIs in which the suspicion of Enterobacterales BSI is low. Whilst this might dilute the effects, the distinction between pneumonia and UTI is sometimes ambiguous and the benefit of potential application of the risk score at admission outweighs the described disadvantages. The Utrecht score was designed for prediction of BSI caused by 3GC-resistant Enterobacterales, whilst we have evaluated it for prediction of EPE-BSI.

An important limitation of this study is that although several medical centres were included, they were all situated in one geographical area, namely Stockholm. The results reflect the epidemiological situation in Stockholm, and the Stockholm score should not be implemented in a different setting without prospective local validation. Nevertheless, this observation is also one important finding of this study, i.e. implementation of the Utrecht score in Stockholm would result in an unacceptable rate of increased carbapenem use. Likewise, implementation of the Stockholm score would result in increased carbapenem use, but to a considerably lesser extent. Prospective validation is recommended to evaluate the performance of the score in clinical practice in Sweden and in countries with a similar epidemiological situation.

Designing a clinically useful score for prediction of EPE-BSI is difficult and is highly dependent on local epidemiology.

5. Conclusion

A prior EPE-positive culture should always be considered when choosing empirical antibiotic in patients presenting with suspected severe infection with Gram-negative bacilli. Recent prostate biopsy and prior healthcare abroad were also found to be important risk factors in the present study.

We believe that use of the Stockholm score, especially in patients with severe disease, could improve the appropriateness of empirical treatment without a substantial increase in unnecessary treatment in Sweden and possibly in countries with a similar epidemiological situation. However, this score should not be uncritically adapted in a different setting without validation. Prospective validation is called for, as the influence of predictors change, with epidemiology, over time.

Awareness of the limitations in sensitivity is very important. This also emphasises the importance of diagnostics, proper sampling and culture, rapid detection and antimicrobial susceptibility testing. The routine of giving broad-spectrum therapy to patients with severe sepsis is pertinent, especially since severity of disease was also associated with a higher risk of EPE-BSI.

Funding

This work was supported by the Swedish Society of Medicine [grant no. SLS-595581], the Department of Clinical Microbiology, Karolinska University Laboratory (Stockholm, Sweden), the Stockholm County Council and the Emil and Wera Cornell Foundation.

Competing interests

None declared.

Ethical approval

This study was approved by the Regional Ethical Review Board in Stockholm [Dnr 2014/277-31]. Patient data were handled in accordance with European General Data Protection Regulations (GDPR).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.02.008.

References

[1] World Health Organization. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva, Switzerland: WHO; 2017 https://www.who.int/medicines/areas/rational_use/prioritization-of-pathogens/en/ [Accessed 29 October 2018].

[2] Tumbarello M, Spanu T, Di Bidino R, Marchetti M, Ruggeri M, Trecarichi EM, et al. Costs of bloodstream infections caused by *Escherichia coli* and influence of extended-spectrum-β-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother 2010;54:4085–91.

[3] Svenska Infektionsläkarföreningen. *Vårdprogram: sepsis och septisk chock – tidig identifiering och initial handläggning* [*Care program: sepsis and septic shock – early identification and initial treatment*]. Svenska Infektionsläkarföreningen; 2015. http://infektion.net/wp-content/uploads/2018/06/revision-sepsis-och-septisk-chock-180626.pdf [Accessed 1 November 2018].

[4] Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749–55.

[5] Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 2010;54:4851–63.

[6] Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376:2235–44.

[7] Tumbarello M, Sanguinetti M, Montuori E, Trecarichi EM, Posteraro B, Fiori B, et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae: importance of inadequate initial antimicrobial treatment. Antimicrob Agents Chemother 2007;51:1987–94.

[8] Trecarichi EM, Cauda R, Tumbarello M. Detecting risk and predicting patient mortality in patients with extended-spectrum β-lactamase-producing Enterobacteriaceae bloodstream infections. Future Microbiol 2012;7:1173–89.

[9] Augustine MR, Testerman TL, Justo JA, Bookstaver PB, Kohn J, Albrecht H, et al. Clinical risk score for prediction of extended-spectrum β-lactamase-producing Enterobacteriaceae in bloodstream isolates. Infect Control Hosp Epidemiol 2017;38:266–72.

[10] Goodman KE, Lessler J, Cosgrove SE, Harris AD, Lautenbach E, Han JH, et al. A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamase-producing organism. Clin Infect Dis 2016;63:896–903.

[11] Goulenok T, Ferroni A, Bille E, Lecuyer H, Join-Lambert O, Descamps P, et al. Risk factors for developing ESBL *E. coli*: can clinicians predict infection in patients with prior colonization? J Hosp Infect 2013;84:294–9.

[12] Johnson SW, Anderson DJ, May DB, Drew RH. Utility of a clinical risk factor scoring model in predicting infection with extended-spectrum β-lactamase-producing Enterobacteriaceae on hospital admission. Infect Control Hosp Epidemiol 2013;34:385–92.

[13] Tumbarello M, Trecarichi EM, Bassetti M, De Rosa FG, Spanu T, Di Meco E, et al. Identifying patients harboring extended-spectrum-β-lactamase-producing Enterobacteriaceae on hospital admission: derivation and validation of a scoring system. Antimicrob Agents Chemother 2011;55:3485–90.
[14] Rottier WC, van Werkhoven CH, Bamberg YRP, Dorigo-Zetsma JW, van de Garde EM, van Hees BC, et al. Development of diagnostic prediction tools for bacteraemia caused by third-generation cephalosporin-resistant enterobacteria in suspected bacterial infections: a nested case–control study. Clin Microbiol Infect 2018;24:1315–21.
[15] Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case–control studies that analyzed risk factors for antibiotic resistance: a systematic review. Clin Infect Dis 2001;32:1055–61.
[16] Rodriguez-Bano J, Picon E, Gijon P, Hernandez JR, Ruiz M, Pena C, et al. Community-onset bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: risk factors and prognosis. Clin Infect Dis 2010;50:40–8.
[17] Lee CH, Chu FY, Hsieh CC, Hong MY, Chi CH, Ko WC, et al. A simple scoring algorithm predicting extended-spectrum β-lactamase producers in adults with community-onset monomicrobial Enterobacteriaceae bacteremia: matters of frequent emergency department users. Medicine (Baltimore) 2017;96:e6648.
[18] Van Aken S, Lund N, Ahl J, Odenholt I, Tham J. Risk factors, outcome and impact of empirical antimicrobial treatment in extended-spectrum β-lactamase-producing *Escherichia coli* bacteraemia. Scand J Infect Dis 2014;46:753–62.
[19] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676–82.
[20] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10.
[21] Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum β-lactamase production in nosocomial Infections. Ann Intern Med 2004;140:26–32.
[22] Isendahl J, Giske CG, Hammar U, Sparen P, Tegmark Wisell K, Ternhag A, et al. Temporal dynamics and risk factors for bloodstream infection with extended-spectrum β-lactamase-producing bacteria in previously-colonized individuals: national population-based cohort study. Clin Infect Dis 2019;68:641–9.
[23] European Committee on Antimicrobial Susceptibility Testing. *Breakpoint tables for interpretation of MICs and zone diameters. Versions 2.0 to 5.0, 2012–2015*. http://www.eucast.org/ast_of_bacteria/previous_versions_of_documents/ [Accessed 29 October 2018].
[24] Russo A, Falcone M, Gutiérrez-Gutiérrez B, Calbo E, Almirante B, Viale PL, et al. Predictors of outcome in patients with severe sepsis or septic shock due to extended-spectrum β-lactamase-producing Enterobacteriaceae. Int J Antimicrob Agents 2018;52:577–85.
[25] Sfeir M, Askin G, Christos P. β-Lactam/β-lactamase inhibitors versus carbapenem for bloodstream infections due to extended spectrum β-lactamase producing Enterobacteriaceae: systematic review and meta-analysis. Int J Antimicrob Agents 2018;52:554–70.
[26] Palacios-Baena ZR, Gutierrez-Gutierrez B, Calbo E, Almirante B, Viale P, Oliver A, et al. Empiric therapy with carbapenem-sparing regimens for bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: results from the INCREMENT cohort. Clin Infect Dis 2017;65:1615–23.
[27] Joo EJ, Park DA, Lee NR, Moon SY, Choi JK, Ko JH, et al. Impact of appropriateness of empiric therapy on outcomes in community-onset bacteremia by extended-spectrum-β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* definitively treated with carbapenems. Eur J Clin Microbiol Infect Dis 2017;36:2093–100.
[28] Ko JH, Lee NR, Joo EJ, Moon SY, Choi JK, Park DA, et al. Appropriate non-carbapenems are not inferior to carbapenems as initial empirical therapy for bacteremia caused by extended-spectrum β-lactamase-producing Enterobacteriaceae: a propensity score weighted multicenter cohort study. Eur J Clin Microbiol Infect Dis 2018;37:305–11.
[29] Vidal L, Gafter-Gvili A, Borok S, Fraser A, Leibovici L, Paul M. Efficacy and safety of aminoglycoside monotherapy: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2007;60:247–57.
[30] Bhavnani SM, Onufrak NJ, Hammel JP, Andes DR, Bradley JS, Flamm RK, et al. Re-appraisal of aminoglycoside (AG) susceptibility testing breakpoints based on the application of pharmacokinetics–pharmacodynamics (PK-PD) and contemporary microbiology surveillance data In: Abstracts of IDWeek 2018; 3–7 October 2018; San Francisco, CA. Open Forum Infect Dis 2018;5(Suppl 1):S71 [abstract no. 2562].
[31] Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791–7.
[32] Ny S, Lofmark S, Borjesson S, Englund S, Ringman M, Bergstrom J, et al. Community carriage of ESBL-producing *Escherichia coli* is associated with strains of low pathogenicity: a Swedish nationwide study. J Antimicrob Chemother 2017;72:582–8.
[33] Aly M, Dyrdak R, Nordstrom T, Jalal S, Weibull CE, Giske CG, et al. Rapid increase in multidrug-resistant enteric bacilli blood stream infection after prostate biopsy—a 10-year population-based cohort study. Prostate 2015;75:947–56.
[34] Banerjee R, Robicsek A, Kuskowski MA, Porter S, Johnston BD, Sokurenko E, et al. Molecular epidemiology of *Escherichia coli* sequence type 131 and its H30 and H30-Rx subclones among extended-spectrum-β-lactamase-positive and -negative *E. coli* clinical isolates from the Chicago region, 2007 to 2010. Antimicrob Agents Chemother 2013;57:6385–8.
[35] Park YS, Bae IK, Kim J, Jeong SH, Hwang SS, Seo YH, et al. Risk factors and molecular epidemiology of community-onset extended-spectrum β-lactamase-producing *Escherichia coli* bacteremia. Yonsei Med J 2014;55:467–75.
[36] Marchaim D, Gottesman T, Schwartz O, Korem M, Maor Y, Rahav G, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by Enterobacteriaceae producing extended-spectrum β-lactamases. Antimicrob Agents Chemother 2010;54:5099–104.