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Original article

Development of diagnostic prediction tools for bacteraemia caused by third-generation cephalosporin-resistant enterobacteria in suspected bacterial infections: a nested case–control study☆

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ABSTRACT

Objectives: Current guidelines for the empirical antibiotic treatment predict the presence of third-generation cephalosporin-resistant enterobacterial bacteraemia (3GCR-E-Bac) in case of infection only poorly, thereby increasing unnecessary carbapenem use. We aimed to develop diagnostic scoring systems which can better predict the presence of 3GCR-E-Bac.

Methods: A retrospective nested case–control study was performed that included patients ≥18 years of age from eight Dutch hospitals in whom blood cultures were obtained and intravenous antibiotics were initiated. Each patient with 3GCR-E-Bac was matched to four control infection episodes within the same hospital, based on blood-culture date and onset location (community or hospital). Starting from 32 commonly described clinical risk factors at infection onset, selection strategies were used to derive scoring systems for the probability of community- and hospital-onset 3GCR-E-Bac.

Results: 3GCR-E-Bac occurred in 90 of 22 506 (0.4%) community-onset infections and in 82 of 8110 (1.0%) hospital-onset infections, and these cases were matched to 360 community-onset and 328 hospital-onset control episodes. The derived community-onset and hospital-onset scoring systems consisted of six and nine predictors, respectively. With selected score cut-offs, the models identified 3GCR-E-Bac with sensitivity equal to existing guidelines (community-onset: 54.3%; hospital-onset: 81.5%). However, they reduced the proportion of patients classified as at risk for 3GCR-E-Bac (i.e. eligible for empirical carbapenem therapy) with 40% (95%CI 21–56%) and 49% (95%CI 39–58%) in, respectively, community-onset and hospital-onset infections.

☆ Results from this study were presented at the 26th European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, The Netherlands (9–12 April 2016, E-poster eP0083), and at ASM Microbe 2016, Boston, MA, USA (16–20 June 2016, session 445). This manuscript is also available as an electronic preprint from www.bioRxiv.org (accessible via doi:10.1101/120550).

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Conclusions: These prediction scores for 3GCR-E-Bac, specifically geared towards the initiation of empirical antibiotic treatment, may improve the balance between inappropriate antibiotics and carbapenem overuse. **W.C. Rottier, Clin Microbiol Infect 2018;24:1315**

Introduction

As a consequence of the emergence of infections caused by third-generation cephalosporin-resistant enterobacteria (3GCR-E, in this paper used synonymously with extended-spectrum β-lactamase-producing enterobacteria, ESBL-PE), physicians are increasingly faced with the question of which patients need empirical antibiotic treatment to cover these pathogens. Current Dutch empirical treatment guidelines designate patients at risk of infection caused by 3GCR-E on the basis of prior colonization or infection with 3GCR-E, or prior exposure to cephalosporins or fluoroquinolones, as these were identified as risk factors in patients with bacteraemia caused by these pathogens [1]. Applying these recommendations to patients needing empirical antibiotic treatment in a setting with a prior probability of 3GCR-E bacteraemia (3GCR-E-Bac) of 0.7% revealed that 19% of all patients were classified as being at risk for 3GCR-E infection and thus eligible for empirical carbapenem therapy (referred to as test positivity rate, TePR), while at the same time only 50% of patients with proven 3GCR-E-Bac were classified as at risk (referred to as sensitivity) [2]. Using only prior identification of 3GCR-E carriage as a risk factor reduced the TePR to 4%, at the cost of a reduction in sensitivity to 42%.

As carbapenems are the treatment of choice for 3GCR-E, adherence to these guidelines may result in overuse of these antibiotics. We aimed to develop prediction rules to better identify, among patients needing intravenous empirical antibiotic therapy, those having 3GCR-E-Bac. We were specifically interested in the balance between sensitivity and TePR. In this derivation study, we compared these quantities to those of the two basic strategies introduced above, which rely on prior identification alone (prior identification model) or in combination with prior exposure to cephalosporins and fluoroquinolones (two-predictor model). We decided to derive separate prediction rules for community-onset and hospital-onset infections, as we assumed that factors driving the spread of 3GCR-E within these two settings are distinct.

Methods

Settings and patients

This was a retrospective nested case–control study involving eight hospitals, of which three were university hospitals, in The Netherlands. Between January 1st 2008 and December 31st 2010, we included all consecutive patients ≥18 years of age in whom a blood culture was obtained and intravenous broad-spectrum β-lactam antibiotics (i.e. not penicillin or flucloxacillin), aminoglycosides, and/or fluoroquinolones were started on the day of, or the day after, blood culture, irrespective of duration. Patients who had already initiated these antibiotics before the day of blood culture were excluded (see Table S1 for examples; see Supplementary material for additional information on hospital characteristics, study periods, inclusion criteria, sample size, and databases used).

Infection episodes were separated into two cohorts: the community-onset cohort comprising episodes in which the first blood culture was collected during the first 3 days of hospitalization, and the hospital-onset cohort comprising episodes in which blood cultures were obtained later during hospitalization. The causative pathogen of each episode was based on the results of blood cultures obtained on the day that antibiotics were started and the day before. In both cohorts, the case population included all consecutive infection episodes with 3GCR-E-Bac (see Table S2 for definition of 3GC resistance in each of the hospitals). The control population was defined as 'all other infection episodes', including non-bacteraemic episodes and episodes with blood cultures yielding non-resistant enterobacteria, other bacteria, or fungi. From this population, four controls were selected for each case matched on hospital, being in the community- or hospital-onset cohort, and being closest in time to the case episode.

Because of the retrospective nature of this study the Dutch Medical Research Involving Human Subjects Act did not apply to it. Informed consent was waived for the study. In each of the participating hospitals, applicable local guidelines for non-interventional studies were followed. Reporting of this study was in accordance with the TRIPOD Statement [3,4].

Data collection

All selected cases and controls were subjected to chart review to obtain information that was available at the time the initial antibiotics were prescribed (referred to as infection onset). Blinding for the outcome during chart review was not considered feasible. Definitions of collected variables are listed in Table S3.

Statistical analysis

Two separate prediction models were constructed: one for community-onset infections and one for hospital-onset infections. After observing the data, we first selected ten promising variables, followed by a backward stepwise logistic regression analysis in which only variables with $p < 0.2$ were retained. A simplified score was created by multiplying the regression coefficients with a constant chosen such that, after rounding, the resulting values would be relatively easy to add up.

Discrimination of this score was assessed with the area under the receiver operating characteristic curves (referred to as C-statistic). Sensitivity, specificity, positive and negative predictive values, and TePR were calculated at different score cut-offs. These performance characteristics were compared with those of the prior identification model (classifying patients with identification of 3GCR-E in the year prior to the infection episode as test-positive) and the two-predictor model (classifying patients also as test-positive in the case of cephalosporin or fluoroquinolone use during the prior 2 months).

More details regarding the statistical procedures—including handling of missing variables, performance evaluation, and internal validation—are provided in the Supplementary material.

Results

Probabilities of 3GCR-E-Bac were 0.4% (n = 90) for the community-onset infection cohort (22 506 episodes) and 1.0% (n = 82) for the hospital-onset infection cohort (8110 episodes) (Fig. 1). These case populations were matched to 360 community-onset control episodes and 328 hospital-onset control episodes (Table 1). Initial antibiotic therapy and isolated pathogens from blood cultures are presented in Tables S5 and S6.

Community-onset infection

The prediction model for 3GCR-E-Bac in community-onset infection consisted of six variables (Table 2). It showed adequate discrimination (C-statistic 0.775, 95%CI 0.705–0.839). The derived scoring system had a very similar performance (Fig. S1a). Table 3 and Fig. 2(a) depict the trade-off between sensitivity and TePR at different cut-offs for being at risk of 3GCR-E-Bac. These can be contrasted with the fixed values for the prior identification model (sensitivity 24.4% and TePR 2.8%) and the two-predictor model (sensitivity 53.9% and TePR 21.5%). For instance, patients with a score of ≥120 would have a probability of 1.7% (positive predictive value) of having 3GCR-E-Bac, and with this score as a cut-off, 45.7% of all patients with 3GCR-E-Bac would be missed (1 − sensitivity). This sensitivity (or proportion missed) is comparable to the simpler two-predictor model; however, the scoring system reduces eligibility for carbapenem use (TePR) by 40% (95%CI 21–56%) from 21.5% to 12.8% (Table S12).

Hospital-onset infection

The hospital-onset prediction model contained nine variables (Table 4), and also showed adequate discrimination (C-statistic 0.811, 95%CI 0.742–0.873). The derived scoring system again performed very similarly (Fig. S1b). In Table 5 and Fig. 2(b), sensitivity and TePR at different score cut-offs are compared to the prior identification model (sensitivity 35.4% and TePR 5.2%) and the two-predictor model (sensitivity 79.3% and TePR 52.8%).

Patients with scores ≥110 have a 3.1% probability of 3GCR-E-Bac, and with this cut-off, 18.5% of all patients with 3GCR-E-Bac would be missed, similarly to the two-predictor model. However, carbapenem eligibility would be reduced by 49% (95%CI 39–58%) from 52.8% to 27.0% (Table S12).

Additional analyses

An analysis stratified by suspected source of infection—namely lower respiratory tract infection versus other sources—indicated that the community-onset scoring system was valuable in both subgroups (see Supplementary material). The absolute reduction in carbapenem use achieved by using a score of 120 as the cut-off was equally divided between the pneumonia subgroup and the remaining aetiologies. Furthermore, internal validation revealed that in future patient populations both the community-onset and the hospital-onset prediction models should be expected to perform slightly worse due to over-optimism (see Supplementary material).

Discussion

We developed scoring systems to more accurately identify patients with bacteraemia caused by 3GCR-E among those in whom empirical intravenous antibiotic therapy aimed at Gram-negative bacteria is initiated. The scores consist of a limited number of clinical predictors that can be assessed on the basis of the information available at the initial examination of a patient presenting with infection, before the prescription of initial antibiotics. The calculated score can be converted directly to a probability that the patient suffers from 3GCR-E-Bac, and depending on this probability, a decision can be made on whether initial antibiotics should include coverage for 3GCR-E or not. Implementing the scoring systems could improve appropriateness of empirical antibiotic therapy and reduce unnecessary use of broad-spectrum antibiotic therapy. Compared to a basic model incorporating only prior 3GCR-E identification and exposure to cephalosporins and/or fluoroquinolones, eligibility for empirical carbapenem use could be reduced by 40–49% while maintaining a similar risk of missing patients with 3GCR-E-Bac.

With the global emergence of antibiotic resistance, physicians must assess the risks of missing resistant causative pathogens when starting empirical antibiotic treatment [5]. Risk avoidance, albeit imaginable in many situations, is one of the driving forces for broad-spectrum antibiotic use, fuelling the global pandemic of antimicrobial resistance. Better prediction rules for infections caused by antibiotic-resistant pathogens are therefore needed. The strength of our study is that it focused on prediction in all patients receiving their first dose of antibiotic therapy aimed at

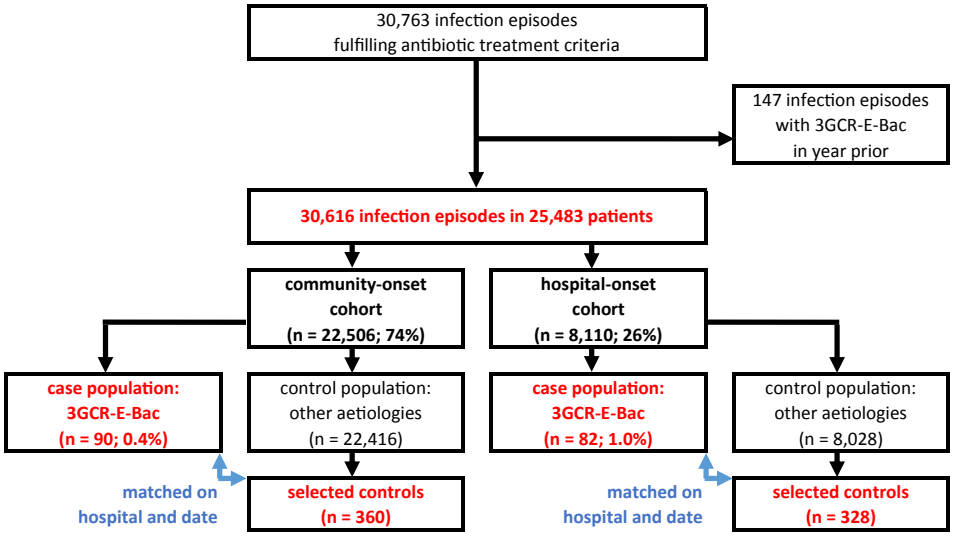

Fig. 1. Patient flowchart. 3GCR-E-Bac, 3rd generation cephalosporin-resistant Enterobacteriaceae bacteraemia.

Table 1
Clinical characteristics of cases and controls from the community-onset and hospital-onset cohorts

Predictor	Community-onset infection			Hospital-onset infection		
	Cases ($n = 90$)[a], n/total number with data (%)	Controls ($n = 360$)[b], n/total number with data (%)	OR (95%CI)[c]	Cases ($n = 82$)[a], n/total number with data (%)	Controls ($n = 328$)[b], n/total number with data (%)	OR (95%CI)[c]
Age in years, median (IQR)	69 (61–76)	63 (50–76)	1.02 (1.00–1.03)	64 (55–73)	64 (52–75)	1.00 (0.99–1.02)
Healthcare-associated infection	50/90 (56)	141/353 (40)	1.81 (1.13–2.89)	NA	NA	
Length of hospital stay prior to infection in days, median (IQR)	NA	NA		20 (10–48)	11 (6–19)	1.03 (1.02–1.04)
Diabetes mellitus	28/90 (31)	83/358 (23)	1.48 (0.89–2.46)	16/81 (20)	62/328 (19)	1.10 (0.60–2.03)
Any solid malignancy	16/90 (18)	60/358 (17)	1.07 (0.58–1.97)	25/81 (31)	70/328 (21)	1.67 (0.97–2.87)
Haematological malignancy	11/90 (12)	28/358 (8)	1.62 (0.77–3.40)	9/81 (11)	44/328 (13)	0.85 (0.40–1.82)
Renal disease	13/90 (14)	21/358 (6)	2.54 (1.22–5.27)	14/81 (17)	17/328 (5)	3.98 (1.87–8.45)
Immunocompromised	27/87 (31)	62/356 (17)	2.03 (1.19–3.46)	16/80 (20)	76/323 (24)	0.85 (0.47–1.56)
Any transplant	14/90 (16)	22/358 (6)	2.67 (1.31–5.45)	15/81 (18)	23/327 (7)	3.10 (1.54–6.23)
Urological patient	25/90 (28)	40/357 (11)	2.96 (1.68–5.22)	5/81 (6)	21/323 (6)	1.05 (0.39–2.83)
Surgical procedure (prior 30 days)	4/90 (4)	34/357 (10)	0.43 (0.15–1.24)	37/82 (45)	116/327 (36)	1.50 (0.92–2.46)
Central vascular catheter (at infection onset)	5/89 (6)	20/344 (6)	0.93 (0.34–2.55)	46/75 (61)	106/299 (36)	2.72 (1.62–4.57)
Signs of hypoperfusion (at infection onset)	12/86 (14)	35/340 (10)	1.46 (0.73–2.93)	25/77 (32)	38/296 (13)	2.82 (1.57–5.06)
Suspected source of infection (at infection onset)						
Urinary tract infection or intra- abdominal infection	55/90 (61)	94/359 (26)	4.44 (2.73–7.22)	26/80 (32)	46/325 (14)	3.00 (1.71–5.26)
Urinary tract infection	41/90 (46)	48/359 (13)	5.44 (3.25–9.11)	12/80 (15)	20/325 (6)	2.85 (1.35–6.04)
Intra-abdominal infection	14/90 (16)	46/359 (13)	1.26 (0.66–2.41)	14/80 (18)	26/325 (8)	2.42 (1.20–4.89)
Lower respiratory tract infection	8/90 (9)	111/359 (31)	0.22 (0.10–0.46)	4/80 (5)	86/325 (26)	0.14 (0.05–0.40)
Other infection	5/90 (6)	42/359 (12)	0.45 (0.17–1.16)	11/80 (14)	35/325 (11)	1.37 (0.66–2.85)
Unknown	22/90 (24)	112/359 (31)	0.71 (0.42–1.21)	39/80 (49)	159/325 (49)	0.98 (0.60–1.60)
Prior identification of 3GCR-E (prior one year)	22/90 (24)	9/359 (2)	11.82 (5.25–26.63)	29/82 (35)	16/328 (5)	10.67 (5.41–21.03)
Any use of antibiotics (prior 2 months)	51/85 (60)	140/346 (40)	2.22 (1.37–3.60)	68/82 (83)	228/324 (70)	2.02 (1.08–3.77)
Cephalosporins or fluoroquinolones	28/85 (33)	66/346 (19)	2.12 (1.26–3.55)	58/82 (71)	165/323 (51)	2.27 (1.34–3.84)
Cephalosporins	14/86 (16)	33/351 (9)	1.91 (0.99–3.68)	49/82 (60)	114/322 (35)	2.67 (1.62–4.39)
Fluoroquinolones	17/85 (20)	44/346 (13)	1.81 (0.98–3.35)	25/82 (30)	81/322 (25)	1.28 (0.75–2.18)
Carbapenems	4/86 (5)	2/351 (1)	4.95 (1.02–24.02)	12/82 (15)	29/321 (9)	1.66 (0.81–3.42)
At risk of 3GCR-E-Bac according to the two-predictor model[d]	46/86 (54)	71/347 (20)	4.32 (2.63–7.09)	65/82 (79)	168/323 (52)	3.46 (1.94–6.17)

'Any solid malignancy' combines malignancies with and without metastases, and 'any transplant' combines solid organ and stem-cell transplants. 'Immunocompromised' combines immunosuppressant use, neutropenia (at infection onset) and solid organ transplant. 'Urological patient' combines recurrent urinary tract infection, obstructive urinary disease, and urological procedure (prior 30 days).
3GCR-E, third-generation cephalosporin-resistant enterobacteria; 3GCR-E-Bac, 3GCR-E bacteraemia; IQR, interquartile range; NA, not available.
[a] Patients with 3GCR-E-Bac.
[b] Sample of patients without bacteraemia or with blood cultures yielding non-resistant enterobacteria, other bacteria, or fungi.
[c] OR calculated with imputed datasets, and hence its value cannot be derived from presented numbers.
[d] Patients scoring positive on use of cephalosporins or fluoroquinolones (prior 2 months) and/or prior identification of 3GCR-E (prior 1 year).

Table 2
Regression model and scoring system for prediction of third-generation cephalosporin-resistant enterobacterial bacteraemia (3GCR-E-Bac) in community-onset infection

Predictor	β coefficient	OR (95%CI)	Score
Intercept	−7.248		
Prior identification of 3GCR-E (prior 1 year)	1.963	7.12 (2.88–17.62)	100
Suspected source of infection: urinary tract infection	1.081	2.95 (1.64–5.29)	50
Immunocompromised	0.491	1.63 (0.87–3.08)	25
Any use of antibiotics (prior 2 months)	0.314	1.37 (0.78–2.39)	25
Age (per 1 year of age)	0.018	1.02 (1.00–1.04)	1
Suspected source of infection: lower respiratory tract infection	−0.896	0.41 (0.18–0.94)	−50

The regression analysis was pooled over 20 imputed datasets reflecting 450 infection episodes (of which 90 cases had 3GCR-E-Bac), and was subsequently corrected for the sampling fraction of controls and over-optimism (see Supplementary material for a full explanation). The predicted probability of 3GCR-E-Bac can be calculated with the following formula: $1/(1 + \exp(-(-7.248 + 1.963 \times$ prior identification of 3GCR-E (prior 1 year) $+ 1.081 \times$ suspected source of infection: urinary tract infection $+ 0.491 \times$ immunocompromised $+ 0.314 \times$ any use of antibiotics (prior 2 months) $+ 0.018 \times$ age in years $- 0.896 \times$ suspected source of infection: lower respiratory tract infection$)))$. For categorical predictors, fill in 1 if present, and 0 if absent. Similarly, the derived score can be calculated with the following formula: 100 x prior identification of 3GCR-E (prior 1 year) + 50 x suspected source of infection: urinary tract infection + 25 x immunocompromised + 25 x any use of antibiotics (prior 2 months) + age in years − 50 x suspected source of infection: lower respiratory tract infection.

enterobacteria. This contrasts with previously published prediction systems which have focused on carriage of or infection with ESBL-producing enterobacteria at hospital admission [6–8], or on distinguishing bacteraemia with ESBL- or carbapenemase-producing pathogens from bacteraemia with susceptible enterobacteria [9–12]. A recently published flow chart for initiating empirical therapy with carbapenem in critically ill patients with suspected Gram-negative infection proposed to apply two of these prediction systems in the decision-making process [13], without acknowledging that these have never been formally evaluated in the setting of prescription of initial antibiotic therapy.

Predicting the probability that a patient is suffering from 3GCR-E-Bac at the moment of presentation involves combining the probabilities that (a) the patient has bacteraemia, (b) the infection is caused by enterobacteria, and (c) these enterobacteria are antibiotic-resistant. Furthermore, because of this dilution effect, the

Table 3
Performance of scoring system for third-generation cephalosporin-resistant enterobacterial bacteraemia (3GCR-E-Bac) in community-onset infection

	Score													
	−31[a]	50	60	70	80	90	100	110	120	130	140	150	160	170	267[b]
Characteristics of interval [prior value, current value)															
Proportion of cohort (%)		33.9	10.1	6.0	9.7	11.3	6.7	4.7	4.8	2.5	2.2	2.3	1.4	1.4	2.9
Probability of 3GCR-E-Bac (%)		0.1	0.1	0.2	0.2	0.2	0.3	0.7	0.8	1.4	1.5	0.8	1.3	2.2	2.6
Characteristics of cut-off ≥ current value for classification as 'at risk of 3GCR-E-Bac'															
TePR (%)		66.1	56.0	50.0	40.3	29.0	22.4	17.7	12.8	10.3	8.1	5.7	4.3	2.9	0.0
Sensitivity (%)		93.2	91.0	87.8	83.3	76.8	72.3	63.7	54.3	45.2	36.6	32.2	27.8	20.0	1.1
Specificity (%)		34.0	44.1	50.1	59.9	71.2	77.8	82.5	87.3	89.8	92.1	94.4	95.8	97.2	100.0
Positive predictive value (%)		0.6	0.6	0.7	0.8	1.1	1.3	1.4	1.7	1.8	1.8	2.3	2.6	2.8	100.0
Negative predictive value (%)		99.9	99.9	99.9	99.9	99.9	99.9	99.8	99.8	99.8	99.7	99.7	99.7	99.7	99.6

These values (means of 20 imputed datasets) have been corrected for the sampling fraction of the controls (meaning that they have been extrapolated to the full community-onset cohort and hence reflect the values as observed in clinical practice), but they have not been corrected for over-optimism (see Supplementary material for a full explanation). The upper part of the table shows the calibration of the score. For example, 33.9% of all patients in the community-onset cohort have scores between −31 and 50. The probability of having 3GCR-E-Bac is low within this interval (0.1%; e.g. compared to 2.9% within the interval between 170 and 267). The lower part of the table shows how a specific cut-off of the score would perform with regard to detecting 3GCR-E-Bac. For example, 66.1% of the cohort has a score of ≥50 (1−33.9%); this is the TePR. The sensitivity of this cut-off is 93.2%, implying that 6.8% of patients with 3GCR-E-Bac have a score <50. Specificity is low because of the ones not having 3GCR-E-Bac; only 34.0% have scores <50. This, combined with the fact that only 0.4% of the cohort has 3GCR-E-Bac, leads to a low positive predictive value: only 0.6% of patients with scores ≥50 have 3GCR-E-Bac. Increasing the score cut-off leads to a lower TePR, higher specificity, and higher positive predictive value, but at the cost of a lower sensitivity. A similar overview relating to the underlying regression model instead of the score is available in Table S7.
TePR, test positivity rate.
[a] Minimum score within the study sample.
[b] Maximum score within the study sample.

prevalence of 3GCR-E-Bac is an order of magnitude lower (0.4–1.0%) than in patients who, in retrospect, had bacteraemia. In a previous study we calculated that an 8.3% 3GC resistance rate among enterobacterial bacteraemia isolates resulted in a 0.7% probability of 3GCR-E-Bac in cases of suspected Gram-negative infection [2].

Although our data originated in 2008-2010, we believe that the prior and predicted probabilities are relevant to the present-day situation, also in other countries. Importantly, the aforementioned dilution process is always in place when initiating empirical therapy. On top of that, the prevalence of 3GC resistance among enterobacteria has only marginally increased in The Netherlands since 2010, and most Western European countries currently have similar prevalence rates of 3GC resistance among enterobacteria, namely between 5% and 15% [14].

Two aspects regarding the patient population in this study should be discussed. First, a large proportion of community-acquired pneumonia (CAP) patients have blood cultures obtained and receive treatment categorized by us as covering Gram-negative bacteria [15]. When setting the patient domain for our community-onset prediction rule, the inclusion of true CAP is debatable since Gram-negatives are rarely encountered as pathogens [16]. However, we found that in the case of a working diagnosis of CAP, the probability of 3GCR-E-Bac is non-zero, and data exists that Gram-negative pathogens (and hence resistant variants) have a higher frequency in specific risk groups [17]. Our community-onset scoring system may not be optimally designed to predict 3GCR-E-Bac in CAP, as the risk factors identified by us are a weighted average of the pneumonia subgroup and all other aetiologies. Nevertheless, it has diagnostic accuracy even in CAP patients, and at the same time the effected reduction in carbapenem eligibility is not only the result of giving low scores to CAP patients, as demonstrated in the subgroup analysis.

The second aspect is that we applied a nested case–control design for this study, which implies that instead of analysing the

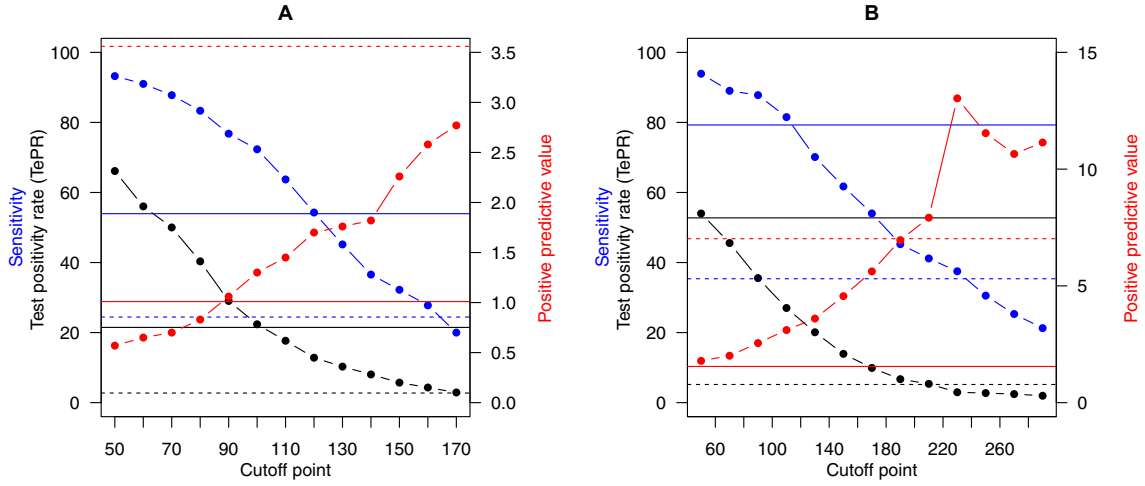

Fig. 2. Performance of community-onset (A) and hospital-onset (B) scoring systems at different cutoff values. Figures show sensitivities (blue), test positivity rates (TePR; black), and positive predictive values (red) at different cutoffs for derived scoring systems above which patients are categorized as *at risk of 3rd generation cephalosporin-resistant Enterobacteriaceae bacteraemia (3GCR-E-Bac)*. These are compared to the (constant) sensitivities, TePR values, and positive predictive values for the basic *two-predictor model* (solid lines) and *prior identification model* (dashed lines). See Tables 3 and 5 for exact values at the score cutoffs.

Table 4
Regression model and scoring system for prediction of third-generation cephalosporin-resistant enterobacterial bacteraemia (3GCR-E-Bac) in hospital-onset infection

Predictor	β coefficient	OR (95%CI)	Score
Intercept	−5.807		
Renal disease	1.372	3.94 (1.55–10.05)	120
Prior identification of 3GCR-E (prior 1 year)	1.353	3.87 (1.67–8.95)	120
Any solid malignancy	0.722	2.06 (1.06–4.01)	80
Signs of hypoperfusion (at infection onset)	0.509	1.66 (0.79–3.49)	40
Surgical procedure (prior 30 days)	0.444	1.56 (0.84–2.91)	40
Central vascular catheter (at infection onset)	0.420	1.52 (0.78–2.95)	40
Use of cephalosporins (prior 2 months)	0.415	1.51 (0.81–2.83)	40
Length of hospital stay prior to infection (per day)	0.011	1.01 (1.00–1.03)	1
Suspected source of infection: Lower respiratory tract infection	−1.729	0.18 (0.06–0.56)	−160

The regression analysis was pooled over 20 imputed datasets reflecting 410 infection episodes (of which 82 cases had 3GCR-E-Bac), and was subsequently corrected for the sampling fraction of controls and over-optimism (see Supplementary material for an explanation). The predicted probability of 3GCR-E-Bac can be calculated with the following formula: 1/(1 + exp(−(−5.807 + 1.372 x renal disease + 1.353 x prior identification of 3GCR-E (prior 1 year) + 0.722 x any solid malignancy + 0.509 x signs of hypoperfusion (at infection onset) + 0.444 x surgical procedure (prior 30 days) + 0.420 x central vascular catheter (at infection onset) + 0.415 x use of cephalosporins (prior 2 months) + 0.011 x length of hospital stay prior to infection in days − 1.729 x suspected source of infection: lower respiratory tract infection))). For categorical predictors, fill in 1 if present, and 0 if absent. Similarly, the derived score can be calculated with the following formula: 120 x renal disease + 120 x prior identification of 3GCR-E (prior 1 year) + 80 x any solid malignancy + 40 x signs of hypoperfusion (at infection onset) + 40 x surgical procedure (prior 30 days) + 40 x central vascular catheter (at infection onset) + 40 x use of cephalosporins (prior 2 months) + length of hospital stay prior to infection in days −160 x suspected source of infection: lower respiratory tract infection.

full cohort, a representative subset of patients without 3GCR-E-Bac (i.e. the control population) was analysed. The case population (i.e. patients with 3GCR-E-Bac), however, was analysed in full. This design was chosen for efficiency reasons, as it reduced the amount of data collection by 95% while accepting a small loss of precision. Knowing the size of the original cohort, we were able to extrapolate the case–control data to the full cohort, the result being that probabilities are generalizable to clinical practice.

When applying our prediction rules in practice, some issues should be noted. First, the scores have been derived solely for predicting bacteraemia, and not for non-bacteraemic infections caused by 3GCR-E; the latter are considerably more common than the former [2]. Future studies may consider classifying non-bacteraemic 3GCR-E infections as outcomes. However, because of the anticipated more benign course, initial treatment with carbapenems may not have a high priority in non-bacteraemic infections.

Second, empirical coverage of 3GCR-E is just one aspect of the selection of appropriate empirical therapy. Other potential pathogens (such as *Pseudomonas aeruginosa*) and resistance mechanisms might justify alterations to empirical treatment even in the absence of risk factors for 3GCR-E. In some countries, high incidences of infections with carbapenemase-producing enterobacteria may limit the usefulness of our prediction rules. On the other hand, escape therapy for 3GCR-E might not necessarily involve carbapenems, because of underlying resistance mechanisms other than ESBL, or favourable patterns of co-resistance. Ideally, frameworks for selecting empirical therapy should evaluate the probability of success of many different antibiotic agents. An example of such an approach is TREAT [18], but predictive performance with regard to 3GCR-E as causative pathogens is currently unknown.

Third, our prediction rules are meant for application only when the initial antibiotic therapy is started. This implies that 3GCR-E-Bac presenting as superinfection while antibiotic therapy is in place will be missed. That this is a relevant subgroup of 3GCR-E-Bac is shown by the fact that in two of the hospitals participating in this study (for which these data were available) such cases amounted to 20–34% of all 3GCR-E-Bac for which anti-Gram-negative therapy was administered on the day of blood culture and/or the day after.

Fourth, the newly developed scoring systems may be used to reduce the proportion of patients eligible for broad-spectrum antibiotics (test-positives), but they can also be used to increase sensitivity, which will simultaneously increase the proportion of test-positivity. A definitive cut-off cannot be defined, as each situation may represent a different balance between the risks associated with overprescribing carbapenems and inappropriate empirical antibiotics. For instance, the acceptance for a delay might be different in a clinically stable patient compared to a haemodynamically unstable patient [19]. Taking the long-term population effects of, for instance, carbapenem overuse into the equation is difficult, as these effects have not been sufficiently quantified [20], and they also depend on extraneous factors such as hospital hygiene and the baseline prevalence of carbapenem-resistant microorganisms [21].

Before implementation of these prediction rules, prospective external validation is required. Our study prone to information bias

Table 5
Performance of scoring system for third-generation cephalosporin-resistant enterobacterial bacteraemia (3GCR-E-Bac) in hospital-onset infection

	Score													
	−159[a]	50	70	90	110	130	150	170	190	210	230	250	270	290	432[b]
Characteristics of interval [prior value, current value)															
Proportion of cohort (%)		46.0	8.4	10.0	8.5	6.9	6.2	4.0	3.2	1.3	2.4	0.2	0.3	0.5	2.0
Probability of 3GCR-E-Bac (%)		0.1	0.6	0.1	0.8	1.7	1.4	2.0	2.8	3.1	1.6	30.2	19.3	8.7	10.6
Characteristics of cut-off ≥ current value for classification as 'at risk of 3GCR-E-Bac'															
TePR (%)		54.0	45.6	35.6	27.0	20.1	13.9	9.9	6.7	5.4	3.0	2.7	2.4	2.0	0.0
Sensitivity (%)		93.9	89.0	87.8	81.5	70.1	61.7	54.0	45.2	41.2	37.5	30.6	25.3	21.3	1.2
Specificity (%)		46.4	54.9	65.0	73.5	80.4	86.5	90.5	93.7	95.0	97.4	97.6	97.8	98.2	100.0
Positive predictive value (%)		1.8	2.0	2.5	3.1	3.6	4.6	5.6	7.0	7.9	13.0	11.5	10.6	11.1	100.0
Negative predictive value (%)		99.9	99.8	99.8	99.7	99.6	99.5	99.5	99.4	99.4	99.3	99.3	99.2	99.2	99.0

These values (means of 20 imputed datasets) have been corrected for the sampling fraction of the controls (meaning that they reflect the values as observed in clinical practice), but they have not been corrected for over-optimism (see Supplementary material for an explanation). The use of this table is exemplified below Table 3. A similar overview relating to the underlying regression model instead of the score is available in Table S8.
TePR, test positivity rate.
[a] Minimum score within the study sample.
[b] Maximum score within the study sample.

due to its retrospective nature, relied on data available in medical charts, and used pragmatic inclusion and exclusion criteria which might not fully reflect intended clinical use. Future studies may try to improve on the definitions of predictors to find a better balance between sensitivity and specificity for 3GCR-E-Bac: for example by modifying the time periods assessed for prior identification of 3GCR-E and prior antibiotic use. Moreover, potentially relevant predictors such as international travel, animal contact, known colonization in household members, dietary preferences, and colonization pressure in the ward were not collected [21,22]. Validation is currently ongoing in regions with a 3GCR-E prevalence comparable to or greater than that in The Netherlands [23]; during this process, it can simultaneously be assessed to what degree model updating is necessary to improve performance in these differing settings [24].

A final limitation of our study is that treating physicians incorporate more factors in their clinical decision-making regarding empirical antibiotics than those provided by current risk-stratification schemes in guidelines. In both this and our previous study [2], empirical carbapenem use was much lower than it would have been with full guideline adherence (Table S5). As a result, achievable reductions in empirical carbapenem use may in reality be lower than anticipated in our study. Nevertheless, we consider it important that antibiotic guidelines do not stimulate unnecessary broad-spectrum antibiotic use [25].

In conclusion, identification of patients with an infection caused by 3GCR-E amongst all patients that need empirical antibiotic therapy remains a trade-off between acceptably low levels of unnecessary empirical carbapenem use and appropriate treatment in true 3GCR-E-Bac cases. The prediction rules derived in this study quantify this trade-off, and might offer improvement in detecting patients with 3GCR-E-Bac compared to current international guidelines. As such, they provide useful starting points for optimizing empirical antibiotic strategies.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.03.023.

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