MAJOR ARTICLE

Predictive Value of Prior Colonization and Antibiotic Use for Third-Generation Cephalosporin-Resistant Enterobacteriaceae Bacteremia in Patients With Sepsis

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Background. To prevent inappropriate empiric antibiotic treatment in patients with bacteremia caused by third-generation cephalosporin (3GC)–resistant Enterobacteriaceae (3GC-R EB), Dutch guidelines recommend β-lactam and aminoglycoside combination therapy or carbapenem monotherapy in patients with prior 3GC-R EB colonization and/or recent cephalosporin or fluoroquinolone usage. Positive predictive values (PPVs) of these determinants are unknown.

Methods. We retrospectively studied patients with a clinical infection in whom blood cultures were obtained and empiric therapy with broad-spectrum β-lactams and/or aminoglycosides and/or fluoroquinolones was started. We determined the PPVs of prior colonization and antibiotic use for 3GC-R EB bacteremia, and the consequences of guideline adherence on appropriateness of empiric treatment.

Results. Of 9422 episodes, 773 (8.2%) were EB bacteremias and 64 (0.7%) were caused by 3GC-R EB. For bacteremia caused by 3GC-R EB, PPVs of prior colonization with 3GC-R EB (90-day window) and prior usage of cephalosporins or fluoroquinolones (30-day window) were 7.4% and 1.3%, respectively, and PPV was 1.8% for the presence of any of these predictors. Adherence to Dutch sepsis guideline recommendations was 27%. Of bacteremia episodes caused by 3GC-R and 3GC-sensitive EB, 56% and 94%, respectively, were initially treated with appropriate antibiotics. Full adherence to guideline recommendations would hardly augment proportions of appropriate therapy, but could considerably increase carbapenem use.

Conclusions. In patients receiving empiric treatment for sepsis, prior colonization with 3GC-R EB and prior antibiotic use have low PPV for infections caused by 3GC-R EB. Strict guideline adherence would unnecessarily stimulate broad-spectrum antibiotic use.

Keywords. extended-spectrum β-lactamases; empiric antibiotic therapy; inappropriate antibiotic therapy; risk factors; carbapenems.

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Infections caused by Enterobacteriaceae resistant to second- and third-generation cephalosporins (2GCs and 3GCs, respectively)—due to production of extended-spectrum β-lactamases (ESBLs), AmpCs, or other mechanisms—are emerging worldwide [1, 2]. Because of their resistance to most β-lactam antibiotics, the risk of inappropriate empiric antibiotic therapy for septic patients has increased. This has stimulated the use of antibiotics that are not affected by these β-lactamases, such as carbapenems [3], thereby enhancing

the risk of carbapenem resistance among gram-negative bacteria.

Physicians are, therefore, challenged to empirically treat those patients with infections caused by 3GC-resistant (3GC-R) Enterobacteriaceae with appropriate antibiotics, and at the same time minimize unnecessary use of last-resort antibiotics, such as carbapenems, in patients with infections caused by susceptible bacteria. Risk stratification based on a combination of suspected source of infection, local pathogen epidemiology, and patient characteristics, such as prior antibiotic use and prior microbiologic culture results, can be used to select empiric antibiotics [4], and in a sample of international guidelines, most advise to do so in general terms (Supplementary Table 1). However, Dutch guidelines, issued by the Dutch Working Party on Antibiotic Policy, specifically recommend the use of carbapenem or β-lactam aminoglycoside combination therapy (BLACT) in patients with sepsis of unknown origin with documented ESBL colonization, and also in those that have used cephalosporins or fluoroquinolones in the prior 30 days [5]. It is, however, unknown how well these criteria predict the presence of ESBL-producing Enterobacteriaceae as a cause of infection, to what extent these recommendations are adhered to, and whether they improve empiric antibiotic therapy.

In this retrospective study we determined, in patients with clinical sepsis receiving empiric parenteral broad-spectrum β-lactam, fluoroquinolone, or aminoglycoside antibiotics, the predictive value of prior colonization with 3GC-R Enterobacteriaceae and prior antibiotic use for infections caused by 3GC-R Enterobacteriaceae. In addition, we estimated the consequences of full adherence to guideline recommendations for antibiotic use.

METHODS

Definitions

Suspected gram-negative sepsis (hereafter referred to as sepsis) was defined as an episode of clinical infection in an adult patient (≥18 years), in which blood cultures were obtained and in which a β-lactam antibiotic and/or a fluoroquinolone and/or an aminoglycoside was started (intravenously or intramuscularly) on the same day or the day after blood culture obtainment. Excluded were episodes (1) in which any of these antibiotics had been initiated before the day of blood culture obtainment and were either continued or switched to any other of the selected antibiotics on the day of blood culture obtainment, (2) in which penicillin or flucloxacillin monotherapy was started for empiric treatment, and (3) in which antibiotics were started within 1 day after previous antibiotic use (with any of the selected antibiotics) ended. Episodes were considered either community onset (if sepsis occurred before the fourth day of hospitalization) or hospital onset.

3GC-R Enterobacteriaceae were defined as isolates being resistant to ceftriaxone, cefotaxime, and/or ceftazidime. Antibiotic susceptibility was based on minimal inhibitory concentration determination in automated systems (Phoenix [BD, Franklin Lakes, New Jersey] or Vitek 2 [bioMérieux SA, Marcy l'Etoile, France]) using 2012 Clinical and Laboratory Standards Institute criteria [6], with minor modifications to adjust for changes in breakpoints for β-lactam antibiotics that occurred during the study period (Supplementary Data) [7].

For each case of sepsis, we determined the occurrence of bacteremia, defined as growth of bacteria or fungi from any of the blood cultures obtained on the day of onset. The onset period involved 2 days if antibiotics were started on the day after the first blood culture. For potential skin contaminants (ie, *Corynebacterium* species, *Bacillus* species, *Propionibacterium* species, coagulase-negative staphylococci, viridans group streptococci, *Aerococcus* species, *Micrococcus* species [8]), 2 separate sets of blood cultures with bacteria belonging to the same genus were required. In addition, we determined for each episode of sepsis the presence of 3GC-R Enterobacteriaceae in any diagnostic culture other than blood that was obtained within 3 days before or after the day(s) of sepsis onset. The presence of 3GC-R Enterobacteriaceae in blood and/or any diagnostic culture was defined as any 3GC-R Enterobacteriaceae infection. Cultures from feces, rectal/perineal swabs, skin swabs, and cultures or swabs from the upper respiratory tract (eg, throat swabs, sinusoidal secretions, but not sputum) were not considered as indicative for infection with 3GC-R Enterobacteriaceae.

Prior colonization was defined as isolation of 3GC-R Enterobacteriaceae from any site within a designated period (90 days and 1 year), until 3 days before the day of sepsis. Prior antibiotic use was defined as use of at least 1 dose of a 2GC, 3GC, or any fluoroquinolone in a designated period (30 days and 90 days) until the day before sepsis.

Appropriate treatment for Enterobacteriaceae bacteremia was defined as treatment that included at least 1 antibiotic for which the causative pathogen was susceptible in vitro. Overtreatment was defined as treatment with a carbapenem or addition of an aminoglycoside or fluoroquinolone to an appropriately covering β-lactam antibiotic in case of infection with a 3GC-sensitive (3GC-S) Enterobacteriaceae.

Data Collection and Analysis

The study was performed in a 1042-bed tertiary hospital (UMCU) and in a 605-bed regional teaching hospital (TGH). The Medical Ethics Review Committee of UMCU determined that this study was exempted from evaluation with regard to the Dutch Medical Research Involving Subjects Act. In both hospitals, all blood cultures obtained between 1 January 2008 and 31 December 2010 were taken as the starting point for identifying sepsis episodes.

These were subsequently linked to other relevant microbiological and pharmaceutical datasets (the latter retrieved from Utrecht Patient Oriented Database for UMCU; see Supplementary Data). Calculations of prevalence, sensitivity, specificity, positive predictive value (PPV), negative predictive value, and positive and negative likelihood ratios were performed using Excel 2010 software (Microsoft Corporation, Redmond, Washington). Figure 4 was created in R version 3.0.2 using the "ggplot2" package (The R Foundation for Statistical Computing, Vienna, Austria).

In one hospital (TGH), antibiotic prescriptions from outpatient clinics were not available, and in the other hospital (UMCU) 16.6% of the antibiotics prescribed in outpatient clinics lacked stopping dates. Therefore, sensitivity analyses were performed in which outpatient antibiotics were included and excluded in the definition of prior antibiotic use, and in which antibiotics with missing stopping dates were assumed to have been prescribed for 1 day.

In one hospital (UMCU), a random sample of 5% of all sepsis episodes occurring before or on the first day of hospital admission, was subjected to manual chart review to determine the diagnosis and differential diagnosis of the sepsis episode and recorded prior antibiotic use, to estimate the prevalence of community-acquired pneumonia and accuracy of electronic data capture of prior antibiotic use.

RESULTS

Sepsis Episodes and Outcomes

There were 9422 sepsis episodes (4959 in UMCU and 4463 in TGH) in 7365 unique patients (Table 1). Most patients (n = 6004 [81.5%]) experienced a single episode, and 159 (2.2%) had ≥4 episodes. Antibiotics were started on the day of sepsis in 7236 episodes (77%) and on the day after in the remaining 2186 episodes (23%).

In 1657 of these 9422 episodes, 1 or more blood cultures became positive (17.6%), of which 773 were caused by Enterobacteriaceae (8.2%; in 100 episodes in combination with non-Enterobacteriaceae isolates) and 64 by 3GC-R Enterobacteriaceae (0.7%; of which 11 were polymicrobial) (Figure 1). Any 3GC-R

Table 1. Prior Colonization and Antibiotic Use as Predictors for Third-Generation Cephalosporin-Resistant Enterobacteriaceae Infection in Suspected Gram-Negative Sepsis

	Suspected Gram-Negative Sepsis (N = 9422)							
	3GC-R EB Bacteremia (n = 64 [0.7%])	Any 3GC-R EB Infection[a] (n = 331 [3.5%])	3GC-S EB Bacteremia (n = 709 [7.5%])	All Episodes (N = 9422)	Positive Predictive Value		Positive Likelihood Ratio	
Predictor	Sensitivity for Outcome			Prevalence	3GC-R EB Bacteremia	Any 3GC-R EB Infection[a]	3GC-R EB Bacteremia	Any 3GC-R EB Infection[a]
Prior[b] colonization with 3GC-R EB: 90 d	27 (42)	125 (38)	30 (4)	363 (4)	7.4	34.4	11.7	14.4
Prior[b] colonization with 3GC-R EB: 1 y	31 (48)	144 (44)	41 (6)	510 (5)	6.1	28.2	9.5	10.8
Prior 2GC or 3GC use: 30 d	15 (23)	85 (26)	61 (9)	997 (11)	1.5	8.5	2.2	2.6
Prior FQ use: 30 d	10 (16)	47 (14)	41 (6)	865 (9)	1.2	5.4	1.7	1.6
Prior 2GC, 3GC, or FQ use: 30 d	20 (31)	111 (34)	88 (12)	1598 (17)	1.3	6.9	1.9	2.1
Prior 2GC, 3GC, or FQ use: 90 d	33 (52)	162 (49)	158 (22)	2211 (23)	1.5	7.3	2.2	2.2
Prior[b] colonization with 3GC-R EB (90 d) or prior 2GC, 3GC, or FQ use (30 d)	32 (50)	172 (52)	107 (15)	1766 (19)	1.8	9.7	2.7	3.0
Prior[b] colonization with 3GC-R EB (1 y) or prior 2GC, 3GC, or FQ use (90 d)	42 (66)	210 (63)	176 (25)	2400 (25)	1.8	8.8	2.6	2.6

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: 2GC, second-generation cephalosporin; 3GC, third-generation cephalosporin; 3GC-R EB, third-generation cephalosporin-resistant Enterobacteriaceae; 3GC-S EB, third-generation cephalosporin-sensitive Enterobacteriaceae; FQ, fluoroquinolone.

[a] Implying that the sepsis episode could either be classified as a 3GC-R EB bloodstream infection or that a 3GC-R EB has been cultured from any other culture (except swabs from the digestive tract or skin, and cultures from feces or the upper respiratory tract) obtained within a 3-day margin around sepsis onset.

[b] Implying that a 3GC-R EB has been isolated from a culture obtained between [sepsis onset and 90 days/1 year] and [sepsis onset and 3 days].

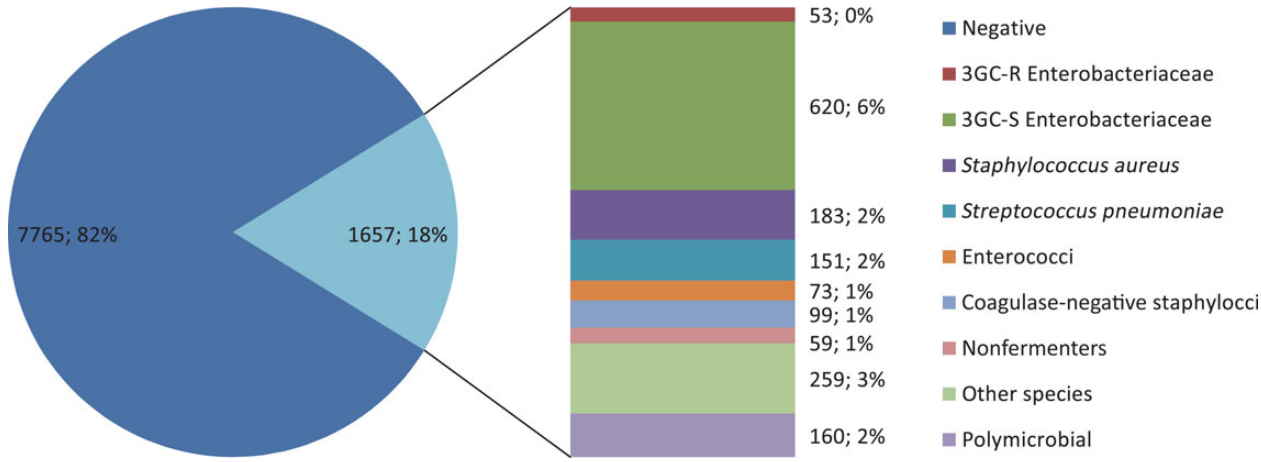

Figure 1. Species isolated from blood cultures in suspected gram-negative sepsis. Abbreviations: 3GC-R: third-generation cephalosporin resistant; 3GC-S, third-generation cephalosporin sensitive.

Enterobacteriaceae infection was present in 3.5% (n = 331; 64 with bacteremia) of the episodes (Figure 2).

Presence of Risk Factors

Colonization with 3GC-R Enterobacteriaceae within 90 days prior to sepsis and prior use of 2GCs/3GCs or fluoroquinolones within 30 days before sepsis, or any of both, achieved sensitivities for 3GC-R Enterobacteriaceae bacteremia of 31%–50% (Table 1; full overview of predictive properties in Supplementary Table 2). The PPV of these risks factors ranged from 1.3% for prior antibiotic use alone to 7.4% for prior colonization. The PPV was 1.8% for the presence of any of both risk factors. Maximum

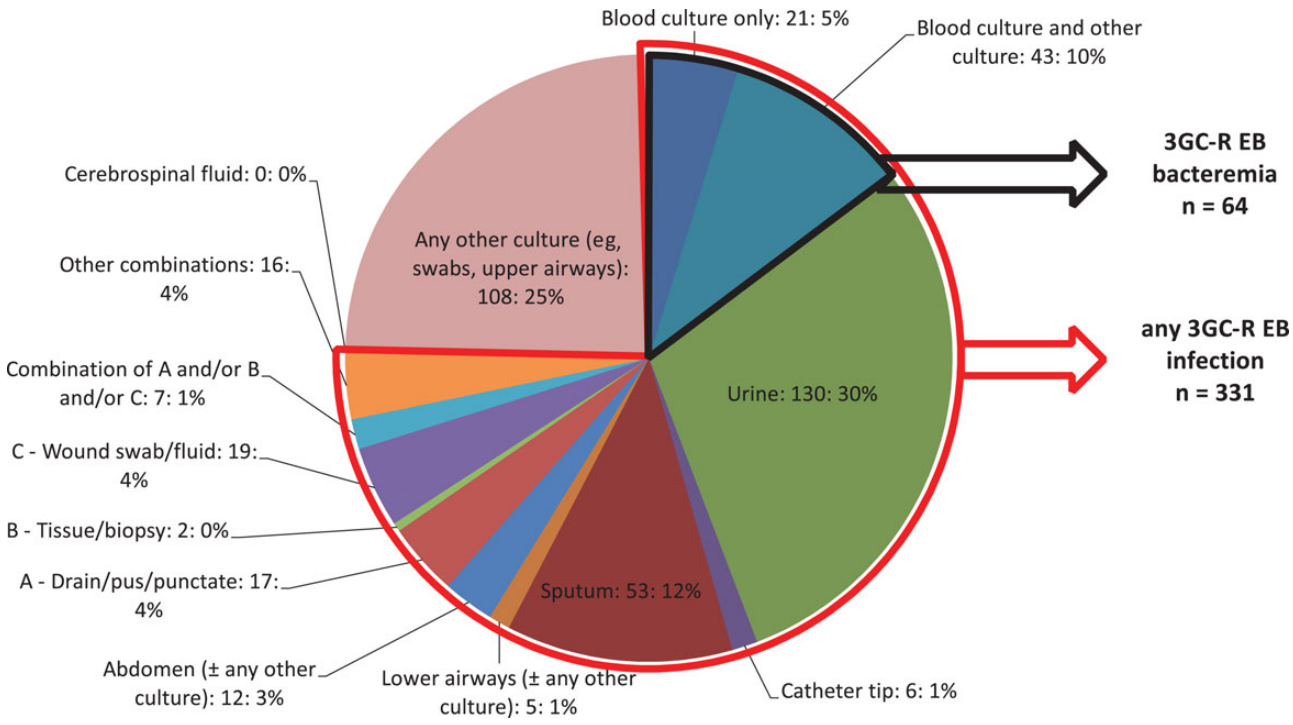

Figure 2. Origin of third-generation cephalosporin-resistant Enterobacteriaceae (3GC-R EB) cultures at onset of suspected gram-negative sepsis.

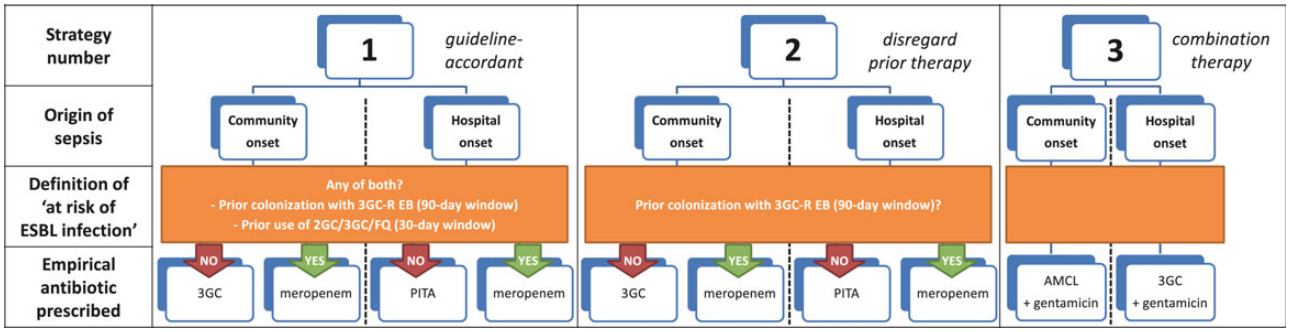

Figure 3. Flow diagrams depicting 3 hypothetical treatment scenarios for adjusting empiric antibiotic regimens for suspected gram-negative sepsis on the basis of the origin of the sepsis (community onset vs hospital onset) and the definition of risk factors for ESBL infection. Abbreviations: 2GC, second-generation cephalosporin; 3GC, third-generation cephalosporin; 3GC-R EB, third-generation cephalosporin-resistant Enterobacteriaceae; AMCL, amoxicillin-clavulanic acid; ESBL, extended-spectrum β-lactamase; FQ, fluoroquinolone; PITA, piperacillin-tazobactam.

sensitivity (66%) was achieved by combining the risk factors and extending the interval for prior colonization to 1 year and for prior antibiotic use to 90 days, while the PPV remained unchanged. Prior 3GC-R Enterobacteriaceae bacteremia had the highest PPV for 3GC-R Enterobacteriaceae bacteremia (28.1%), but a sensitivity of 14%. Sensitivity analyses including cultures requested by general practitioners and outpatient antibiotic prescription did not change interpretation (Supplementary Tables 3 and 4). Furthermore, results obtained for any 3GC-R Enterobacteriaceae infection were very similar to those for 3GC-R Enterobacteriaceae bacteremia with regard to sensitivity (Table 1). Finally, analyses restricted to sepsis episodes with positive blood cultures only resulted in positive likelihood ratios comparable to those obtained for all sepsis episodes (Supplementary Table 5).

Antibiotic Therapy Prescribed and Potential Treatment Strategies

Carbapenem or BLACT were prescribed in 1144 episodes of sepsis (12%). More than half of these episodes involved carbapenems (n = 661 [7%]), mostly in the UMCU (629 episodes). Of all patients considered at risk of ESBL infection (prior colonization within 90 days or use of 2GCs/3GCs or fluoroquinolones within 30 days; n = 1766), 474 (27%) received guideline-adherent therapy (ie, a carbapenem or BLACT).

Initial antibiotic therapy was considered appropriate in 653 of 698 episodes of bacteremia caused by 3GC-S Enterobacteriaceae (94%; 11 were excluded due to absence of an antibiogram) and in 36 of 64 episodes (56%) caused by 3GC-R Enterobacteriaceae ($P < .001$, Pearson χ^2 test). In contrast, BLACT or carbapenems were prescribed empirically in 133 of 698 (19%) bacteremia episodes caused by 3GC-S Enterobacteriaceae.

Table 2. Appropriate Treatment and Overtreatment of Enterobacteriaceae Bacteremia for Observed Situation and 3 Hypothetical Treatment Scenarios

	Rate of Appropriate Treatment[a]		Rate of Inappropriate Treatment[a]	Rate of Overtreatment[b]	Rate of Carbapenem Use
Strategy	3GC-R EB Bacteremia (n = 64)	3GC-S EB Bacteremia (n = 698)	All EB Bacteremias (n = 762)	All EB Bacteremias (n = 762)	All EB Bacteremias (n = 762)
0 – Observed	56%	94%	9.6%	18%	8.3%
1 – Hypothetical, guideline-accordant	59%	100%	3.5%	14%	18%
2 – Hypothetical, disregard prior therapy	56%	99%	4.2%	4%	7.4%
3 – Hypothetical, combination therapy	69%	99%	3.5%	77%	0%

Abbreviations: 3GC-R, third-generation cephalosporin resistant; 3GC-S, third-generation cephalosporin sensitive; EB, Enterobacteriaceae.

[a] Appropriate treatment was defined as treatment that included at least 1 antibiotic for which the causative pathogen had in vitro susceptibility.

[b] Overtreatment was defined as treatment with a carbapenem or addition of an aminoglycoside or fluoroquinolone to a β-lactam antibiotic in case of infection with 3GC-S Enterobacteriaceae.

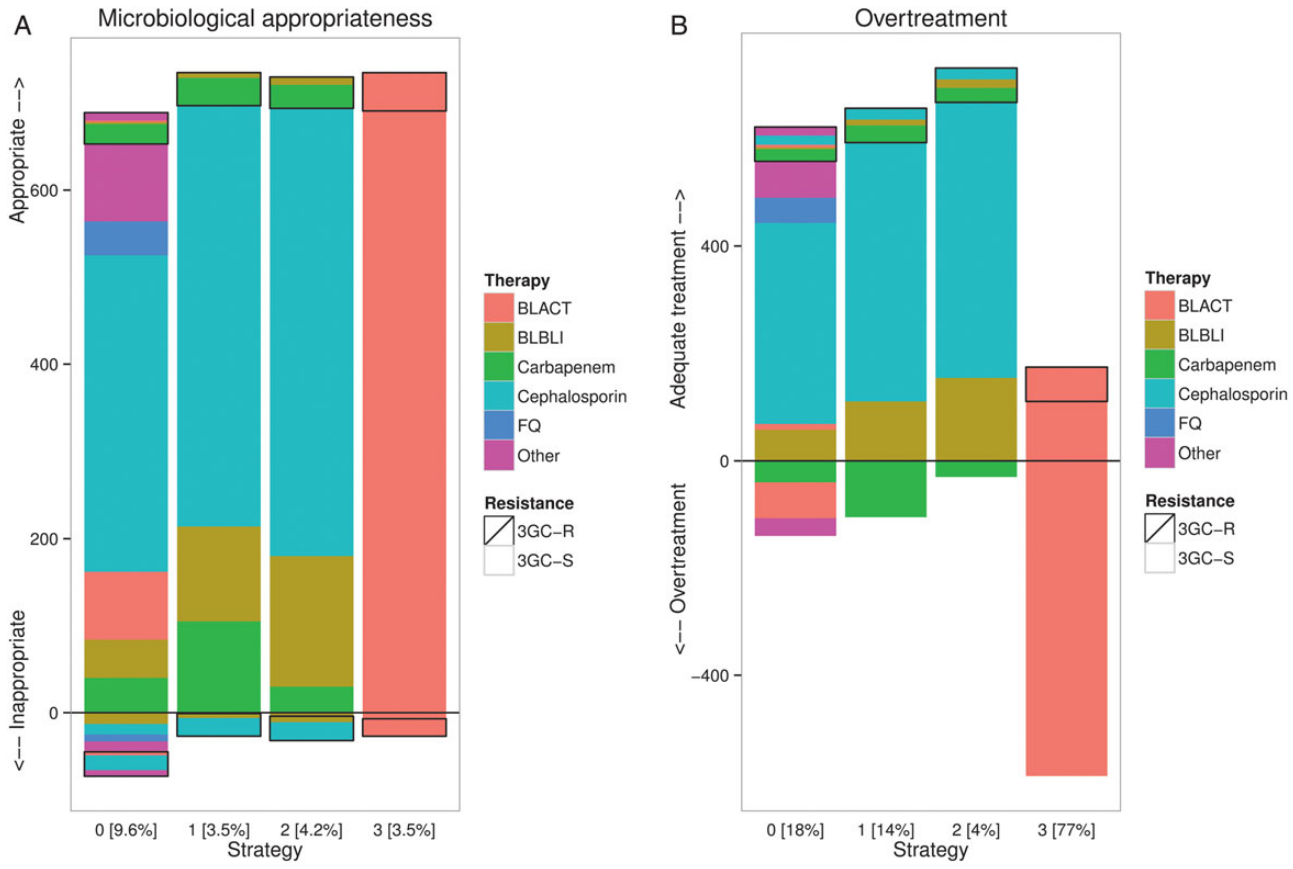

Figure 4. Microbiological appropriateness of treatment (*A*) and overtreatment (*B*) of 762 episodes of Enterobacteriaceae bacteremia for the observed real-life setting (strategy 0) and the 3 hypothetical treatment strategies presented in Figure 3. Values between square brackets reflect inappropriateness and overtreatment proportions in the respective figures. Appropriate treatment was defined as treatment that included at least 1 antibiotic for which the causative pathogen had in vitro susceptibility. Overtreatment was defined as treatment with a carbapenem or addition of an aminoglycoside or fluoroquinolone (FQ) to a β-lactam antibiotic in case of infection with 3GC-S Enterobacteriaceae. Relevant rates are also presented in Table 2. Abbreviations: 3GC-R, third-generation cephalosporin resistant; 3GC-S, third-generation cephalosporin sensitive; BLACT, β-lactam aminoglycoside combination therapy; BLBLI, β-lactam/β-lactamase inhibitor combination.

We defined 3 hypothetical treatment scenarios that differed with regard to the definition of being at risk of ESBL infection and evaluated their effect on appropriateness and overtreatment for all Enterobacteriaceae bacteremias in our cohort (Figure 3). Full adherence to any of these recommendations would have resulted in a >50% reduction of inappropriate treatment for Enterobacteriaceae bacteremia as compared to the observed situation: from 9.6% to 3.5%, 4.2%, and 3.5% (scenario 1, 2, and 3, respectively) (Table 2 and Figure 4). This benefit almost exclusively results from improvement of coverage for 3GC-S Enterobacteriaceae bacteremia. Strategies 1 and 2 would result in a similar amount of appropriateness (56%–59%) for bacteremia caused by 3GC-R Enterobacteriaceae as in the observed setting (56%), but in scenario 1, which represents full adherence to the Dutch guideline, this would be at the cost of increasing carbapenem use by 117%. Only universal BLACT (scenario 3) would improve appropriateness (to 69%), but at the cost of increasing overtreatment by approximately 325%.

Sample Results

Medical records review of 123 sepsis episodes upon hospital admission in UMCU (5%) revealed misclassification of origin of infection in 4 patients (3.3%; not community onset) and of use of 2GCs/3GCs or fluoroquinolones in the 30 days prior to sepsis in 5 patients (increasing the prevalence from 12% based on electronic identification to 15%). The respiratory tract was considered the most likely source of infection in 36 episodes (29%).

DISCUSSION

This study reveals that in the Netherlands, among patients with a clinical infection in which blood cultures were obtained and

empiric antibiotics were started, the likelihood of any infection caused by 3GC-R Enterobacteriaceae was 3.5%, and the likelihood of bacteremia caused by these pathogens was 0.7%. The PPVs of broadly recognized risk factors for 3GC-R Enterobacteriaceae bacteremia, such as prior colonization with 3GC-R Enterobacteriaceae or recent usage of cephalosporins or fluoroquinolones, were 7.4% and 1.3%, respectively. With an observed 27% adherence to Dutch guideline recommendations, 94% and 56% of bacteremias caused by 3GC-S and 3GC-R Enterobacteriaceae, respectively, received appropriate empiric therapy. Yet, 100% adherence to such recommendations would hardly increase appropriateness of empiric therapy for 3GC-R Enterobacteriaceae bacteremia, but has the potential to substantially increase carbapenem use. If these guidelines are adopted, we propose to omit prior antibiotic use as a risk factor. Better coverage of 3GC-R Enterobacteriaceae bacteremia can only be achieved with combination treatment for all septic patients, but at the expense of massive unnecessary prescription of aminoglycosides. These findings underscore the need for better prediction rules to optimize empiric antibiotic treatment in patients with sepsis.

Prior use of cephalosporins or fluoroquinolones has been identified as a risk factor for infections caused by ESBL-producing bacteria in many studies [9]. Yet, apart from 2 case-control studies focusing on patients in whom blood cultures were obtained [10, 11], these associations generally have been established in patient cohorts with microbiologically proven Enterobacteriaceae infections only. These studies, therefore, do not offer guidance for physicians at the moment that empiric antibiotics must be initiated. To the best of our knowledge, there is only 1 other study in which a prediction rule for presence of ESBL-producing Enterobacteriaceae was derived [12], but it included all patients upon hospital admission, which may not necessarily coincide with patients for whom empiric therapy for suspected gram-negative sepsis is prescribed. In another study, focusing like we did on septic patients, an automated decision support system, called TREAT, was used to comprehensively predict pathogens and resistance patterns, including ESBL-producing pathogens [13]. It provided individual advice on antibiotic treatment based on a causal probabilistic model calibrated on data from literature, large databases, and local epidemiology, and taking clinical and laboratory data as input. Unfortunately, performance data on predicting specific resistant variants of gram-negative organisms are not available.

Empiric regimens for an infectious syndrome are generally based on the expected susceptibility of pathogens most likely to be involved [14]. For some infections, thresholds have been recommended for adapting empiric regimens, such as a 10% threshold for penicillin-intermediate strains for *Streptococcus pneumoniae* in meningitis [15], and a 20% threshold for trimethoprim-sulfamethoxazole resistance among *Escherichia coli* in uncomplicated cystitis [16]. Yet, these cutoff percentages are limited to single pathogens, whereas, as acknowledged by the recently proposed weighted-incidence syndromic combination antibiogram (WISCA), it is essential to determine the proportion of pathogens that will be covered by a certain empiric regimen [17]. Still, WISCAs are not geared toward the clinical scenario to which prescription guidelines apply. Inclusion of all episodes (including those with negative culture results) is essential to establish the effect of guidelines on antibiotic prescribing in clinical practice. Although culture-negative infections may also be due to resistant microorganisms, restricting analyses to culture-positive infections only introduces poor generalizability of such episodes to culture-negative infections [18].

Balancing appropriateness of therapy and antibiotic overuse is a challenge [19]. Reports on the consequences of inappropriate empiric therapy differ. In a meta-analysis, inappropriate treatment appeared to be detrimental to the outcome of patients with sepsis [20], which was not confirmed in a study on ESBL-producing Enterobacteriaceae bacteremia in Dutch hospitals [21]. On the other hand, antibiotic use may have adverse effects on an individual level (ie, resistance development and adverse effects), as well as the population level by increasing resistance. In particular, unnecessary use of carbapenems should be avoided as it selects for carbapenemase-producing isolates [22, 23]. As demonstrated in this study, strict adherence to current guideline recommendations may stimulate overuse of antibiotics, and proposed treatment algorithms in guidelines should be improved. In this respect, it seems logical to include the severity of illness in the risk stratification, as is in fact the case in many guidelines (Supplementary Table 1). Another strategy might be to increase screening for resistant microorganisms to guide empiric therapy, which will increase sensitivity for detecting carriage in those proceeding to infection during hospitalization. Yet, given the low rate of such infections, such a strategy might not be cost-effective [24, 25].

Several limitations of the current study must be addressed. First, we analyzed 3GC-R Enterobacteriaceae instead of ESBL-producing Enterobacteriaceae, although Dutch guidelines specifically refer to ESBL. Although risk factors might deviate slightly, 3GC resistance and not ESBL positivity is the only relevant clinical outcome. In a Dutch national survey, 80% of 3GC-R Enterobacteriaceae harbored ESBL genes [26].

Second, using 3GC-R Enterobacteriaceae bacteremia as outcome of interest might be too narrow a definition of severe 3GC-R Enterobacteriaceae infection. Therefore, we also performed a sensitivity analysis involving a very broad definition of 3GC-R Enterobacteriaceae infection, in which guideline performance was equal with regard to sensitivity.

Third, from our random sample of community-onset infections, it appears that 15% of our cohort may consist of community-acquired pneumonia, as blood cultures are usually obtained and treatment often consists of broad-spectrum

β-lactams or fluoroquinolones. As Enterobacteriaceae play a minor role in the etiology of community-acquired pneumonia [27], these episodes might be considered less relevant for our study domain.

Fourth, we considered all included episodes to be sepsis of unknown origin, whereas in practice, these episodes might be classified as specific syndromes or occur in specific wards, which warrants different empiric treatment regimens, such as in the case of neutropenic sepsis.

Fifth, antibiotic records were not complete for outpatient antibiotic use or antibiotic use in other hospitals, which could have led to misclassification of prior antibiotic use. The same may have occurred for microbiological culture results. However, better information would only have increased the prevalence of the risk factors, and, based on our sensitivity analyses (Supplementary Tables 3 and 4), this would not have led to substantial improvement of sensitivity for 3GC-R Enterobacteriaceae bacteremias. Moreover, much of this information would not be promptly available to treating physicians in daily practice either.

Last, this study has been performed in the Netherlands, a country with low resistance rates for most nosocomial pathogens [1]. However, the epidemiology of infections caused by 3GC-R Enterobacteriaceae in the Netherlands is not that different from other countries. For instance, in 2012, resistance rates to 3GCs of invasive *E. coli* and *Klebsiella pneumoniae* isolates were comparable to those from Germany and the United Kingdom [1]. In addition, prevalence of carriage with ESBL-producing Enterobacteriaceae in nonhospitalized subjects in the Netherlands was 5.1% [28], which is also similar to reported prevalences from other Western European countries, such as Germany (6.3%) [29] and France (6%) [30]. Yet even in countries with higher proportions of resistance among gram-negative organisms in patients with documented infections, the actual proportion of infections caused by 3GC-R Enterobacteriaceae would still represent a minor part of all sepsis episodes.

In conclusion, current guideline recommendations do not accurately predict the presence of 3GC-R Enterobacteriaceae as a cause of infection. Therefore, they do not promote the prudent use of antibiotics. Better prediction rules are needed, and these should be developed for the relevant scenario, being a clinical suspicion of infection in which Enterobacteriaceae are considered as a potential cause.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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