Universiteit Leiden
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Rational empiric antibiotic therapy in clinical practice and policy making: uncertainties, probabilities, and ethics

Lambregts, M.M.C.

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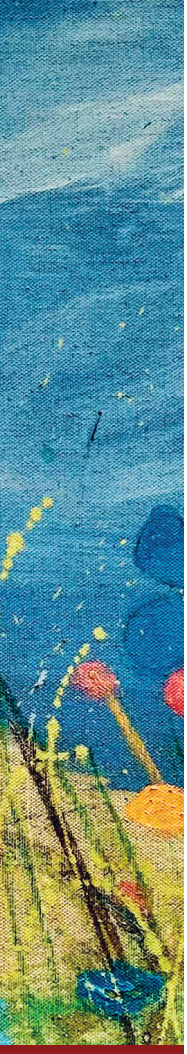

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Using local clinical and microbiological data to develop an institution specific carbapenem-sparing strategy in sepsis: a nested case-control study

Merel M.C. Lambregts, Bart J.C. Hendriks, Leo G. Visser, Alexandra T. Bernards, Mark G.J. de Boer

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ABSTRACT

Background: From a stewardship perspective it is recommended that antibiotic guidelines are adjusted to the local setting, accounting for the local epidemiology of pathogens. In many settings the prevalence of Gram-negative pathogens with resistance to empiric sepsis therapy is increasing. How and when to escalate standard sepsis therapy to a reserve antimicrobial agent, is a recurrent dilemma. The study objective was to develop decision strategies for empiric sepsis therapy based on local microbiological and clinical data, and estimate the number needed to treat with a carbapenem to avoid mismatch of empiric therapy in one patient (NNTC).

Methods: We performed a nested case control study in patients (>18 years) with Gram-negative bacteraemia in 2013-2016. Cases were defined as patients with Gram-negative bacteraemia with in vitro resistance to the combination 2nd generation cephalosporin AND aminoglycoside (C-2GC+AG). Control patients had Gram-negative bacteraemia with in vitro susceptibility to cefuroxime AND/OR gentamicin, 1:2 ratio. Univariate and multivariable analysis was performed for demographic and clinical predictors of resistance. The adequacy rates of empiric therapy and the NNTC were estimated for different strategies.

Results: The cohort consisted of 486 episodes of Gram-negative bacteraemia in 450 patients. Median age was 66 years (IQR 56-74). In vitro resistance to C-2GC+AG was present in 44 patients (8.8%). Independent predictors for resistance to empiric sepsis therapy were hematologic malignancy (adjusted OR 4.09, 95%CI 1.43-11.62, p<0.01), previously cultured drug resistant pathogen (adjusted OR 3.72. 95%CI 1.72-8.03, p<0.01) and antibiotic therapy during the preceding 2 months (adjusted OR 12.5 4.08-38.48, p<0.01). With risk-based strategies, an adequacy rate of empiric therapy of 95.2% - 99.3% could be achieved. Compared to treating all patients with a carbapenem, the NNTC could be reduced by 82.8% (95%CI 78.5-87.5%) using the targeted approaches.

Conclusions: A risk-based approach in empiric sepsis therapy has the potential to better target the use of reserve antimicrobial agents aimed at multi-resistant Gram-negative pathogens. A structured evaluation of the expected antimicrobial consumption and antibiotic adequacy rates is essential to be able to weigh the costs and benefits of potential antibiotic strategies and select the most appropriate approach.

INTRODUCTION

Current guidelines on antibiotic stewardship recommend to adapt empiric therapy to local microbiological data.[1] However, specific recommendations on when and how to change the empiric treatment guidelines in response to increasing resistance rates are lacking. The empiric strategy may need to be broadened to guarantee coverage of the most common pathogens. The downside of this action is an increase in selective pressure, driving further emergence of resistance.[2] Therefore, whether or not to escalate empiric treatment guidelines in response to new resistance data is a recurrent dilemma in antibiotic policy committees all over the world.

Strategies that break the vicious circle of increasing resistance and increasing antibiotic consumption are needed.[3-5] The use of a risk-based discrimination in empiric therapy has this potential. If patients with a high probability of infection with a resistant pathogen can be identified upfront, empiric therapy can be escalated selectively.[6,7] This approach combines the two major aims of antibiotic stewardship: promoting effective antimicrobial therapy in all patients, while limiting antibiotic usage where possible.[8] Both aims are especially relevant in sepsis guidelines.[9] The importance of prompt initiation of effective empiric therapy in this patient category is well recognized.[10–14] and the antibiotic consumption associated with empiric treatment for (presumed) sepsis is substantial.[15,16]

In the Netherlands and other countries with low to moderate resistance rates, the standard treatment for sepsis of unknown origin often is a second or third generation cephalosporin (2GC or 3GC) combined with an aminoglycoside (AG).[17] The prevalence of Gram-negative pathogens that are resistant to this empiric treatment combination, due to production of extended spectrum β-lactamases (ESBL) and other mechanisms, is increasing.[18] This development warrants regular re-evaluation of empiric sepsis therapy recommendations and consideration of escalation to a carbapenem.

The study objective was to explore a practical method to design institutional strategies for empiric therapy based on local microbiological and clinical data, and to estimate the potential treatment adequacy rates and reserve antimicrobial consumption for each of these strategies.

METHODS

The study was conducted according to the approach described in Table 1. This 7-step method is illustrated using local data. The risk factors for bloodstream infection with a Gram-negative organism with reduced susceptibility to standard sepsis treatment were identified in the case-control study. The effect of different targeted empiric therapy approaches on the proportion of patients that receive adequate empiric treatment and the

Table 1. 7-step method for the development of institution specific empiric treatment guidelines.

	Description	Example
Step 1 The clinical question	Define A) the clinical syndrome for which empiric treatment is re-evaluated, B) the patient population and C) the current empiric treatment guideline.	The clinical syndrome is sepsis. The target patient population is adult patients in an academic medical center. The current empiric treatment for sepsis is C-2GC-AG.
Step 2 Susceptibility data	Determine the local prevalence of resistance to the current empiric treatment (syndrome and population specific)	Of all patients with suspected sepsis, 6.7% are diagnosed with Gram-negative bacteraemia.* Gram-negative resistance for C-2GC-AG in blood culture isolates is 8.8 %. In the study center. Methicillin resistant *Staphylococcus aureus* (MRSA) and penicillin resistant pneumococcal species are very rare in the Netherlands.
Step 3 Definition of risk factors	Identify available predictors for resistance to the current empiric treatment	Independent risk factors of resistance to empiric sepsis therapy in the study population are prior antimicrobial use and prior isolates with a DRP.
Step 4 Targeted strategies	Identify potential targeted treatment strategies	Option A: A carbapenem in patients with a DRP cultured the previous 6 months and C-2GC-AG in other patients. Option B: a carbapenem in all patients with sepsis
Step 5 Estimating benefit	Estimate the proportion of patients that would be adequately treated if empiric sepsis therapy was changed	Option A: 95.2 % of Gram-negative bloodstream infections would be treated adequately Option B: 99.8 % of Gram-negative bloodstream infections would be treated adequately
Step 6 Estimating costs	Identify the number needed to treat (NNTC)	Option A: NNTC is 42 patients. Option B: NNTC is 173 patients.
Step 7 Selection of empiric treatment strategy	Balance the cost and benefits of phase 5 and 6 to select the most appropriate strategy.	A moral deliberation with stakeholders to decide on the most appropriate antibiotic therapy for sepsis in the institution.
Implementation and evaluation	Evaluate the costs and benefits of the selected approach	Option A was selected. After implementation adequacy rates, outcome, side-effects of antimicrobials and antimicrobial consumption were evaluated.

Legend: NNTC = number of patients needed to treat with a carbapenem instead of cefuroxime/gentamicin to prevent one case of inappropriate empiric therapy, C-2GC-AG=cefuroxime combined with gentamicin , DRP = Drug resistant pathogen.
* To estimate the overall blood culture positivity rate, the proportion of bacteraemia was determined during two separate months, June and December 2014. During this period, all patients in whom blood cultures were obtained because of fever were included. In this pilot period, of all patients with suspected infection, 53/778 (6.7%) had positive blood cultures with a Gram-negative pathogen. All other data used in the example provided in column 3 are cohort data.

number of patients needed to treat with a carbapenem to avoid mismatch of empiric therapy in one patient (NNTC), were estimated applying the case control study (2013–2016) and the cohort data (2013–2014). The reporting of the results was performed in accordance with STROBE guidelines for cohort and case-control studies.[19]

Setting and patient population

The study period was defined as from January 2013 to December 2016. The Leiden University Medical Center (LUMC) is a tertiary care hospital in the Netherlands. Standard empiric sepsis therapy in the institution consisted of a second generation cephalosporin, cefuroxime, combined with gentamicin (C-2GC + AG). In 2013– 2014, all patients > 18 years of age, with monomicrobial Gram-negative bacteraemia were included (cohort 2013– 2014). Both community acquired and nosocomial episodes were eligible for inclusion. Patients were identified through search of the microbiology laboratory database.

Gram-negative bacteraemia was defined as one or more positive blood cultures with a Gram-negative micro-organism. Cases were defined as adult patients with bacteraemia with Gram-negative micro-organisms with reduced susceptibility to C-2GC + AG. Reduced susceptibility was defined as intermediate sensitivity (I) or resistance (R) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria to 2GC and AG.

Control patients were defined as patients with Gram-negative bacteraemia with a micro-organism susceptible to 2GC, AG or both. Two control patients per case patient were randomly selected from the cohort. Using the patient identification code, every third patient meeting the criteria for control was selected.

The inclusion period for the case selection was prolonged with two additional years (2013–2016) compared to the cohort (2013–2014), because of the relatively low incidence of combined 2GC and AG resistance. It was assumed that the characteristics of the control and case populations were not variable over the period of study.

Clinical data

Clinical data were collected from the electronic medical records and included demographics, co-morbidities, clinical characteristics at the time of presentation and known risk factors of antimicrobial resistance such as a history of recurrent urinary tract infections (UTI's), previous hospital stays and previous antibiotic treatment. [6,8,20-23]

Previous antibiotic treatment was defined as administration of one or more antibiotic doses during the previous 2 months. Current antibiotic use was defined as at least one

administration of antibiotics during the 24 h preceding the collection of blood specimens. For in-hospital and outpatient clinic prescriptions these data were obtained from the institutional electronic prescription system. For other prescriptions, the documented patient history, referral letters and correspondence with other health care providers were searched.

Prior known colonization or infection with a drug resistant pathogen (prior-DRP) was defined as the isolation of one of the following pathogens from any body site, including rectal swabs: vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus*, Enterobacterales with in vitro resistance to AG, second and/or third generation cephalosporins and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporins, AG or quinolones.

In clinical practice, physicians may defer from standard sepsis therapy for a variety of reasons, including a high suspicion of antimicrobial resistance. To assess current practice, the antibiotics that constituted the initial empiric therapy were extracted from the patient records. Empiric therapy was considered adequate if at least one of the antibiotics matched the in vitro susceptibility of the isolated pathogen. Multiple episodes of bacteremia per patient were allowed if the antimicrobial therapy for the previous episode had been completed and clinical and microbiological cure had been achieved.

Microbiological data

Microbiological data were retrieved from the database of the Microbiology department and included the isolated micro-organism and susceptibility patterns of the current and previous episodes. Blood cultures were incubated using the BACTEC™ blood culture system (Becton Dickinson Benelux, Erembodegem, Belgium).

Identification of isolates was performed using matrix-assisted laser desorption/ionisation-time of flight spectrometry (MALDI-TOF) using the Microflex system (Bruker, Bremen, Germany). Antimicrobial susceptibility testing was performed with the VITEK2 system and E-tests (BioMérieux, Brussels, Belgium). Extended-spectrum beta-lactamase (ESBL) production was determined by the use of the combination disc diffusion test.[23] Minimum inhibitory concentration (MIC) breakpoints for resistance and intermediate sensitivity were based on EUCAST criteria.[24]

Statistical analysis

Imputation for missing data was not applied. Categorical variables were reported as counts and percentages and continuous variables as medians with interquartile ranges (IQR).

Univariate analysis of clinical predictors of reduced susceptibility to empiric therapy was performed using the Fisher's exact test and reported as odds ratios (OR) with 95% confidence interval (95% CI). All variables that showed a trend towards an association ($P < 0.2$) were included in the logistic regression analysis. Potential targeted empiric treatment strategies were designed based on the strongest independent predictors of resistance to C-2GC + AG. The proportion of patients with bacteraemia that would receive adequate treatment with the strategy (adequacy rate) and the number of patients needed to treat with a carbapenem to avoid mismatch of therapy in one patient (NNTC) were estimated using the formula described in the Supplementary data. The data for these estimations were derived from the study cohort: The frequency of the strategies risk factor(s) (cohort 2013/ 2014), the frequency of reduced susceptibility to gentamicin/cefuroxime and to carbapenems (cohort 2013/2014), and the sensitivity of the specific risk-based strategy for the presence of resistance to cefuroxime/gentamicin (cases 2013–2016). The NNTCs of the risk-based strategies were compared to the theoretical scenario of uniform application of the local sepsis guideline and the actual clinical practice data. The NNTC was assessed for different theoretical probabilities of Gram-negative bacteraemia in patients treated empirically for presumed sepsis. All statistical analyses were performed with IBM SPSS Statistics, version 23.

RESULTS

The cohort (2013–2014) consisted of 486 episodes of Gram-negative aerobic bacteraemia in 450 patients. The final database had < 2% missing data. Median age was 66 years (IQR 56–73), in 263 (54.1%) episodes, the patient was male. In this cohort in vitro reduced susceptibility to 2GC monotherapy was present in 176 patients (36.2%), reduced susceptibility to AG in 84 patients (12.6%) and to the combination C-2GC + AG in 43 patients (8.8%). In 95/486 (19.5%) a drug resistant pathogen (DRP) was cultured previously, in 54/95 (56.8%) the prior-DRP was isolated during the preceding 6 months. A total of 144/486 (29.6%) patients were already on antibiotic therapy when they were evaluated for suspected sepsis and 257/486 patients (52.9%) had been treated with antibiotics in the preceding 2 months. Empiric therapy contained a carbapenem in 27/486 (5.6%) of patients. Of the 43/486 (8.8%) patients with in vitro resistance to C-2GC + AG, 12/43 (27.9%) received adequate empiric treatment. The 30-day mortality rate for the cohort was 59/486 (12.1%). Resistance to carbapenems was 1/486 (0.2%).

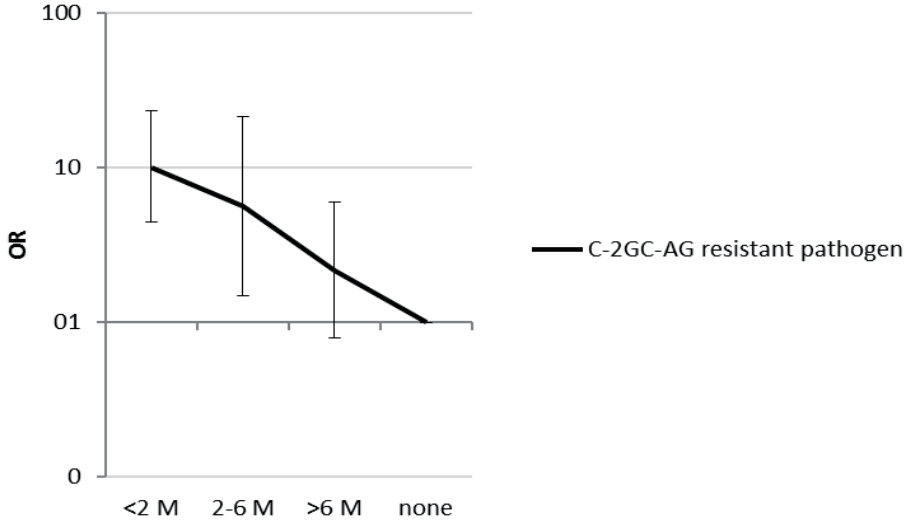
After applying the case criterion for Gram-negative bacteraemia with in vitro reduced susceptibility to cefuroxime and gentamicin, 71 patients (2013–2016) were identified as cases and 142 controls were randomly selected from the remaining patients in the

cohort. The demographic and clinical characteristics of cases and controls are shown in Table 2. The pathogen distribution is described in the Supplementary data. The causative pathogen was ESBL producing in 64.8% (46/71) and 6.3% (9/142) in cases and controls respectively ($p < 0.001$).

Risk factors for non-susceptibility to empiric therapy

The result of the univariate analyses are shown in Table 2. Patients with hematologic malignancy or neutropenia were at increased risk of a pathogen with reduced susceptibility to C-2GC + AG. Pre-treatment with antibiotics in the 2 months prior to presentation and antibiotic treatment at the day of presentation were associated with presence of reduced susceptibility to C-2GC + AG. In addition, previous admission on general wards, ICU wards and length of hospital stay were strong predictors of reduced susceptibility to standard empiric therapy. The strongest crude predictor was prior isolation of a resistant micro-organism from any site, including rectal swabs. Figure 1 depicts the odds ratio for infection with a pathogen with reduced susceptibility to C-2GC + AG, depending on the time elapsed between the DRP cultures and the current presentation with infection.

Figure 1. Odds ratio for resistance to empiric therapy related to time since the last drug resistant pathogen (DRP) was cultured



Legend. M=months. C-2GC+AG= Combination 2nd generation cephalosporin and aminoglycoside. Prior-DRP = drug resistant pathogen(s) isolated from any body site: Vancomycin resistant enterococci, multi resistant *Staphylococcus aureus*, enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacterales and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporin's, aminoglycosides or quinolones. Odds ratio for infection with cefuroxime and gentamicin resistant Gram-negative pathogen, for patients with prior-DRP isolated compared to patients without prior-DRP isolates, for different time intervals in months since the last DRP was cultured. Note that the y-axis is on a logarithmic scale.

Table 2. Demographics and clinical characteristics of cases and controls.

Characteristic	Cases n (%)	Controls n (%)	*P* Value	OR (95% CI)
Patient demographics				
Male gender	45 (63.4)	80 (56.3)	.38	1.34 (0.75-2.41)
Age >65	32 (43.7)	73 (51.4)	.31	0.77 (0.44-1.38)
Medical history				
Diabetes mellitus	19 (26.8)	50 (35.2)	.28	0.67 (0.36-1.26)
Corticosteroid therapy (prior 6 months)	32 (45.1)	47 (33.1)	.10	1.66 (0.93-2.97)
Neutropenia	14 (19.7)	9 (6.3)	.005	3.62 (1.49-8.87)
Solid organ transplantation	14 (19.7)	23 (16.2)	.57	1.27 (0.61-2.65)
Hematologic malignancy	18 (25.4)	9 (6.3)	<.001	5.01 (2.12-11.87)
Non-hematologic malignancy	12 (16.9)	33 (23.2)	.37	0.67 (0.32-1.40)
Chronic urologic disorder	13 (18.3)	33 (23.2)	.48	0.74 (0.36-1.52)
Chronic pulmonary disease	7 (9.9)	19 (13.4)	.51	0.71 (0.28-1.77)
Recurrent urinary tract infections	7 (9.9)	14 (9.9)	1.00	1.00 (0.38-2.60)
Clinical presentation				
Fever (temperature>38.5 °C)	49 (69.0)	104 (73.2)	.31	0.81 (0.43-1.53)
EMV-score <15	21 (30.6)	29 (20.4)	.23	1.57 (0.81-3.02)
Hypotension[a]	18 (25.4)	23 (16.2)	.14	1.79 (0.89-3.63)
Current antibiotic use[b]	49 (69.0)	37 (26.1)	<.001	6.32 (3.38-11.84)
Antibiotic usage preceding 2 months	67 (94.4)	67 (47.2)	<.001	18.75 (6.49-54.19)
ICU/MCU > 2 days	11 (15.5)	7 (4.9)	.02	3.54 (1.31-9.57)
ICU/MC preceding 6 months	23 (32.4)	16 (11.3)	<.001	3.77 (1.84-7.75)
Hospital stay preceding 6 months	49 (69.0)	65 (45.8)	.001	2.64 (1.45-4.82)
Hospitalization >5 days	32 (45.1)	28 (19.7)	<.001	3.34 (1.79-6.24)
Prior-DRP[c]	42 (59.2)	27 (19.0)	<.001	6.17 (3.28-11.61)
Source of infection			.06	-
Urinary tract	23 (32.4)	68 (47.9)		
Intra-abdominal tract	22 (31.0)	44 (31.0)		
Respiratory tract	3 (4.3)	9 (6.4)		
Skin/soft tissue	6 (8.6)	4 (2.8)		
Other	7 (9.9)	7 (4.9)		
Unidentified	10 (14.1)	10 (7.0)		

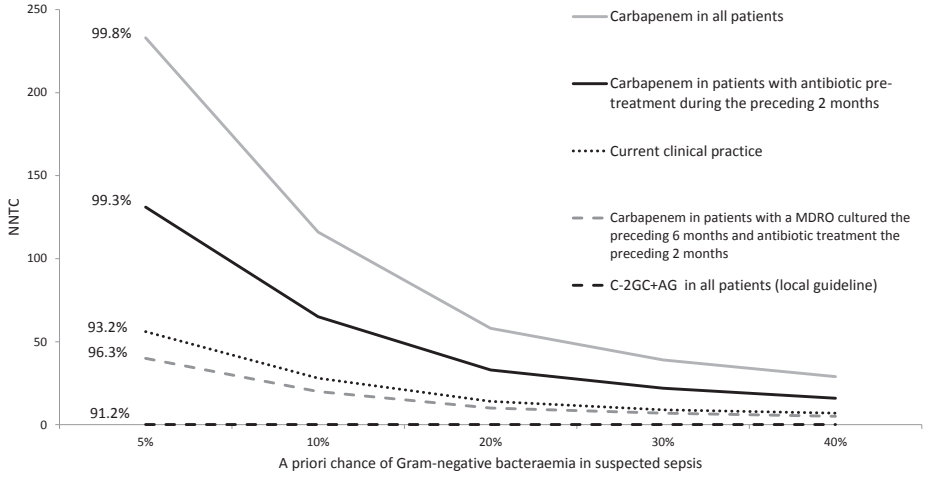
Legend. Data are presented as No. (%). P values are calculated by Fisher exact test. Abbreviations**:** OR= odds ratio, EMV-score: eye-motor-verbal score. ICU/MCU = intensive care unit / medium care unit. IQR= interquartile range. [a] Hypotension = systolic blood pressure <90 mmHg or requirement for intravenous vasopressor agents. [b] 'Current antibiotic use' = at least one administration of antibiotics during the 24 hours preceding the collection of blood specimens . [c]'Prior-DRP' = one of the following drug resistant pathogens isolated from any body site: Vancomycin resistant enterococci, multi resistant *Staphylococcus aureus*, enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacterales and/or quinolones, Pseudomonas aeruginosa with resistance to third generation cephalosporins, aminoglycosides or quinolones.

In the multivariable analysis a previous culture with a DRP (adjusted OR 3.72 95%CI 1.72–8.03, p < 0.01), antibiotic use during the preceding two months (adjusted OR 12.5, 95%CI 4.08–38.48, p < 0.01), and a hematologic malignancy (adjusted OR 4.09, 95%CI 1.43–11.62, p < 0.01) were independently associated with reduced susceptibility (Supplementary files)

Exploring the effect of risk-based sepsis guidelines: Calculated estimations

The relevant risk factors for resistance to empiric therapy derived from the multivariable analysis were used to design five different risk-based empiric sepsis treatment strategies. The calculated effect of these individual strategies on the proportion of patients with Gram-negative sepsis that would be treated adequately and the corresponding NNTC are shown in Table 3, and for a selection of strategies in Fig. 2.

Figure 2. Estimation of the effect of the different empiric strategies on effective therapy rate and consumption of carbapenems, differentiated by a priori probability of bacteraemia and compared to other strategies for selection of empiric therapy.



Legend. NNTC = number of patients needed to treat with a carbapenem instead of cefuroxime/gentamicin to avoid mismatch of empiric therapy in one patient. C-2GC+AG = 2nd generation cephalosporin/aminoglycoside combination therapy. DRP= drug resistant pathogen(s) isolated from any body site: Vancomycin resistant enterococci, multi resistant *Staphylococcus aureus*, enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacterales) and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporins, aminoglycosides or quinolones.. Current clinical practice: 2GC+AG as standard therapy, escalation to a carbapenem according to judgment of treating physician. The percentages (91.2-99.0%) indicate the proportion of patients with bacteraemia that would receive adequate treatment if the strategy was implemented. For example: if all patients were to be treated with a carbapenem, the overall rate of adequate therapy in patients with bacteraemia would be 99.0%. In case of an a priory risk of bacteraemia of 10%, the corresponding NNTC is 128 patients.

Table 3. Estimated effects of implementation of different empiric sepsis treatments on effective therapy rate and consumption of carbapenems in a population suspected of Gram-negative bacteraemia.

Treatment strategy	Sensitivity of the criterion for presence of combined resistance*	Proportion of patients with Gram-negative BSI adequately treated	Proportion of patients with Gram-negative BSI treated with carbapenem	Estimated NNTC** with carbapenem according to frequency of Gram-negative bacteraemia in suspected sepsis *A priori* probability of Gram-negative bacteraemia in suspected sepsis [a]				
				5%	10%	20%	30%	40%
1. Cefuroxime/gentamicin in all patients with sepsis	0	.912	0	-	-	-	-	-
2. Carbapenem in all patients with sepsis	1.000	.998	1.000	233	116	58	39	29
3. Only a carbapenem in patients with antibiotic pre-treatment on day of culture.	.690	.971	.296	100	50	25	17	13
3. Only a carbapenem in patients with antibiotic treatment <2 months	.943	.993	.529	130	65	33	22	16
4. Only a carbapenem in patients with a DRP[b] cultured <6 months	.465	.952	.111	55	28	14	9	7
5. Only a carbapenem in patients with a DRP cultured previously (no time restriction)	.592	.963	.195	76	38	19	13	10
7. Only a carbapenem in patients with a DRP previously and antibiotic treatment < 2 months	.549	.961	.101	42	21	11	7	5
8. Current Practice	.225	.931	.056	57	29	14	10	7

Legend [A] Frequency of Gram-negative bacteraemia as percentage of the total No. of patients with suspected sepsis in whom empiric therapy is started. [B] Drug resistant pathogen(s) (DRP) isolated from any body site: Vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus*, Enterobacterales with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacteriaceae) and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporins, aminoglycosides or quinolones.* The sensitivity was derived from the study data (cases 2013-2016) ** NNTC = Number needed to treat with carbapenem instead of cefuroxime/gentamicin to avoid mismatch of empiric therapy for Gram-negative bacteraemia in one patient. For the calculation of the NNTC the formula in the Supplementary files was applied.

Example, strategy 5: Standard empiric treatment is cefuroxime/gentamicin, carbapenems are reserved for patients with a history of drug resistant pathogen (DRP). This results in prescription of a carbapenem in 19.5% of patients with Gram-negative bacteraemia. With this strategy, empiric treatment of patients with cefuroxime/gentamicin resistant bacteraemia is adequate in 59.2% and the overall treatment adequacy rate in Gram-negative bacteraemia is 96.3%. In the scenario of a pre-test probability of Gram-negative bacteraemia of 10%, 38 patients would be treated with a carbapenem to avoid mismatch of empiric therapy for Gram-negative bacteraemia in 1 patient.

The NNTC is to a large extent dependent on the number of patients that are empirically treated for sepsis. This number is much larger than the number of patients that are eventually diagnosed with Gram-negative bacteraemia. To account for these differences in prevalence of Gram-negative bacteraemia amongst patients that are empirically treated for presumed sepsis, the NNTC was assessed for different probabilities of Gram-negative bacteraemia. (Fig. 2, Table 3).

In the scenario of 'standard empiric carbapenem therapy in all patients', the adequacy rate of empiric therapy was 99.8%. The corresponding NNTC was 29 to 233, depending on the probability (i.e. high: 40% to low: 5%) of Gram-negative bacteraemia. Alternatively, risk-based strategies resulted in an estimated adequacy rate of 95.2–99.3%. Compared to treating all patients with a carbapenem empirically, the NNTC in the targeted approaches was a factor 2.3 to 4.6 lower, depending on the selected approach. The NNTC was lowest if a carbapenem would be reserved for patients in whom a DRP was cultured previously and antibiotic treatment had been administered in the preceding 2 months. The estimated reduction of carbapenem use was 82.8% (95%CI 78.5–87.5%). This strategy had a treatment adequacy rate of 96.1% of patients with Gram-negative bacteraemia. This is an absolute increase in adequacy rate of 4.9% compared to the local guideline and an absolute increase of 3.0% compared to clinical practice (Fig. 2, Table 3).

DISCUSSION

Using real-life clinical and microbiological data, we propose a method to develop risk-based empiric antibiotic policies and to estimate the potential costs and benefits of policy changes (Table 1).

Although there are multiple previous prediction rules for infection with resistant pathogens, the applicability of these rules to the selection of institutional empiric antimicrobial treatment is limited. The majority of prediction score studies focused on a specific pathogen or a specific mechanism of resistance, for example ESBL.[6,20,25–27] For clinical practice, it is more relevant to predict susceptibility to an empiric regimen in a predefined clinical syndrome, instead of predicting the presence of a specific mechanism of resistance. Secondly, the consequences of implementation of the prediction scores on adequacy rate and/or NNTC are frequently lacking.[6,7] Thirdly, the susceptibility of pathogens and the risk factors for resistance may vary substantially amongst institutions, making it is necessary to base empiric treatment recommendations on local epidemiology. Our 7-step method can be used to develop institutional empiric policy

for a variety of clinical syndromes, and focusses on applicability of the results in daily clinical practice.

In response to increasing resistance rates, we applied the method to improve empiric coverage of causative Gram-negative micro-organisms in sepsis, while maintaining a responsible antimicrobial policy with regard to antibiotic consumption. Our data show that in current practice, clinicians already incorporate an assessment of the risk of a resistant pathogen in decision-making, with a relatively low NNTC. The treatment adequacy rate however, can be further increased using targeted strategies, without increasing inappropriate reserve antimicrobial consumption. The NNTC was stratified according to the theoretical probability of Gram-negative bacteraemia. Previous literature on positivity rates in consecutive blood cultures, shows probabilities of Gram-negative bacteraemia below 5%.[28,29] However, the positivity rate varies substantially depending on the patient population, to up to 41% in septic shock.[28-34] As a result, the NNTC in the critically ill is considerably lower than in a low acuity population.[16,29] The strategies were based on bacteraemia. Including non-bacteraemic infections, would further decrease the NNTC. We focused on bacteraemia, as the importance of adequate empiric treatment is higher in bacteraemic, compared to non-bacteraemic episodes.

A limitation of the study is the retrospective data collection. There is potential underreporting of antibiotic pre-treatment. However, this effect is limited, given the use of electronic prescription systems. In addition, potentially important predictive factors, such as travel history, may have been missed, because of limited availability of specific information in the medical charts. Incorporating more determinants, could improve the strategies and further reduce NNTC. A second limitation is that, in our analysis of the NNTC, we assumed that the identified predictors of antimicrobial resistance are independent of the a priori risk of Gram-negative bacteraemia. On theoretical grounds, we do not expect previous antibiotic use and colonization with DRP's to have an important etiologic effect on the a priori risk of Gram-negative bacteraemia itself. Thirdly, the inclusion period for cases was prolonged compared to the initial cohort, because of the low incidence of C-2GC + AG resistance. Although the epidemiology of antimicrobial resistance is subject to change over time, it is unlikely that the prolonged inclusion period would affect risk factors associated with C-2GC + AG resistance (step 3).

The reported results on Gram-negative bacteraemia are institution specific. Differences in antimicrobial susceptibility rates, patient population and treatment guidelines between institutions may all affect treatment adequacy rates and the NNTC. However, the method that was used to determine a center-specific NNTC is applicable in every setting.

From a scientific perspective, prospective validation within the institution is preferable, before implementation is considered. However, prospective validation would hamper a timely response to the latest resistance data, resulting in a difficult process of catch-up because of changing epidemiology. Therefore, cyclic evaluation and optimization within the institution after implementation is - from a practical point of view - preferable to further improve targeted antibiotic strategies.

In step 7, the benefits of adequate therapy and the costs of the associated antimicrobial consumption need to be weighed to select the most appropriate strategy. The rate of inadequate empiric therapy that clinicians are willing to accept, varies according to the severity of the clinical syndrome. For sepsis, and especially septic shock, the optimal balance between antibiotic adequacy rate and consumption of reserve antimicrobial agents is incomparable to the setting of more benign infections, for example cystitis. How to balance these aspects is highly complex. This also involves ethics, as decisions do not merely affect patients today, but impacts future generations as well.[35] The number needed to treat with reserve antimicrobial agents contributes to this ethical discussion. This study demonstrates the feasibility of generating these numbers for the local situation.

CONCLUSIONS

The present study exemplifies a method to develop risk-based empiric antibiotic policies and estimate the effects on treatment adequacy and antimicrobial consumption. The approach has the potential to target the use of reserve antimicrobial agents and can be applied in different clinical settings to optimize empiric antibiotic therapy.

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SUPPLEMENTARY DATA

Formula for the estimation of the number needed to treat with a carbapenem

$$NNTC = \frac{\text{PropRf}}{(\text{PropRx} - \text{PropRy}) \times \text{SensRF}} \times \frac{1}{\text{Gramnegbac}}$$

NNTC= Number needed to treat with a carbapenem instead of cefuroxime/gentamicin to avoid mismatch of therapy in one patient.

PropRf = The frequency of cases with the risk factor (or risk factor combination) as a proportion of the total No. of cases in the study cohort "Gram-negative bacteraemia".
PropRX = The frequency of cases with a pathogen that has reduced susceptibility to the combination therapy gentamicin and cefuroxime (C-2GC+AG) as a proportion of the total No. of cases in the study cohort "Gram-negative bacteraemia" .
PropRy = The frequency of cases with a pathogen with reduced susceptibility to carbapenems as a proportion of the total No. of cases in the study cohort "Gram-negative bacteraemia" .

SensitivityRF = Sensitivity of the risk factor (or risk factor combination) for combined resistance to gentamicin and cefuroxime in patients with bloodstream infection with a pathogen with reduces susceptibility to C-2GC+AG.

Gramnegbac: A priori probability of Gram-negative bacteraemia in suspected sepsis: The frequency of Gram-negative bacteraemia as a proportion of the total No. of patients with suspected sepsis in whom empiric therapy is started.

Example*:*
In the study cohort, the resistance rate to the combination cefuroxime/gentamicin was 8.8%. In this cohort, a drug resistant pathogen (DRP) was diagnosed the previous 6 months in 11.1% of cases. Of all patients with bacteraemia with a pathogen with reduced susceptibility to C-2GC+AG in 45,5% a drug resistant pathogen was isolated the preceding 6 months. In the study center 6.7 percent of patients in whom blood cultures are obtained are diagnosed with Gram-negative bacteraemia.

$$NNTC = \frac{0.111}{(0.088 - 0.002) \times 0.0.465} \times \frac{1}{0.067} = 42$$

The number needed to treat with a carbapenem instead of cefuroxime/gentamicin to treat one patient adequately = 42.

Pathogen distribution

Table S1. Isolated pathogens in cases (n=71) and controls (n=142).

	Cases n (%)	Controls n (%)	p-value*
Pathogen			.12
Escherichia coli	34 (47.9)	83 (58.5)	
Klebsiella species	13 (18.3)	25 (17.6)	
Pseudomonas aeruginosa	9 (12.7)	11 (7.7)	
Serratia marcescens	7 (9.9)	9 (6.3)	
Other Gram-negative pathogens**	8 (11.3)	14 (9.9)	

Legend: *p-value calculated by Fisher exact test. ** *Citrobacter spp*, *Enterobacter spp*, *Proteus spp*, *Morganella spp* and *Providencia spp*.

Multivariable analysis

Table S2 Multivariable analysis of predictors of infection with a pathogen with reduced susceptibility to treatment with cefuroxime and gentamicin.

	OR	95% CI	p-value
Hematologic malignancy	4.09	1.43-11.62	<0.01
Admitted to IC/MC unit ≥ 2 days	1.25	0.38-4.12	0.72
Hospital stay during the preceding 6 months	0.94	0.44-2.04	0.88
Current hospital stay ≥ 5days	1.05	0.45-2.42	0.92
Prior-DRP	3.72	1.72-8.03	<0.01
Antibiotic therapy during preceding 2 months	12.5	4.08-38.48	<0.01

Legend. Logistic regression analysis. OR = Adjusted odds ratio, 95%CI = 95% confidence interval. IC/MC = intensive care/ medium care. Prior-DRP = Drug resistant pathogen, defined as the isolation of one of the following pathogens from any body site, including rectal swabs: vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus*, Enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporins and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporin's, aminoglycosides or quinolones.

Prediction tools for antimicrobial resistance in daily clinical practice: balancing optimal empiric treatment and consumption of reserve antimicrobials

Letter

The following letter was written as a reply to the study 'Development of diagnostic prediction tools for bacteraemia caused by 3rd generation cephalosporin-resistant *Enterobacteriaceae* in suspected bacterial infections' by Rottier, *et al*. In their nested case-control study, a prediction tool was developed to estimate the risk of bloodstream infection with third-generation cephalosporin-resistant Enterobacterales. In our letter we calculate the number needed to treat with a reserve antimicrobial agent that would be associated with the proposed cut-off, illustrating the method described in the first part of Chapter 5.

Merel M.C. Lambregts, Alexandra T Bernards, Leo G. Visser, Mark G.J. de Boer

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With great interest, we read the recent publication by Rottier *et al*. In their nested case control study, a prediction tool was developed to estimate the risk of bloodstream infection with 3rd generation cephalosporin resistant (3GCR) Enterobacterales.[1] Such practical tools, that break the vicious circle of inappropriate use of reserve antimicrobial therapy and increasing resistance levels, are urgently needed. The scoring system provides the clinician with the probability that the patients suffers from 3GCR-E bacteraemia. The authors report a potential 40 percent reduction in consumption of carbapenems using this prediction score in community acquired infection. In view of the high incidence of presumed sepsis, the relative gain on inappropriate antibiotic consumption compared to the use of a third generation cephalosporins is promising.

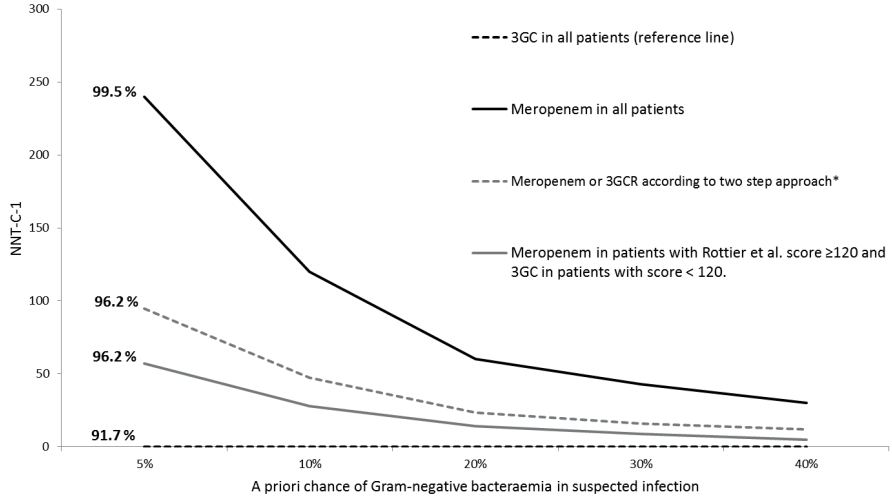
However, to quantify the absolute gain of the scoring system, calculation of the number of patients needed to treat with carbapenems to prevent one case of mismatch of empiric therapy (NNT-C-1) is highly relevant. The authors do not provide these data. Nonetheless, the NNT-C-1 is important from the perspective of the individual patient as well as from an antibiotic stewardship point of view. The prevalence of 3GCR-E-BAC was very low - 0.4% for community acquired infection - in the cohort of empirically treated patients. The proposed cut-off in the scoring system is 120 points. If the rule was to be implemented, according to Table 3, this would lead to prescription of a carbapenem in 12.8% of these patients to prevent mismatch between pathogen and antibiotic in 0.2% of patients. Compared to empiric treatment with a third generation cephalosporin in all patients, the NNT-C-1 with a carbapenem to avoid mismatch in one patient would be approximately 59 (Box 1).

Box 1 Calculation of the NNT-C-1

The prevalence of 3GCR-E bactaeremia in the study cohort was 0.4% (90/22506). The sensitivity of the prediction tool for the cutoff of 120 points was 54.3 %. Therefore 0.2% (prevalence of bactaeremia x sensitivity of the rule) of the population would be adequately treated because of administration of a carbapenem *(A)*. Table 3 in the study by Rottier et al. states that, using the same cut-off, 12.8 % of patients would be prescribed a carbapenem (*B*). The NNTC-1 is 59. ($^{B}/_{A}$)

Hence, a relatively high number of patients (59 minus 1) would be prescribed a carbapenem unnecessarily. The high NNT-C-1 is the result of the relatively low *a priori* probability of Gram-negative bacteraemia in the study cohort. When deciding over empirical therapy, the probability of bacteraemia is highly relevant. In septic shock for example, the a priori chance of bacteraemia is approximately 20-30%.[2] Based on a 8.3% resistance of all Gram-negative pathogens to third generation cephalosporins.[1,3] the NNT-C-1 in septic shock would be 9-14 patients, an approximate 5-fold reduction (Figure 1). This illustrates that the reduction in NNT-C-1 that can be achieved by accounting for the *a priori* risk of bacteraemia, is much higher than the gain that can be expected by optimization of the risk score for predicting antimicrobial resistance. In addition, the potential harm of empirical mismatch in these severely ill patients is substantially more threatening than in hemodynamically stable patients. Accounting for the severity of illness in more detail is therefore important and would improve risk based antibiotic strategies.[4] Although signs of hypoperfusion are incorporated in the tool by Rottier *et al*, they are attributed only 40 out of 480 points.

Figure 1. Estimation of the effect of the Rottier et al. scoring system on effective therapy rate and consumption of carbapenems in community-acquired infection, differentiated by a priori risk of bacteraemia and compared to other strategies for selection of empiric therapy.



Legend: 3GC= 3rd generation cephalosporin. NNT-C-1 = number of patients needed to treat with a carbapenem to prevent one case of mismatch of empiric therapy. * Two step approach (current Dutch sepsis guideline) = a carbapenem in patients with cephalosporin or quinolone use during the prior 2 months or identification of 3GC resistant pathogen during the prior year. The percentages (91.7-99.5 %) indicate the proportion of patients with bacteraemia that would receive appropriate treatment if the strategy was implemented. For example: if all patients were to be treated with a carbapenem, the overall rate of appropriate therapy in patients with bacteraemia would be 99.5 percent (assuming 0.5 % carbapenem resistance). In case of an a priory chance of bacteraemia of 10 percent, the corresponding NNT-C-1 with a carbapenem is 120 patients to prevent mismatch in one patient. If the scoring system of Rottier et al. would be applied, the NNT-C-1 would be reduced to 28, for the same a priori probability of bacteraemia. This figure was based on the data provided in the publication by Rottier et al

A second aspect that influences the NNT-C-1 is the standard of care, which the risk strategy is compared to. In their study Rottier *et al*. defined standard of care as treatment with a third generation cephalosporin or a carbapenem, based on the a two-predictor model. However, in many hospitals in the Netherlands and other European countries with low to moderate resistance rates of Enterobacterales standard empiric treatment for presumed sepsis has changed since the period the study by Rottier *et al*. was conducted (2008-2010). Empiric therapy now consists of a 2nd or 3rd generation cephalosporin (or a betalactam plus betalactamase inhibitor) combined with an aminoglycoside. The addition of an aminoglycoside intends to improve effective empiric therapy rates in case of cephalosporin resistant Gram-negative pathogens, due to ESBL-production or other mechanisms of resistance.[5] Of note, susceptibility rates for cephalosporin/aminoglycoside combination therapy may be less favorable than susceptibility rates for carbapenems. Plasmids responsible for ESBL production frequently carry genes encoding resistance to aminoglycosides. Nevertheless, in many countries, the *a priori* risk for resistance to this empiric combination regimen is considerably lower than resistance to monotherapy with a 3rd generation cephalosporin.[3, 5] This is relevant, as it would further increase the NNT-C-1. Since the study focusses on 3GCR-E-BAC, the research question does not fully address the clinical dilemma currently at hand. Therefore, reporting on the performance of a clinical decision rule with regard to the current standard regimen would provide better insight in the potential benefit of this clinical tool. For antibiotic stewardship reasons, empiric use of the carbapenem class should be avoided if aminoglycosides provide a good alternative. It would be helpful if the authors could provide the results of this alternative analysis of the data.

Ultimately, we look forward to data from comparative clinical studies about patient outcomes (i.e. 'hard endpoints') and the antibiotic consumption directed by this and other clinical antibiotic stewardship tools.

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