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Evaluation of early clinical failure criteria for gram-negative bloodstream infections

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ABSTRACT

Objectives: The aim was the development of early clinical failure criteria (ECFC) to predict unfavourable outcomes in patients with Gram-negative bloodstream infections (GN-BSI).

Methods: Adults with community-onset GN-BSI who survived hospitalization for ≥72 hr at Prisma Health-Midlands hospitals in Columbia, SC, USA from January 1, 2010 to June 30, 2015 were identified. Multivariable logistic regression was used to examine the association between clinical variables between 72 and 96 hr after GN-BSI and unfavourable outcomes (28-day mortality or hospital length of stay >14 days from GN-BSI onset).

Results: Among 766 patients, 225 (29%) had unfavourable outcomes. After adjustments for Charlson Comorbidity Index and appropriateness of empirical antimicrobial therapy in multivariable model, predictors of unfavourable outcomes included systolic blood pressure <100 mmHg or vasopressor use (adjusted odds ratio (aOR) 1.8, 95% confidence interval (CI) 1.2–2.9), heart rate >100 beats/minute (aOR 1.7, 95% CI 1.1–2.5), respiratory rate ≥22 breaths/minute or mechanical ventilation (aOR 2.1, 95% CI 1.4–3.3), altered mental status (aOR 4.5, 95% CI 2.8–7.1), and white blood cell count >12 000/mm^3 (aOR 2.7, 95% CI 1.8–4.1) between 72 and 96 hr after index GN-BSI. Area under receiver operating characteristic curve of ECFC model in predicting unfavourable outcomes was 0.77 (0.84 and 0.71 in predicting 28-day mortality and prolonged hospitalization, respectively).

Conclusions: Risk of 28-day mortality or prolonged hospitalization can be estimated between 72 and 96 hr after GN-BSI using ECFC. These criteria may have clinical utility in management of GN-BSI and may improve methodology of future investigations assessing response to antimicrobial therapy based on a standard evidence-based definition of early clinical failure. **H. Rac, Clin Microbiol Infect 2020;26:73**

Introduction

Bloodstream infections (BSIs) occur in over 1.8 million individuals in Europe and North America costing nearly 240 000 lives each year [1]. Whereas mortality remains the most objectively measurable outcome in Gram-negative BSI (GN-BSI) studies, improved survival over time has left many studies underpowered to detect a significant difference in mortality based on empirical antimicrobial therapy, particularly those focused on one microorganism, a specific resistance mechanism or a patient population with relatively low acute severity of illness [2,3]. Alternatively, hospital length of stay (HLOS) has been utilized as a primary outcome of GN-BSI in patients with low predicted mortality [4].

While there are numerous acute severity of illness and other more complex scores for prediction of mortality using baseline clinical variables at GN-BSI onset [5,6], objective evidence-based criteria for early clinical failure within the first 3–4 days of GN-BSI remain undefined. This has led to adoption of various heterogeneous definitions for early clinical failure endpoints in patients with GN-BSI throughout the literature [7–14]. Development of evidence-based early clinical failure criteria (ECFC) that directly

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correlate to clinical outcomes, such as mortality and HLOS, establishes standardized endpoints for clinical studies that may not have adequate power to directly examine mortality. In addition, utilization of ECFC allows clinicians to objectively assess patients' clinical progress early during hospitalization for GN-BSI, which may prompt adjustments in diagnostic and treatment plans. The purpose of this retrospective cohort is to derive and evaluate ECFC between 72 and 96 hr following community-onset GN-BSI that predict unfavourable outcomes.

Methods

Setting

The study was conducted at Prisma (previously Palmetto) Health Richland and Baptist Hospitals, which are part of the largest healthcare system in the Midlands in South Carolina, USA. The Institutional Review Board at Prisma Health-Midlands approved the study and waived informed consent.

Definitions

GN-BSI was defined as monomicrobial growth of any aerobic or facultative anaerobic Gram-negative bacillus in a blood culture. Primary source of BSI, site of infection acquisition and immunocompromised status were previously defined [15–17]. Appropriateness of empirical antimicrobial therapy was based on dose, route and *in vitro* antimicrobial susceptibility testing results [3]. Unfavourable outcome was defined as all-cause 28-day mortality or HLOS >14 days from collection of index blood culture.

Case ascertainment

All hospitalized patients ≥18 years old with GN-BSI from 1 January 2010 to 30 June 2015 were identified through Prisma Health-Midlands microbiology laboratory databases (n = 1376). Polymicrobial (n = 166) and recurrent episodes of BSI (n = 47) were excluded. In addition, patients with hospital-onset BSI (n = 238) were excluded since mortality and HLOS might be influenced by primary admission diagnosis. Candidate clinical variables manually collected from the electronic medical records were evaluated between 72 and 96 hr after GN-BSI onset, defined as date and time of index blood culture collection. In cases where evaluation of clinical variables during the specified time frame was not possible, patients were excluded, e.g. patients who died within 72 hr (n = 74), were discharged from the hospital within 72 hr (n = 84) or had missing vital signs between 72 and 96 hr (n = 1). The remaining 766 unique patients with the first episode of monomicrobial community-onset GN-BSI were included in the analysis.

Statistical analysis

The primary objective of this retrospective cohort was to determine clinical variables between 72 and 96 hr after GN-BSI onset that predicted unfavourable outcomes (mortality or prolonged hospitalization). Logistic regression was used to examine association between clinical variables between 72 and 96 hr after GN-BSI and unfavourable outcomes. Demographics, chronic comorbidities as summarized in Charlson comorbidity index (CCI) score, BSI source (dichotomized into urinary or non-urinary sources) and appropriateness of empirical antimicrobial therapy were examined in logistic regression model. Mental status as documented in nursing assessment or physical examination was analysed as a binary variable (altered or normal). For intubated patients, nursing assessments were performed during sedation interruption. After recording the worst measurement between 72 and 96 hr after GN-BSI in electronic medical records, continuous variables were dichotomized into binary ones based on best breakpoint cut-offs in the respective receiver operating characteristic (ROC) curves and were rounded to the closest whole number. Bimodal models were used to determine the need for high and low breakpoints for continuous variables. The use of vasopressors between 72 and 96 hr after GN-BSI was incorporated into systolic blood pressure (SBP) to account for the potential change in SBP due to vasopressor use. Similarly, presence of mechanical ventilation was added to respiratory rate since the rate per the ventilator settings might not reflect persistent respiratory failure. Multiple imputation was used to account for missing peripheral white blood cell (WBC) counts between 72 and 96 hr after GN-BSI. Variables were included in multivariable logistic regression model if $p < 0.05$ in univariable analysis using backward selection. Testing for co-linearity was performed and variance inflation factor for correlation between any two independent predictors was <4. Risk factors were retained in final multivariable model if independently associated with unfavourable outcomes with $p < 0.05$ in multivariable logistic regression using likelihood ratio test and individually retained in ≥95% of 200 bootstrap samples. Each bootstrap sample was derived by applying the same model entry and retention criteria.

ECFC included variables between 72 and 96 hr after GN-BSI onset that were retained in the final model. For simplicity, one point was allocated for each ECFC present. The area under the ROC curve was used to quantify the discriminative ability of the ECFC model to predict unfavourable outcomes.

In addition to bootstrap resampling, model calibration was examined to internally validate the ECFC model. Deciles of predicted risk of unfavourable outcomes were plotted from the ECFC model by the actual fraction of patients who had unfavourable outcomes to visually access calibration.

A secondary analysis was performed to examine the discriminative ability of the ECFC model to individually predict 28-day mortality and prolonged hospitalization. The predicted probabilities of mortality and prolonged hospitalization obtained from the ECFC model were plotted by the number of ECFC to visualize the estimated risk of mortality and prolonged hospitalization separately.

JMP Pro (version 13.0, SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The level of significance for statistical testing was defined as $p < 0.05$ (two-sided), unless otherwise specified.

Results

During the study period, 766 patients with community-onset GN-BSI were included. The median age was 67 years and 438 (57%) were women. *Escherichia coli* (426; 56%) was the most common bloodstream isolate, followed by *Klebsiella* spp. (133; 17%), *Proteus mirabilis* (58; 8%), *Enterobacter* spp. (37; 5%), *Pseudomonas aeruginosa* (36; 5%) and other Gram-negative bacilli (76; 10%). The majority of GN-BSI (408; 53%) were community-acquired, whereas the remaining were healthcare associated. Overall, 225 (29%) patients had unfavourable outcomes, including mortality (53; 7%), prolonged hospitalization (156; 20%) or both (16; 2%).

Risk factors for unfavourable outcomes in the univariable logistic regression included age, healthcare-associated BSI, CCI score, inappropriate empirical therapy and altered mental status (AMS) between 72 and 96 hr after GN-BSI. Temperature, SBP, heart rate, respiratory rate and white blood cell (WBC) counts between 72 and 96 hr after GN-BSI were all associated with unfavourable outcomes when analysed as continuous variables. These variables were dichotomized based on the best breakpoints in respective ROC curves (Table 1). Female sex, urinary source of infection and *E. coli* BSI were associated with lower risk of unfavourable outcomes.

Table 1
Univariable logistic regression model results for risk factors of unfavourable outcomes

Variable	Favourable Outcome ($n = 541$)	Unfavourable Outcome ($n = 225$)	OR (95% CI)	p
Age, median (IQR) (OR per decade)	66 (54–78)	68 (58–80)	1.1 (1.0–1.3)	0.008
Female sex	327 (60)	111 (49)	0.6 (0.5–0.9)	0.005
White race	262 (48)	107 (48)	0.97 (0.7–1.3)	0.83
Diabetes mellitus	229 (43)	94 (42)	1.0 (0.7–1.3)	0.89
ESRD	47 (9)	30 (13)	1.6 (1.0–2.6)	0.053
Liver cirrhosis	17 (2)	12 (5)	1.7 (0.8–3.7)	0.15
Cancer	66 (12)	54 (24)	2.3 (1.5–3.4)	<0.001
Immune compromised	63 (12)	29 (13)	1.1 (0.7–1.8)	0.63
Surgical procedure within 30 days of BSI	75 (14)	36 (16)	1.2 (0.8–1.8)	0.44
Indwelling central venous catheter	80 (15)	36 (16)	1.1 (0.7–1.7)	0.67
Indwelling urinary catheter	47 (9)	18 (8)	0.9 (0.5–1.6)	0.76
Healthcare-associated BSI	231 (43)	127 (56)	1.7 (1.3–2.4)	<0.001
CCI score, median (IQR) (OR per point)	1.5 (0–3)	2 (1–3)	1.1 (1.1–1.2)	<0.001
Urinary source of BSI	349 (65)	108 (48)	0.5 (0.4–0.7)	<0.001
BSI due to *Escherichia coli*	327 (60)	99 (44)	0.5 (0.4–0.7)	<0.001
Inadequate source control	25 (5)	15 (7)	1.4 (0.6–3.1)	0.40
Inappropriate empirical therapy	25 (5)	31 (14)	3.3 (1.9–5.7)	<0.001
Temperature <36 or >38°C[a]	50 (9)	39 (17)	2.1 (1.3–3.2)	0.002
SBP <100 mmHg or vasopressor use[a]	72 (13)	81 (36)	3.7 (2.5–5.3)	<0.001
Heart rate >100 beats/min[c]	128 (24)	107 (48)	2.9 (2.1–4.1)	<0.001
Respiratory rate ≥22 breaths/min or mechanical ventilation[a]	108 (20)	115 (51)	4.2 (3.0–5.9)	<0.001
Altered mental status[a]	53 (10)	102 (45)	7.6 (5.2–11.2)	<0.001
Peripheral WBC count >12 000/mm^3 [a,b]	82/481 (17)	96/214 (45)	4.0 (2.8–5.7)	<0.001

All data are shown as number (percentage) unless otherwise specified. BSI, bloodstream infection; CCI, Charlson Comorbidity Index; CI, confidence intervals; ESRD, end stage renal disease; IQR, interquartile range; OR, odds ratio; SBP, systolic blood pressure; WBC, white blood cell.
[a] Variables between 72 and 96 hr after Gram-negative bloodstream infection onset.
[b] Only 695 patients had peripheral WBC count results between 72 and 96 hr after Gram-negative bloodstream infection onset.

After adjustments in the multivariable model, age (adjusted odds ratio (aOR) 1.1 per decade, 95% confidence intervals (CI) 1.0–1.3, p 0.11), female sex (aOR 0.8, 95% CI 0.5–1.1, p 0.17), healthcare-associated GN-BSI (aOR 1.4, 95% CI 0.9–2.0, p 0.14), urinary source (aOR 0.8, 95% CI 0.5–1.3, p 0.41), *E. coli* BSI (aOR 0.7, 95% CI 0.5–1.1, p 0.09) and temperature <36°C or >38°C between 72 and 96 hr after GN-BSI (aOR 1.3, 95% CI 0.7–2.4, p 0.34) were not independently associated with unfavourable outcomes. CCI score, inappropriate empirical therapy, SBP <100 mmHg or vasopressor use, heart rate >100 beats/minute, respiratory rate ≥22 breaths/minute or mechanical ventilation, AMS and WBC counts >12 000/mm^3 between 72 and 96 hr after GN-BSI were independently associated with unfavourable outcomes (Table 2).

All ECFC were retained after bootstrap resampling (Table 3). Since 71 patients did not have WBC count results between 72 and 96 hr, area under ROC curve of the ECFC model was examined in the remaining 695 patients who had available results for all ECFC. The model's area under the ROC curve to predict unfavourable outcomes was 0.77 (Fig. S1). Model calibration looked satisfactory as predicted probabilities of unfavourable outcomes were close to actual ones (Fig. S2). The risk of unfavourable outcomes increased in the presence of each additional ECFC (OR 2.3 per criterion, 95% CI 2.0–2.7; p < 0.001). Based on the ROC curve of the model, the presence of two or more ECFC represented the best breakpoint in determining an increased risk of unfavourable outcomes. In the evaluable cohort of 695 patients, 262 (38%) had no ECFC, 175 (25%) had one ECFC and the remaining 258 (37%) had two or more ECFC.

In a secondary analysis, area under the ROC curves of the ECFC model were 0.84 and 0.71 in predicting 28-day mortality and hospitalization >14 days separately, respectively. Predicted 28-day mortality increased from 1% in patients with no ECFC to 3%, 7%, 16%, 32% and 54% in the presence of each additional criterion (p < 0.001). Predicted HLOS was 7.5 days in patients without any ECFC and increased by 4.0 days (95% CI 3.1–4.9, p < 0.001) in the presence of each additional criterion.

ECFC predicted unfavourable outcomes in patients who received appropriate and inappropriate empirical antimicrobial therapy (area under ROC curve 0.76 and 0.78, respectively). Predicted probabilities of mortality and prolonged hospitalization were higher with inappropriate than appropriate empirical antimicrobial therapy for the same number of ECFC and are shown in Figs. 1 and 2.

Discussion

The proposed ECFC estimated the risk of an unfavourable outcome (mortality or prolonged hospitalization) based on

Table 2
Final multivariable model for prediction of unfavourable outcome

Variable	aOR	(95% CI)	P
CCI score (per point)	1.2	(1.1–1.3)	0.002
Inappropriate empirical antimicrobial therapy	3.5	(1.8–6.8)	<0.001
SBP <100 mmHg or vasopressor use[a]	1.8	(1.2–2.9)	0.010
Heart rate >100 beats/minute[a]	1.7	(1.1–2.5)	0.014
Respiratory rate ≥22 breaths/minute or mechanical ventilation[a]	2.1	(1.4–3.3)	<0.001
Altered mental status[a]	4.5	(2.8–7.1)	<0.001
Peripheral WBC count >12 000/mm^3 [a]	2.7	(1.8–4.1)	<0.001

aOR, adjusted odds ratio; CCI, Charlson Comorbidity Index; SBP, systolic blood pressure; WBC, white blood cell.
[a] Variables collected between 72 and 96 hr after Gram-negative bloodstream infection onset.

Table 3
Early clinical failure criteria between 72 and 96 hr after Gram-negative bloodstream infection onset

Early clinical failure criteria
Systolic blood pressure <100 mmHg or vasopressor use
Heart rate >100 beats/minute
Respiratory rate ≥22 breaths/minute or mechanical ventilation
Altered mental status
Peripheral white blood cell count >12 000/mm^3

variables obtained between 72 and 96 hr after GN-BSI (Table 3). The ECFC model had fair discrimination; however, it performed better in predicting 28-day mortality than prolonged hospitalization.

There are notable similarities between ECFC and quick Sepsis-related Organ Failure Assessment (qSOFA) score [18]. The qSOFA score has been extensively evaluated in predicting mortality at the onset of presentation with BSI or other infections [18–20]. To our knowledge, it has not been previously evaluated between 72 and 96 hr after onset. There is also overlap between ECFC, systemic inflammatory response criteria, and the Pitt bacteraemia score with notable differences in certain breakpoints [21]. The major difference is the absence of temperature in ECFC. This is conceivable since persistence of fever up to 3 days is relatively common in patients with acute pyelonephritis, the most common source of GN-BSI, even in the absence of serious complications [22]. Since poor clinical outcomes following GN-BSI were associated with major chronic comorbidities and inappropriate empirical antimicrobial therapy in previous studies [3–5], CCI and appropriateness of empirical therapy were not included in ECFC to avoid making the model too complex and time-consuming. If ECFC were used for stratification in future studies, adjustments for major comorbidities and appropriateness of therapy should be performed.

Various definitions for early clinical response or failure have been used in previous studies of GN-BSI based on expert opinions of investigators (Table S1) [7–14]. Interestingly, almost all previous studies included fever as a criterion. Some included microbiological persistence as a criterion for early treatment failure; however, follow-up blood cultures are not routinely recommended in GN-BSI [9,23].

ECFC have many implications for clinical practice and future research. ECFC offer healthcare providers objective criteria to determine a patient's response to antimicrobial therapy. The presence of multiple ECFC despite appropriate empirical antimicrobial therapy may prompt further diagnostic work up to optimize source control. Precise estimation of 28-day mortality based on clinical response to therapy may allow more meaningful discussion with patients' families regarding expectations of care. ECFC may also have implications in discharge planning and important treatment decisions, such as switching from intravenous to oral antimicrobial therapy and selection of personalized treatment duration. For example, patients with less than two ECFC receiving appropriate empirical antimicrobial therapy may be ideal candidates for shorter treatment durations thus reducing emergence of resistance.

After external validation, ECFC may be used as a primary end point to examine effectiveness of various empirical antimicrobial strategies in clinical studies that may not have adequate power to directly examine mortality or HLOS. Moreover, ECFC may be used to establish a new baseline in investigations evaluating definitive antimicrobial therapy after 3–4 days of GN-BSI. Prior cohort studies examining intravenous to oral switch and antimicrobial treatment duration assessed patients with GN-BSI based on acute severity of illness and other clinical variables at initial presentation [24–28]. However, it is more intuitive to evaluate or stratify patients at the time of decision-making regarding intravenous to oral switch therapy or selection of treatment duration, i.e. after 72–96 hr of GN-BSI, based on ECFC in future investigations. This concept was recently emphasized in a clinical trial examining duration of antimicrobial therapy; patients were not randomized on the first day of GN-BSI, but rather on day seven if meeting certain clinical criteria [29]. Following external validation, ECFC may be used as an evidence-based stratification tool at the time of randomization, as early as day 5, in future clinical trials.

To our knowledge, this is the first study to derive and evaluate ECFC between 72 and 96 hr after GN-BSI onset. The study shares common limitations of retrospective cohorts, including the possibility of missing variables. The study was conducted at two hospitals within the same healthcare system. Multicentre studies may provide more diverse populations and microbiology. Validation of ECFC in other geographical and healthcare settings may provide reassurance regarding the model precision. Finally, ECFC were derived in hospitalized adults with community-onset GN-BSI. Utilization of prediction scores according to baseline variables remains more applicable in ambulatory settings [5,6,18–21]. Extrapolation of results to children, hospital-onset infections, or BSI due to other bacteria is discouraged without assessment of ECFC in the respective patient population.

In summary, unfavourable outcomes, including 28-day mortality and prolonged hospitalization, can be predicted between 72 and 96 hr after GN-BSI using ECFC. These criteria may have clinical utility in the management of GN-BSI, such as assisting the drive for short versus long courses of antimicrobials. ECFC may also be used

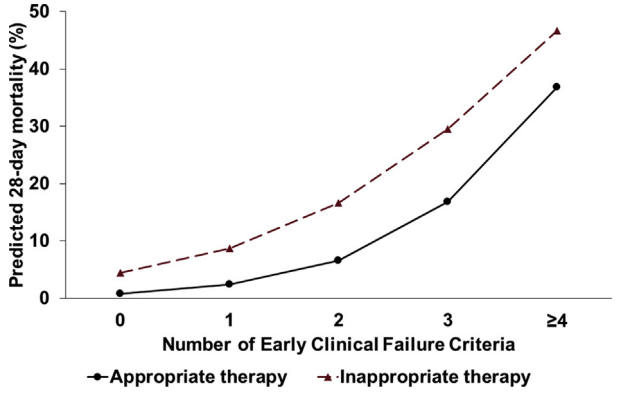

Fig. 1. Predicted risk of mortality following Gram-negative bloodstream infections using early clinical failure criteria and appropriateness of empirical therapy.

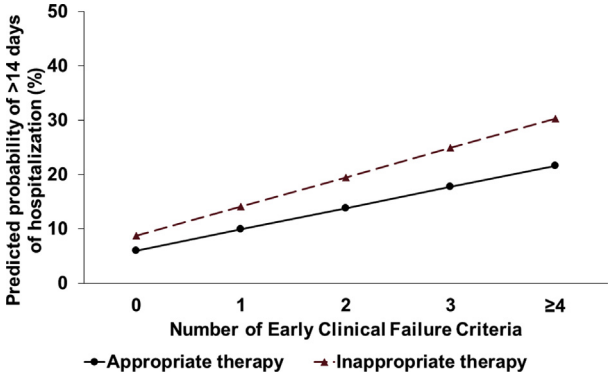

Fig. 2. Predicted risk of prolonged hospitalization following Gram-negative bloodstream infections using early clinical failure criteria and appropriateness of empirical therapy.

to improve the design of future clinical investigations examining effectiveness of empirical or definitive antimicrobial regimens for GN-BSI.

Transparency declaration

H.R. and M.N.A. have full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analysis. The study has no external source of funding. P.B.B.: Advisory board member, Melinta Therapeutics; Program content developer and speaker, FreeCE.com; Grant support, ALK Abello. M.N.A.: Continuing medical education steering committee, Rockpointe Corporation. H.R.: Speaker, ALK Abello. A.P.G., J.J., J.K.: no conflicts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.05.017.

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