Original Contribution

Predictive model of antimicrobial-resistant Gram-negative bacteremia at the ED

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Abstract

Background: Despite numerous studies identifying the risk factors related to Gram-negative antimicrobial resistance, an epidemiological model to reliably predict antimicrobial Gram-negative resistance in clinics, before the bacterial culture result is available, has not yet been developed.

Objectives: The aim of this study was to develop a predictive model to assist physicians in selecting appropriate antimicrobial agents before the details of the microbiology and drug susceptibility are known.

Materials and Methods: A prospective study was conducted between June 1, 2001, and May 31, 2002, at the emergency department (ED) of National Taiwan University Hospital. Enrollees were patients with Gram-negative bacteremia (GNB) at ED. Other information collected included demographic characteristics, underlying comorbidities, hospital exposure and health care-associated factors, and details of initial presentation. Two primary outcomes were defined, including cefazolin-resistant (CZ-RES) GNB and ceftriaxone-resistant (CTX-RES) GNB. Two thirds of the data was randomly allocated to a derivation data set (for developing predictive models), and the rest, to a validation data set (for testing model validity). Simplified models, using a coefficient-based scoring method, were also developed for clinical applications.

Results: Based on 695 episodes of GNB, predictors of CZ-RES GNB were time since last hospitalization (increased risk for durations <1 month), prior infection with a CTX-RES strain, post-transplantation immunosuppressant use, residence in a nursing home or history of stroke with repeated choking, and poor oxygen saturation (<95%) at admission to ED. Cirrhosis showed a protective effect by reducing the odds of antimicrobial-resistant GNB. The area under receiver operating characteristic (ROC) curve for the CZ-RES model was 0.76 (95% confidence interval, 0.71–0.81).

The CTX-RES model included all the variables that were in the CZ-RES model plus abnormal

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leukocyte count (<1000 or >15000 /mm³) at entry to ED. In this case, however, previous hospitalization within the last 2 weeks was a key factor. The area under this ROC curve was 0.82 (95% confidence interval, 0.76–0.88). There was lacking of difference in the area under the ROC curve between the 2 final (simplified) models either based on the derivation or validation data sets.

Conclusion: We have developed 2 models for predicting risk of antimicrobial Gram-negative infection by identifying and quantifying associated risk factors. These models could be used by physicians to determine the most appropriate choice of antibiotic for first-line therapy, particularly in situations where the culture result is not yet known.

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1. Introduction

Gram-negative bacterial infections are becoming increasingly prevalent in many populations and have, because of their association with unfavorable clinical outcomes, attracted much attention over the past decade. In particular, such infections often lead to longer hospital stays, increased attributable mortality, and greater hospitalization costs [1–5]. The identification of risk factors affecting susceptibility to antibiotic resistant Gram-negative pathogens is therefore of paramount importance.

Risk factors identified in previous studies included demographic characteristics, underlying comorbidities, and the type or pattern of medical care. Subjects who are older than 65 years have been reported as being a high-risk group [6], although few studies have corroborated this. Having hepatic failure or end-stage renal disease [7], or having had gastrointestinal (GI) surgery or an organ transplant [8–10] makes infection with an antimicrobial-resistant Gram-negative pathogen more likely. Although diabetes mellitus is more susceptible to infection, it was not associated with antimicrobial resistance in many reviews [6–16]. Hospital exposure and health care-associated factors were investigated in many studies, more specifically, long-term hemodialysis at clinics or hospital [11,12], residence in a nursing-home [12,13], history of prolonged hospital stays [8,9,14] having an indwelling catheter (such as central venous, arterial [7,13], or urinary) [7,15,16], requiring mechanical ventilation [7,15,16], and being tube-fed [10]. Previous anti-infective treatment with fluoroquinolones [8,9] and multiple antibiotic exposure lasting longer than 14 days [6,10] were also considered as risk factors.

There are 3 deficiencies in these previous findings. Firstly, most of the research was based on retrospective studies that used a slightly different definition of antibiotic resistance, making the results difficult to interpret. Secondly, with so many risk factors identified, a physician may be faced with an impossible task when trying to choose an appropriate antibiotic. Finally, as antimicrobial resistance develops through the use of antibiotics, which varies from country to country, the findings from studies carried out in the west may not be generalized to other populations.

As cases of antimicrobial-resistant Gram-negative bacterial infection differ considerably as regards host factors, the objective of this study was to use background patient information to develop a series of predictive models that could help physicians identify high-risk patients and decide which antimicrobial agent to prescribe.

2. Materials and methods

2.1. Design, setting, and enrollees

Patients with bacteremia were identified prospectively during the period June 1, 2001, through May 31, 2002, from attendees at the emergency department (ED) of National Taiwan University Hospital (NTUH) in Taipei, which has a capacity of 2400 beds and more than 100 000 ED visits annually. Note that only nontrauma adult patients (ie, >15 years old) with proven Gram-negative bacteremia (GNB) were enrolled in this study. The details of study process from initial report of bacterial growth to the identification of exposure and outcome assessment are summarized in Fig. 1. This study was approved by the institutional review board of NTUH.

Cephalosporins were extensively used to treat Gram-negative bacterial infections in Taiwan [17]. First-generation cephalosporin remains sensitive to most Gram-positive and Gram-negative pathogens. When the in vitro test shows susceptibility, they are a better choice because they are inexpensive and induce resistance less than the second- and third-generation cephalosporins [18,19]. In contrast, third-generation cephalosporin has the widest spectrum of Gram-negative activity and is preferred in most serious Gram-negative infection. Furthermore, if the pathogen is suspected of being nonfermenting, Gram-negative bacilli or extended-spectrum β -lactamase *Enterobacter* spp, a stronger antimicrobial agent, such as imipenem, will be prescribed.

2.2. Exposures assessment

To develop a predictive model for antimicrobial-resistant bacteremia, we collected information on as many of the previously identified predictors of antimicrobial-resistant Gram-negative bacterial infection as possible. Table 1 specifies 60 items of exposures, including 4 blanket terms:

Fig. 1 Flowchart of study design.

demographic characteristics, underlying comorbidities, hospital exposure and health care-associated factors, and initial presentation. Medical history and clinical presentations of all eligible patients were obtained by person-to-person interview and detail medical chart review by the stationed physician. During this evaluation stage, the physician who carried out all the questionnaire interviews and chart reviews was unaware of the details of the infection and blind to the outcome of antibiotic resistance because the final microbiology report would not have been available until 3 to 5 days after the first laboratory telephone report.

2.3. Outcome management

We set out 2 prediction models to assist physicians' in choosing antibiotics. The first model is related to the resistance to first-generation cephalosporin, defined as cefazolin-resistant (CZ-RES) GNB, and the second is pertinent to the resistance to third-generation cephalosporin

(without anti-*Pseudomonas* activity), defined as ceftriaxone-resistant (CTX-RES) GNB. Data relating to bacteremic episodes caused by *Salmonella* spp, *Aeromonas* spp, *Vibrio* spp, or *Campylobacter* spp were excluded from analysis because the clinical features, predominant risk factors, and prescribing practice with such infections were largely different from those of the most common Gram-negative infections [20-25].

2.4. Microbiological assessments and antimicrobial susceptibility

Blood from patients was stored in BACTEC standard or BACTEC PLUS culture bottles in a BACTEC 9000 system (Becton Dickinson, Cockeysville, Md) for blood culture. Identification of the isolates and susceptibility testing was performed at the central laboratory in NTUH using standard bacteriologic techniques and an automated system (VITEK, bioMerieux Inc, USA).

2.5. Statistical method for predictive models

We adapted derivation-validation method to develop predictive models. Detailed processes of the enrollment and randomization are given in Fig. 2. Continuous data were categorized by splitting into groups with appropriately chosen cut points. Univariate associations between categor-

* The number of episodes of clinically proven bacteremia was less than the sum of the numbers with gram-positive, gram-negative and anaerobic bacteremia because some episodes were poly-microbial bacteremia.

Fig. 2 Enrollment, data collection, and assignment.

Table 1 Univariate analyses of derivation data set (n = 460)

Exposure: E (+)	Total E (+)	CZ-RES			CTX-RES		
		Cases	OR	95% CI	Cases	OR	95% CI
Demographic factors							
Sex							
Male	230	74	1.5*	1.0-2.3	35	1.3	0.8-2.2
female	230	55	1.0	—	28	1.0	—
Age (y)							
≤40	53	15	1.0	—	7	1.0	—
41-64	145	35	0.8	0.4-1.6	22	1.2	0.5-2.9
65-75	128	37	1.0	0.5-2.1	14	0.8	0.3-2.1
≥75	134	42	1.2	0.6-2.3	20	1.2	0.5-2.9
Comorbidity factors							
Diabetes mellitus	139	38	1.0	0.6-1.5	18	0.9	0.5-1.6
Liver cirrhosis	48	6	0.3*	0.1-0.8	2	0.3	0.1-1.1
End-stage renal disease	11	4	1.5	0.4-5.2	2	1.4	0.3-6.7
Stroke with repeat choking history	52	27	3.2**	1.8-5.8	16	3.4**	1.8-6.6
Bedridden							
Bedridden, no bedsore	46	22	2.7**	1.5-5.1	13	3.0**	1.5-6.2
Bedridden, with bedsore	13	6	2.6	0.8-7.8	4	3.4*	1.0-11.6
Alcohol consumption	7	1	0.4	0.1-3.6	0	—	—
Long-term steroid needed	14	4	1.0	0.3-3.3	2	1.1	0.2-4.8
Hematological malignancy	25	15	4.2**	1.9-9.7	8	3.3**	1.3-7.8
Solid organ malignancy							
GI tract malignancy	62	19	1.7	0.8-3.9	11	4.1**	1.7-9.7
Non-GI tract malignancy	26	10	1.2	0.7-2.2	9	1.7	0.8-3.4
Chemotherapy	36	18	2.8**	1.4-5.6	13	2.8**	1.4-5.6
Immunosuppressant	10	4	1.7	0.5-6.3	2	1.6	0.3-7.9
Autoimmune disease	9	3	1.3	0.3-5.2	2	1.8	0.4-9.0
Health care-associated factors							
Patient source							
Community	390	91	1.0	—	42	1.0	—
Nursing home	16	10	5.5**	1.9-15.5	5	3.8*	1.3-11.4
Long-term health care needed	30	11	1.9	0.9-4.2	4	1.3	0.4-3.8
Hospitalization in last month	24	17	8.0**	3.2-19.8	12	8.3**	3.5-19.6
Time since the last discharge (d)							
<7	46	30	8.3**	4.2-16.5	21	10.9**	5.1-23.4
8-14	19	9	4.0**	1.5-10.4	6	6.0**	2.0-17.8
15-21	20	11	5.4**	2.1-13.8	1	0.7	0.1-5.4
22-30	19	8	3.2*	1.2-8.4	4	3.5*	1.1-11.6
31-45	18	4	1.3	0.4-4.0	4	3.7*	1.1-12.5
46-365	100	23	1.3	0.8-2.3	10	1.4	0.6-3.3
No hospitalization with the last year	238	44	1.0	—	17	1.0	—
Last admitted hospital							
No hospitalization with the last year	238	44	1.0	—	17	1.0	—
Admitted, not at NTUH	37	21	5.8**	2.8-12.0	12	6.2**	2.7-14.6
Admitted at NTUH	165	64	2.3**	1.5-3.6	34	2.9**	1.6-5.4
Length of last hospital stay (d)							
No hospitalization within last year	238	46	1.0	—	17	1.0	—
<7	54	22	14.1**	4.9-40.6	12	14.3**	5.3-38.4
8-15	65	22	3.4**	2.1-5.5	11	3.8**	2.0-7.3
16-30	58	23	1.1	0.5-2.3	13	1.1	0.4-3.4
>30	43	16	1.3	0.5-3.3	10	2.0	0.6-6.4
Cause of prior hospitalization							
No hospitalization with the last year	238	44	1.0	—	17	1.0	—
Infectious disease	144	60	2.7*	1.2-5.8	33	2.1*	1.2-3.8
Noninfectious disease	77	25	3.9**	2.1-7.3	13	3.2**	2.0-5.0

Table 1 (continued)

Exposure: E (+)	Total E (+)	CZ-RES			CTX-RES		
		Cases	OR	95% CI	Cases	OR	95% CI
Prior infectious sites							
None	316	69	1.0	—	30	1.0	—
Low respiratory tract	20	8	2.4	0.9-6.1	6	4.1**	1.5-11.4
Intra-abdominal	45	12	1.3	0.6-2.7	7	1.8	0.7-4.3
Urinary tract	34	12	2.0	0.9-4.1	8	2.9*	1.2-7.1
Others	26	16	5.7**	2.5-13.2	9	5.1**	2.1-12.3
Prior antibiotic exposure	166	69	2.8**	1.8-4.2	37	3.0**	1.7-5.1
Prior infection with resistant strain							
CZ-RES	25	12	2.5*	1.1-5.7	7	2.6*	1.1-6.6
CTX-RES	56	28	3.0**	1.7-5.3	17	3.4**	1.8-6.5
Vancomycin needed at OPD	20	13	5.2**	2.0-13.3	8	4.7**	1.8-11.9
Procedure at OPD							
No procedure needed at OPD	423	115	1.0	—	56	1.0	—
Chemotherapy at OPD	19	3	0.5	0.1-1.8	1	0.4	0.1-2.8
Hemodialysis	7	4	1.9	0.9-4.0	2	1.6	0.7-3.7
Others	11	7	0.6	0.1-5.8	4	1.6*	1.0-2.4
Mechanical valve	5	1	0.6	0.1-5.7	0	—	—
Arteriovenous fistula for dialysis	9	4	2.1	0.6-8.0	2	1.8	0.4-9.0
Intravascular catheter	7	5	3.1**	1.7-5.6	3	3.0**	1.5-5.9
Foley catheter	16	10	4.6**	1.6-12.8	8	7.1**	2.6-19.6
Other urinary drainage	5	3	3.9	0.7-23.7	0	—	—
Missed discharged at ED*	34	10	1.1	0.5-2.3	5	1.1	0.4-2.9
Recalling to ED	20	8	1.8	0.7-4.4	4	1.6	0.5-5.0
Initial presentations							
Fever duration							
No fever	124	36	1.0	—	20	1.0	—
0-3 d	294	77	0.9	0.5-1.4	35	0.7	0.4-1.3
>4 d	42	16	1.5	0.7-3.1	8	1.2	0.5-3.0
Systolic blood pressure (mm Hg)							
Low (≤ 90)	96	39	1.9*	1.2-3.2	21	1.8	1.0-3.4
Normal (91-140)	209	55	1.0	—	28	1.0	—
High (≥ 141)	155	35	0.8	0.5-1.3	14	0.6	0.3-1.3
Diastolic blood pressure (mm Hg)							
Low (≤ 60)	72	38	3.4**	2.0-5.7	20	2.9**	1.6-5.3
Normal (60-89)	330	82	1.0	—	39	1.0	—
High (≥ 90)	58	9	0.6*	0.3-1.2	4	0.6	0.2-1.6
Body temperature (°C)							
<35.9	31	14	2.2*	1.0-4.7	9	2.6*	1.1-6.1
36-38.2	210	58	1.0	—	29	1.0	—
38.3-39.4	154	43	1.0	0.6-1.6	20	0.9	0.5-1.7
>39.5	65	14	0.7	0.4-1.4	5	0.5	0.2-1.4
Heart rate (per min)							
≤ 59	5	1	0.6	0.1-5.8	1	1.8	0.2-17.2
60-99	140	40	1.0	—	17	1.0	—
≥ 100	315	88	1.0	0.6-1.5	45	1.0	0.7-2.2
Oxygen saturation							
SpO ₂ = 96-100%	426	118	1.0	—	57	1.0	—
SpO ₂ < 95%	34	11	1.5	1.0-2.3	6	2.4**	1.4-4.1
WBC count (10 ⁹ /L)							
≤ 1000	20	11	4.0**	1.6-10.1	8	6.7**	2.5-17.9
1001-5000	47	13	1.3	0.6-2.5	10	2.7**	1.2-6.1
5001-15 000	287	67	1.0	—	26	1.0	—
$\geq 15 001$	106	38	1.8*	1.1-3.0	19	2.2*	1.2-4.2
Neutrophil percentage of WBC							

(continued on next page)

Table 1 (continued)

Exposure: E (+)	Total E (+)	CZ-RES			CTX-RES		
		Cases	OR	95% CI	Cases	OR	95% CI
≤49	25	17	6.3**	2.3-16.9	12	6.4**	2.2-18.2
50-80	71	18	1.0	—	9	1.0	—
≥81	355	90	1.0	0.6-2.0	40	0.9	0.4-1.9
Band-form percentage of WBC							
No band-form cell	337	94	1.0	—	48	1.0	—
119%	31	7	0.8	0.3-1.8	1	0.1	0.0-1.5
≥10%	83	23	1.0	0.6-1.7	12	1.0	0.5-2.0
Hemoglobin level (g/dL)							
<10	146	51	1.6*	1.0-2.5	32	2.6**	1.5-4.5
10.1-12.9	272	68	1.0	—	27	1.0	—
>13	42	10	0.9	0.4-2.0	4	1.0	0.3-2.9
Thrombocyte count (10 ⁹ /L)							
≤99	123	40	1.4	0.9-2.2	22	1.6	0.9-2.9
100-399	320	82	1.0	—	38	1.0	—
≥400	17	7	2.0	0.8-5.5	3	1.6	0.4-5.8

OPD indicates outpatient department; WBC, white blood cell.

* $P < .05$

** $P < .01$

ical variables and the outcomes (CZ-RES and CTX-RES) were then assessed using the χ^2 test or Fisher exact test, as appropriate. If a test was significant ($P < .05$), the corresponding variable was considered to be univariately predictive of outcome. All variables showing an association with outcome ($P < .25$) were entered into the multivariate logistic regression analysis.

We used stepwise method to select the parsimonious model. Collinearity of covariates was assessed by the variance inflation factor. Receiver operating characteristic (ROC) curves were constructed for assessing predictive validity on the basis of the area under the curve (AUC) and their confidence intervals (CIs) calculated with Hanley-McNeil formula [26]. The model fitting was assessed using the Hosmer-Lemeshow goodness-of-fit test.

To make the prediction models easy to use, we simplified them to make a prediction rule [27,28] using a regression coefficient-based scoring method. With this, a simple integer-based point score was generated for each predictor by doubling the value of the corresponding β -coefficient in

the model and rounding up to the nearest integer. The overall risk score was calculated by adding the individual scores for each of the predictors together [29]. The resulting total scores were grouped to demonstrate the predictive performance of the models. All analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, NC).

3. Results

There was a total of 1346 episodes of positive bacteremia identified at the ED during the study period, of which 695 episodes were of Gram-negative infection from 659 patients, with 25 patients having repeated episodes within a year. As shown in Fig. 2, these 695 episodes were randomly allocated (in the ratio of 2:1) to the derivation and validation groups. Univariate analyses of collected variables were listed in Table 1. Of the *demographic characteristics*, there were 349 men and 310 women; average age of study population was $63.9 \pm$

Table 2 Predictors and assigned scores from the multivariate analysis of CZ-RES model

Parameter	β -Coefficient	OR	95% CI	P	Scores
Time since last discharge: within 7 d	2.1492	8.6	4.2-17.4	<.0001	4
Time since last discharge: between 8 and 30 d ^a	1.5444	4.7	2.4-9.0	<.0001	3
Immunosuppressant use	1.3610	3.9	1.0-15.1	.0488	3
Prior infection with a CTX-RES strain	0.9694	2.6	1.4-5.0	.0039	3
Residence in a nursing home or stroke with history of repeated choking	1.1062	3.0	1.6-5.7	.0006	2
Oxygen saturation <95% ^a	0.6009	1.8	1.1-3.0	.0209	1
Liver cirrhosis	-1.2143	0.2	0.1-0.6	.0043	-2

^a Nonpredictors or different assigned scores in comparing to CTX-RES model.

Table 3 Predictors and assigned scores for the CTX-RES model

Parameter	β -Coefficient	OR	95% CI	P	Scores
Time since last discharge: within 7 d	2.2256	9.3	4.3-20.1	<.0001	4
Time since last discharge: between 8 and 14 d*	1.1744	3.2	0.9-11.2	.063	2
Prior infection with a CTX-RES strain	1.2874	3.6	1.6-8.1	.0017	3
Immunosuppressant use	1.6440	5.2	0.9-28.8	.0606	3
WBC count >1000/mm ³ *	1.3278	3.9	1.8-8.8	.0008	3
Oxygen saturation <95%*	1.2155	3.4	1.7-6.6	.0004	2*
Residence in a nursing home or stroke with history of repeated choking	1.0725	2.9	1.3-6.4	.0078	2
WBC count >15 000/mm ³ *	0.7170	2.0	1.0-4.2	.0515	1
Liver cirrhosis	-1.2336	0.2	0.1-1.1	.0671	-2

* Nonpredictors or different assigned scores in comparing to CZ-RES model.

16.9 years (mean $\pm$ SD). In the univariate analysis, men were more likely to develop CZ-RES (odds Ratio [OR], 1.5; 95% CI, 1.1-2.3) compared to women, but this was not statistically significant in the multivariate regression. Some *underlying comorbidities* also showed a strong association with resistance, in particular, having a history of stroke with repeated choking or hematological malignancy. Cirrhosis of liver showed a significant inverse association with CZ-RES but not with CTX-RES in univariate analysis. Many of the hospital exposure and health care-related factors were significantly associated with elevated risk of developing resistance, the strongest indicators being time since last hospitalization and previous infection with a resistant strain. Of the initial presentations, we found that abnormal vital signs, and abnormally high or low complete blood cell and differential counts were associated with greater risk. Poor oxygen saturation was related to CTX-RES but not to CZ-RES.

Final predictors and assigned coefficient-based scores for CZ-RES model and CTX-RES model were listed in Table 2 and Table 3. The covariates for CZ-RES model were discharge from hospital within the last month, prior

infection with a CTX-RES strain, residence in a nursing home or history of stroke with repeated choking, use of immunosuppressants in transplantation patients, leucopenia [<1000 (1/mm)] or leukocytosis [$>15\,000$ (1/mm)] at first blood test, and poor oxygen saturation ($\text{SpO}_2 <95\%$). Surprisingly, after adjusting for other factors in the multivariate analysis, cirrhosis of the liver had a protective effect with regard to CZ-RES and was retained in the final model. For ease of clinical use, it was also kept in the final CTX-RES model, although it was only marginally significant there. Predictors included in the final CTX-RES model were all those already included in the CZ-RES model plus abnormal leukocyte count (<1000 or $>15\,000/\text{mm}^3$) at first blood test. Besides, shorter interval since prior hospitalization, particularly within 2 weeks, led to an increase risk for antimicrobial-resistant bacteremia. Hosmer-Lemeshow goodness-of-fit test shows a satisfactory model fitting ($P = .83$ for CZ-RES and $P = .28$ for CTX-RES).

The ROC curves for the CZ-RES and CTX-RES models were plotted in Fig. 3 and Fig. 4, respectively. For the CZ-RES models, the AUC of the primary coefficient model

The approximation of four curves indicates the proximate predictive performance of coefficient-based and score-based models, both in derivation and validation dataset.

Fig. 3 The ROC curves for assessing predictive validity of CZ-RES models.

The approximation of four curves indicates the proximate predictive performance of coefficient-based and score-based models, both in derivation and validation dataset.

Fig. 4 The ROC curves for assessing predictive validity of CTX-RES models.

Table 4 CZ-RES scoring model: predictive performance for different scores

Range of scores		-2 to 1	2-3	4-5	6-7	≥8	Total
Derivation	CZ-RES	43	33	29	22	2	129
	Subtotal	290	90	49	28	3	460
	Risk	15%	37%	59%	79%	67%	28%
Validation	CZ-RES	24	25	10	6	2	67
	Subtotal	155	46	21	10	3	235
	Risk	15%	54%	48%	60%	67%	29%

(abbreviating to coefficient derivation) was 0.76 (95% CI, 0.71-0.81). For the CTX-RES models, the AUC of the primary coefficient model (coefficient derivation) was 0.82 (95% CI, 0.76-0.88). The closeness of the 4 ROC curves (coefficient and score models applied to both the derivation and validation data sets) in both models suggests good predictive validity.

To develop the scoring models into a practical tool for clinical decision making, the optimal cut points were identified, and the predictive accuracy at these points was assessed. For the CZ-RES model, from the derivation data, we estimated this to be “score ≥ 2 ” (giving sensitivity and specificity of 67% and 75%, respectively), and from the validation set, “score ≥ 3 ” (reducing sensitivity to 60% but increasing specificity to 80%). Applying the same approach to the CTX-RES model, we found the equivalent optimal cut points to be score ≥ 3 (yielding 81% sensitivity and 65% specificity) and “score ≥ 4 ,” which yielded 63% sensitivity and 84% specificity.

To assess whether the performance of this decision tool is adequate for clinical use, we ascertained its predictive ability for a range of different scores. As shown in Tables 4 and 5, the overall proportion in the derivation and validation

sets with CZ-RES GNB was 28% and 29%, respectively. However, the results by score indicate that the proportion with resistant infection increases with score and that the decision rules, therefore, has good predictive properties. There was a slight decrease in the proportion with resistant infection in the “score ≥ 8 ” group, but this may well be due to the fact that so few were in this category. Similarly, the proportion with CTX-RES GNB in the derivation and validation data sets was 14% and 17% respectively. Again, the score ≥ 8 group was relatively small, but the resistant rate otherwise increased with score. Thus, it appears that the decision rules we developed do have sufficient predictive power to make them useful in clinical setting, that is, they are able to differentiate between the cases most likely to have resistant or nonresistant disease.

4. Discussion

In this study, we used a derivation-validation method to develop 2 decisions rules to predict antibiotic-resistant GNB in patients at ED by a simple scoring system that uses only the clinical information that is readily available

Table 5 CTX-RES scoring model: predictive performance for different scores

Range of scores		2-3	2-3	4-5	6-7	≥8	Total
Derivation	CTX-RES	7	16	15	12	13	63
	Subtotal	200	157	58	29	16	460
	Risk	4%	10%	26%	41%	81%	14%
Validation	CTX-RES	7	8	13	7	4	39
	Subtotal	120	61	33	11	10	235
	Risk	6%	13%	39%	64%	40%	17%

at the time. We tried to adhere to the standard criteria in development of prediction model [26,27]. To the best of our knowledge, it is also the first study to elucidate the association between clinical risk factors and antimicrobial resistance in Taiwan. Our prediction models appear to be useful for clinical practice by incorporating relevant risk factors.

Because GNB may ensue from inadequate antibiotic treatment, the choice of first-, second-, or third-generation antibiotic is of paramount importance, yet the decision often has to be made before the culture result is available. Physicians tend to prescribe a second generation of antibiotic for infected patients with risk factors suggestive of resistance. However, if the patient is stable clinically and the doctor is unaware of a risk factor (eg, recent hospitalization within the last month), he may be in a dilemma as to which antibiotic to prescribe. Our CZ-RES and CTX-RES models, which were derived from a large study according to respected scientific guidelines, provide a good evidence-based reference in this circumstance. Such a model would enable physicians to commence treatment earlier and therefore reduce morbidity, mortality, and the related economic costs.

Hospital exposure and health care-associated factors, as widely documented in previous literature, were also significant in our cohort. Friedman et al [11] found that patients living in nursing home had similar bloodstream infections to those in hospital settings, particularly methicillin-resistant *Staphylococcus aureus*. However, the antibiotic resistance of Gram-negative pathogens was not further analyzed in their study. From a case-control study, Schippa et al [13] reported an OR of 3.6 for ceftazidime-resistant GNB in nursing home residents, comparing to general population. In our prospective cohort, although nursing home residence was significant in univariate analysis, it lost significance after being adjusted by other covariates (OR, 1.6; 95% CI, 0.6-6.2). Similar results were found for history of stroke with repeated choking, but after dealing with the problem of collinearity of these 2 variables by selecting a composite measure, the factor turned out to be significant in final models.

Associations between initial clinical presentation and antimicrobial resistance have barely been addressed before. Leukocytopenia ($<1000/\text{mm}^3$) has long been suspected of being related to serious Gram-negative infection (such as *Pseudomonas spp.*). Besides, Jaimes et al [30] found

leukocytosis ($>12\,000/\text{mm}^3$) to be an independent predictor of positive bacteremia but did not investigate the effect on antibiotic resistance. We found that leucopenia ($<1\,000/\text{mm}^3$) and leukocytosis ($>15\,000/\text{mm}^3$) were both associated with antimicrobial-resistant GNB. Theoretically, bacteremia leads to a more severe systemic response than focal infections, but whether cephalosporin resistant pathogens have the same effect on each case is still under investigation. Poor oxygen saturation was also related to antimicrobial resistance in our study, probably because of its association with severe pneumonia. However, because the infectious focus might be unknown initially at ED, we did not take this variable (ie, final diagnosis) into account when developing our prediction rules.

Liver cirrhosis was inversely associated with cephalosporin-resistant GNB in our study, although many studies have emphasized that their outcomes are poorer in comparison to the general population. The poor outcome is perhaps due to the severity of disease rather than the infectious pathogen [31-34]. Graudal et al reported that there was no difference of bacterial strains when bacteremia occurred in cirrhotic patients versus noncirrhotic patients [35]. Because of chronic hepatitis B viral infection, liver cirrhosis is relatively common in the Chinese and Taiwanese. Our study includes a larger proportion of cirrhotic patients than would be found in western studies, which may partly explain the novel finding of inverse association. Of course, the biologic rationale should be clarified in future research.

There are several limitations to this study. Firstly, there is a lack of clinical data from patients with negative blood cultures at ED. Thus, the decision rules developed here are not applicable to all ED patients with suspected blood infection because the ED deals with more than 100 000 patients per year and our research team was unable to follow-up those whose blood cultures turned out to be negative. Secondly, we did not collect information on the antimicrobial agents prescribed by the primary care physicians at ED. If this data were available, we would have been able to compare the accuracy of our model predictions with that of clinician judgment. Thirdly, the questionnaire used to collect medical history data was constructed by the principal researchers specifically for this study, so it was never formally validated. Finally, because our samples were derived from the ED of a tertiary hospital, our results may not be representative of patients in other community hospitals. Antimicrobial resistance is an extremely complex problem worldwide. Multicenter studies may be needed in the future.

5. Conclusion

We have developed 2 models for predicting risk of antimicrobial Gram-negative infection by identifying and quantifying associated risk factors. These models could be

used by physicians to determine the most appropriate choice of antibiotic for first-line therapy, particularly in situations where the culture result is not yet known.

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