Development and Validation of a Risk Scoring System for Cephamycin-Associated Haemorrhagic Events

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Background

Cephamycin-associated hemorrhages have been reported since their launch. This study aims to define the risk factors for cephamycin-associated hemorrhages using NTU Hospital (NTUH) electronic medical record, and to establish a risk scoring system that can be easily adapted in clinical settings in order to efficiently enhance the patient care quality.

Methods

Adults inpatients who consecutively used study antibiotics for more than 48 hours at NTUH during January 1st, 2009 to December 31st, 2015 were included. The population was divided into two cohorts for evaluation of risk factors and validation of the scoring system. Multi-variate logistic regression was used for the assessment of the adjusted association between factors and the outcome of interest. Results were treated as the foundation to develop the risk scoring system. Model performance comprised the area under the receivers operating curve (AUROC) for discrimination assessment and Hosmer-Lemeshow goodness-of-fit test for calibration purpose. Finally, Cochran-Armitage trend test was used to evaluate if the score and outcome occurrence were positively correlated.

Results

There were 46402 and 22681 episodes identified in the year 2009-2013 and 2014-2015 cohorts with 356 and 204 hemorrhagic events among respective cohorts (Table 1). Use of cephamycins was associated with an increased risk for hemorrhagic outcomes (aOR 2.03, 95% CI 1.60-2.58). Other risk factors included chronic hepatic disease, at least 65 years old, prominent bleeding tendency, and bleeding history.

Table 1. Patient characteristics of study antibiotics users

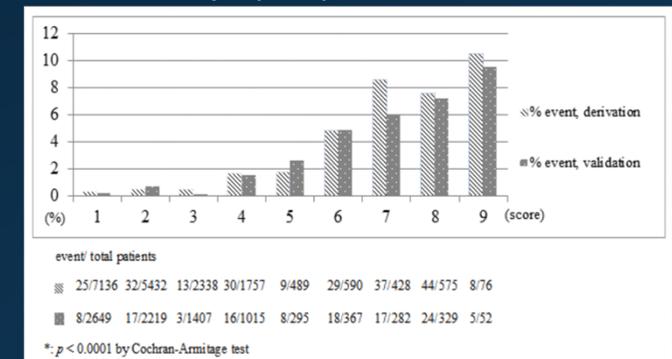| Variable	Derivation Model		Validation Model	
	Cephamycin n=18821 (%)	Reference n=27581 (%)	Cephamycin n=8615 (%)	Reference n=14066 (%)
Male	9495 (50.45)*	15987 (57.96)	4491 (52.13)*	7995 (56.84)
Age (range), years	61.5 (49.7-73.8)*	64.7 (50.9-78.1)	63.2 (52.1-74.9)*	64.8 (52.3-78.2)
Comorbidity				
Chronic hepatic disease	1488 (7.91)*	1307 (4.74)	874 (10.15)*	895 (6.36)
Chronic renal disease	793 (4.21)*	1661 (6.02)	428 (4.97)*	1071 (7.61)
Coagulopathy	7 (0.04)	17 (0.06)	2 (0.02)	13 (0.09)
Operation hx[b]	2262 (12.02)*	2825 (10.24)	1009 (11.71)*	1408 (10.01)
Prolonged INR[c]	243 (1.29)*	294 (1.07)	199 (2.31)	351 (2.5)
Hemorrhaged[d]	2081 (11.06)*	2326 (8.43)	1265 (14.68)*	1585 (11.27)
Thrombocytopenia	642 (3.41)	1021 (3.70)	498 (5.78)	830 (5.9)
Liver dysfunction	1032 (5.48)*	604 (2.19)	1212 (14.07)*	798 (5.67)
Renal dysfunction	654 (3.47)*	1430 (5.18)	802 (9.31)*	1881 (13.37)
Concurrent medications[d]				
Antiplatelets	768 (4.08)*	2991 (10.84)	295 (3.42)*	1300 (9.24)
Anticoagulants	427 (2.27)*	1581 (5.73)	258 (2.99)*	772 (5.49)
Vitamin K_1	346 (1.84)*	320 (1.16)	99 (1.15)	137 (0.97)
TPN	1973 (10.48)*	582 (2.11)	675 (7.84)*	232 (1.65)

[a]Median (IQR); [b]within previous 30 days; [c]within previous 7 days; [d]within previous 180 days prior to index date; *p-value<0.05 compared with reference antibiotics.

A nine-score risk scoring system (AUROC=0.8035, 95% CI 0.7794-0.8275, Hosmer-Lemeshow goodness-of-fit test p=0.1044 in the derivation group; AUROC=0.7550, 95% CI 0.7198-0.7902, Hosmer-Lemeshow goodness-of-fit test p=0.0641 in the validation group) was developed based on the identified risk factors (Table 2). An increasing trend of the events as the risk score increased was observed in both cohorts (figure 1). The Cochran-Armitage trend tests also showed significant results (p < 0.0001).

Table 2. Details of the risk scoring system

Risk score	Predictor 1	Predictor 2	Predictor 3
	Study antibiotics	Chronic hepatic dz	Age (years)
0	Reference	No	< 65
1	Cephamycin	Yes	≥ 65
	Bleeding tendency		
0	No		
2	Yes		
	History of bleeding		
0	No		
4	Yes		

Figure 1. Increasing risk of bleeding events with higher risk score among cephamycin users

event/ total patients

\ 25/7136 32/5432 13/2338 30/1757 9/489 29/590 37/428 44/575 8/76

▦ 8/2649 17/2219 3/1407 16/1015 8/295 18/367 17/282 24/329 5/52

*: p < 0.0001 by Cochran-Armitage test

Conclusions

Cephamycins was associated with more hemorrhagic events compared with commonly used penicillins and cephalosporins. The established scoring system may help clinicians identify high-risk patients and modify antibiotic regimen according to the predictive risk, and eventually enhance the overall quality of care.