Development of Risk Score to Guide Therapy for Carbapenem-Resistant Pathogens

Andrew J. Vogler, PharmD;[1,2] Kathleen A. Fairman, MA, PhD;[1] Nikki Mai, PharmD, BCIDP;[2] Chad M. VanDenBerg, PharmD, MS, BCPP;[3] Vanthida Huang, PharmD, BSPHM, FCCP[1,2]

[1]Midwestern University College of Pharmacy-Glendale Campus, Glendale, AZ; [2]HonorHealth John C. Lincoln Medical Center, Phoenix, AZ; [3]Midwestern University Clinical Research Services, Glendale AZ

avogle@midwestern.edu
@avogue22

BACKGROUND

Carbapenem resistance is a major concern of the World Health Organization (WHO) and Centers for Disease Control (CDC).[1,2] The mortality of carbapenem-resistant infection ranges from 26-44%.[3-5] Delays in appropriate antibiotic therapy can lead to increased mortality and longer hospital stay.[6] Studies have identified several risk factors associated with carbapenem resistance including mechanical ventilation, indwelling devices, recent invasive surgery, severity of illness, recent hospitalization, and prior antibiotic exposure.[5,7,8] However, most of these studies include Enterobacterales and not *Acinetobacter baumannii* or *Pseudomonas aeruginosa*. Therefore, we aimed to identify risk factors associated with carbapenem resistance to all pathogen types and develop a risk scoring tool.

METHODS

Study Design: Observational, nested, case-control study of hospitalized patients with culture-confirmed Gram-negative (GN) organisms with carbapenem susceptibilities to either meropenem or imipenem from January 1, 12016-January 1, 2022.

Case	Control
• Carbapenem-**Resistant** GN cohort (n=1,020)	• Carbapenem-**Susceptible** GN cohort (n=51,157)

Only first occurrence monomicrobial cultures were included. Duplicate cultures with the same organisms obtained from any sources of infection at any subsequent time from the same patient, regardless of susceptibility or phenotypic profile were excluded.

Patient Characteristics Analyzed:
- Patient demographics (age, gender, race, and comorbidities)
- APACHE-II Score
- Admission location (emergency department (ED), intensive care unit (ICU), etc.)
- Number of admissions in the past year
- Arrival from outside facility
- Previous antibiotic use in the past 90 days
- Invasive surgery/procedure in the past 90 days
- Mechanical ventilation in the past 90 days
- Infection characteristics (sources, pathogens, community vs. nosocomial)

Statistical Analysis: Using accumulated data and logistic regression backwards-stepwise analysis, a scoring tool was created with c-statistic validation performed on randomize equal-sized subsample.

RESULTS

Table 1: Baseline Demographics (N=52,177)

	Case (n=1,020)	Control (n=51,157)	Control, Subsample (n=1,020)	P-Value
Mean Age (years)	61.9	61.3	61.2	0.29
• Age 46-79 years	[78%]	[64.4%]	[63.6%]	<0.01
Male	57.0%	28.9%	28.7%	<0.01
Caucasian	84.4%	89.0%	90.1%	<0.01
Other Races	15.6%	11%	9.9%	<0.01
APACHE-II (mean)	21.6	8.7	8.69	<0.01
• Score ≥15	[43.4%]	[10.0%]	[11.8%]	<0.01
Comorbidities				
Cancer	8.9%	8.2%	9.2%	0.81
Cardiovascular disease	34.1%	26.6%	24.0%	<0.01
Diabetes	32.4%	24.4%	24.3%	<0.01
Immunosuppression	3.3%	1.5%	1.4%	<0.01
Chronic liver disease	4.4%	1.5%	1.8%	<0.01
Chronic renal disease	25.9%	18.2%	16.4%	<0.01
Respiratory disease	31.8%	21.0%	17.8%	<0.01
Admissions Location				
ED	5.2%	32.6%	33.5%	<0.01
General unit	58.7%	59.5%	58.5%	0.93
ICU	36.1%	7.9%	7.9%	<0.01

Table 2: Infection Characteristics (N=52,177)

	Case (n=1,020)	Control (n=51,157)	Control, Subsample (n=1,020)	P-Value
Nosocomial	34.7%	8.3%	8.4%	<0.01
Sources of Infection				
Urine	29.0%	78.0%	78.8%	<0.01
Blood	6.7%	8.2%	7.3%	0.60
Skin	14.4%	7.1%	6.9%	<0.01
Respiratory	47.1%	4.3%	4.6%	<0.01
Other	3.2%	2.4%	2.5%	0.34
Pathogen				
Acinetobacter baumannii	18.9%	0.5%	0.4%	<0.01
Enterobacterales	14.5%	91.1%	92.3%	<0.01
Pseudomonas aeruginosa	66.6%	8.4%	7.4%	<0.01

RESULTS

Table 3: Carbapenem-Resistance Risk Factors

	Case (n=1,020)	Control (n=51,157)	Control, Subsample (n=1,020)	P-Value
>1 Prior admission	61.7%	33.0%	33.9%	<0.01
Outside facility	9.2%	2.7%	2.6%	<0.01
Prior antibiotic use	88.2%	37.6%	39.5%	<0.01
Prior invasive procedure	50.1%	10.7%	11.0%	<0.01
Prior surgery	16.6%	16.9%	17.6%	0.54
Prior ventilation	7.0%	1.7%	1.6%	<0.01

Two scoring tools were created, utilizing risk factors with and without identified pathogen (c-statistic, 0.879 vs. 0.941).

SCORING TOOL

Patients are evaluated using below risk factors, given a score of 1 or 0 based on whether risk factors are present or missing. Risk scoring equation(s) are then utilized to determine the risk for carbapenem resistance. Each risk factor is individually weighted to determine a score (range 0-1). Scores >0.5 are considered to have a high probability (>90%) of carbapenem-resistance. Two separate risk scoring equations were used; one with and without pathogen identification available.

Without Pathogen	**With Pathogen**
• Age 46-79 years • Male • Prior admission • Prior invasive procedure • Prior antibiotic use • Admission location (ED or ICU) • APACHE II score • Chronic diseases • Cardiovascular • Liver • Renal • Respiratory • Site of infection • Respiratory • Urine • Nosocomial infection	• Prior admission • Prior invasive procedure • Prior antibiotic use • ICU admission • Chronic diseases • Immunosuppression • Renal • Respiratory • Respiratory infections • Nosocomial infections • Pathogens • *A. baumannii* • *P. aeruginosa*

CONCLUSION

Utilizing obtainable risk factors, a straightforward scoring tool can be created and used to predict carbapenem resistance and guide treatment decisions. Further validation of the scoring tool is warranted.

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-327
2. Centers for Disease Control and Prevention (U.S.). Antibiotic resistance threats in the United States, 2019. Centers for Disease Control and Prevention (U.S.); 2019.
3. Soontaros S, Leelakanok N. Association between carbapenem-resistant Enterobacteriaceae and death: A systematic review and meta-analysis. Am J Infect Control. 2019;47(10):1200-1212
4. Wilson GM, Suda KJ, Fitzpatrick MA, et al. Risk factors associated with carbapenemase-producing carbapenem-resistant Enterobacteriaceae positive cultures in a cohort of US veterans. Clin Infect Dis. 2021;73(8):1370-1378.
5. Zhou R, Fang X, Zhang J, et al. Impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae: a systematic review and meta-analysis. BMJ Open. 2021;11(12):e054971.
6. Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest. 1999;115(2):462-474.
7. Ferrer R, Soriano A, Cantón R, et al. A systematic review and expert's analysis of risk factors of infections in adults due to carbapenem-resistant Pseudomonas aeruginosa or Acinetobacter baumannii in Spain. Rev Esp Quimioter. 2021;34(4):298-307.
8. Bar-Yoseph H, Cohen N, Korytny A, et al. Risk factors for mortality among carbapenem-resistant Enterobacteriaceae carriers with focus on immunosuppression. J Infect. 2019;78(2):101-105.