Comparison of clinical outcomes of patients infected with KPC- and NDM-producing Enterobacterales: a retrospective cohort study

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Abstract

Objectives: We aimed to compare clinical outcomes of patients with *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacterales and those with New-Delhi-Metallo-beta-lactamase (NDM)-producing Enterobacterales.

Methods: We performed a retrospective cohort study of all adult patients with KPC- or NDM-producing Enterobacterales isolates in a 2700-bed tertiary referral hospital in Seoul, South Korea between 2010 and 2019. The primary outcome was 30-day mortality after first isolation of KPC- or NDM-producing Enterobacterales. The secondary outcome was the development of infection within 30 days by the colonizing isolates, among colonized patients. We performed Cox regression analysis for 30-day mortality and competing risk analysis for development of infection.

Results: A total of 859 patients were identified during the study period; 475 (55%) had KPC and 384 (45%) had NDM. Thirty-day mortality was significantly higher in the KPC group compared with the NDM group (17% [81/475] vs 9% [33/384]; *P*<0.001). The KPC group developed infection within 30 days from the initial colonization after first isolation more frequently than the NDM group (8% [27/353] vs. 3% [10/295]; *P*=0.02). Multivariable analysis revealed that independent risk factors for 30-day mortality were solid cancer (adjusted hazard ratio [aHR], 2.51; 95% confidence interval [CI], 1.66–3.79 ; *P*<0.001), solid organ transplant (aHR, 0.32; 95% CI, 0.17–0.61, *P*<0.001), a high APACHE II score (aHR, 1.11; 95% CI, 1.08–1.13, *P*<0.001), KPC-producing Enterobacterales (aHR, 1.69; 95% CI, 1.02–2.79, *P*=0.04), previous carbapenem use within 3 months (aHR 1.86; 95% CI, 1.26–2.75, *P*<0.001) and site of KPC- or NDM-producing Enterobacterales infection at the time of the first culture (*P*<0.001).

Conclusions: Our study suggests that KPC-producing Enterobacterales is significantly associated with poorer outcomes compared with NDM-producing Enterobacterales.

Background

There is no data regarding whether the clinical outcomes differ according to the type of carbapenemase in patients with CPE isolates. This study aims to compare the outcomes between KPC and NDM-producing Enterobacterales and to identify the risk factors for development of infection and 30-day mortality after first isolation of KPC or NDM-producing Enterobacterales.

Methods

- This retrospective observational study was performed at the Asan Medical Center, a 2700-bed tertiary referral center in Seoul, South Korea, between January 2010 and December 2019.
- All patients (≥16 years old) with CPE-positive clinical or surveillance cultures were identified.
- Only the first positive culture with CPE was included.
- All patients who shared a room with CPE-positive patients underwent surveillance cultures for CPE.
- Active surveillance for CPE was performed when an outbreak was confirmed.

Results

Table 1. Characteristics of patients with carbapenemase-producing Enterobacterales isolates at the time of first isolation according to carbapenemase type

	KPC (n = 475)	NDM (n = 384)	*P* value
Age (y), median (IQR)	62 (54-72)	62 (54-71)	0.38
Male sex	338 (71)	255 (66)	0.13
Site of acquisition			
Community-acquired acquisition	7 (2)	7 (2)	0.69
Nosocomial acquisition	386 (81)	327 (85)	0.13
Healthcare-associated acquisition	82 (17)	50 (13)	0.09
McCabe and Jackson classification			0.69
Nonfatal	36 (8)	47 (12)	
Ultimately fatal	385 (81)	281 (73)	
Rapidly fatal	54 (11)	56 (15)	
Charlson comorbidity index, median (IQR)	6 (4-8)	5 (3-6)	< 0.001
Pre-existing medical condition			
Previous surgery within 6 months	253 (53)	191 (50)	0.30
Diabetes mellitus	160 (34)	119 (31)	0.40
Liver cirrhosis	196 (41)	110 (29)	< 0.001
Chronic kidney disease	144 (30)	72 (19)	< 0.001
Congestive heart failure	56 (12)	70 (18)	0.01
Immunosuppressant use	239 (50)	123 (32)	< 0.001
Solid cancer	214 (45)	138 (36)	0.01
Chemotherapy within 6 months	77 (16)	52 (14)	0.28
Solid organ transplant	154 (32)	70 (18)	< 0.001
Haematologic malignancy	44 (9)	50 (13)	0.08
Neutropenia	19 (4)	35 (9)	0.002
APACHE II score, median (IQR)	11 (8-17)	10 (7-14)	< 0.001
Septic shock at time of first isolation	46 (10)	21 (6)	0.02
Indwelling device	390 (82)	289 (75)	0.01
Previous antibiotics within 3 months	464 (98)	345 (90)	< 0.001
Previous carbapenem use within 3 months	183 (39)	109 (28)	0.002
Initial CPE-positive specimen			
Stool	276 (58)	223 (58)	0.99
Urine	72 (15)	55 (14)	0.73
Sputum	56 (12)	16 (4)	< 0.001
Blood	28 (6)	34 (9)	0.10
Bile	24 (5)	17 (4)	0.67
Other	39 (8)	37 (10)	0.47
Organism			
Klebsiella pneumoniae	439 (92)	101 (26)	< 0.001
Escherichia coli	32 (7)	67 (17)	< 0.001
Enterobacter cloacae	3 (1)	89 (23)	< 0.001
Initial presentation			0.40
Colonization	353 (74)	295 (77)	
Infection	122 (26)	89 (23)	
Site of infection			
Bloodstream infection	28 (23)	36 (40)	0.01
Urinary tract infection	23 (19)	18 (20)	0.80
Pneumonia	35 (29)	5 (6)	< 0.001
Abdominal infection	31 (25)	27 (30)	0.43
Other[c]	5 (4)	3 (3)	> 0.99
No. of patients who developed infection within 30 days from colonization	27/353 (8)	10/295 (3)	0.02
30-day mortality from initial positive culture	81 (17)	33 (9)	< 0.001
No. of patients with KPC or NDM-producin Enterobacterales infection within 30 days from first isolation	149 (31)	99 (26)	0.07
Appropriate treatment within 3 days	45/149 (30)	32/99 (32)	0.72
30-day mortality from onset of infection	50/149 (34)	17/99 (17)	0.004

Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

Table 2. Risk factors for 30-day mortality from the initial positive culture date in patients with KPC- or NDM- producing Enterobacterales (n = 859)

Model 1

	Univariate analysis		Multivariable analysis	
Risk factor	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age	1.03 (1.01–1.04)	< 0.001	1.00 (0.98–1.01)	0.66
Chronic kidney disease	1.50 (1.01–2.23)	0.04	1.40 (0.90–2.19)	0.14
Solid cancer	1.75 (1.21–2.53)	< 0.001	2.51 (1.66–3.79)	< 0.001
Solid organ transplantation	0.32 (0.17–0.58)	< 0.001	0.32 (0.17–0.61)	< 0.001
APACHE II score	1.12 (1.09–1.14)	< 0.001	1.11 (1.08–1.13)	< 0.001
KPC-producing Enterobacterales	2.06 (1.38–3.10)	< 0.001	1.69 (1.02–2.79)	0.04
Previous carbapenem use	2.36 (1.63–3.41)	< 0.001	1.86 (1.26–2.75)	< 0.001
Indwelling device	1.66 (0.98–2.81)	0.06	1.09 (0.62–1.91)	0.76
Site of infection at the time of the first culture				
Colonization at baseline	(reference)		(reference)	< 0.001
Bloodstream infection	4.24 (2.55–7.07)	< 0.001	2.95 (1.67–5.20)	< 0.001
Urinary tract infection	3.07 (1.56–6.01)	< 0.001	2.48 (1.22–5.04)	0.01
Pneumonia	7.95 (4.76–13.25)	< 0.001	3.50 (1.97–6.21)	< 0.001
Abdominal infection	1.01 (0.40–2.52)	0.99	0.58 (0.22–1.49)	0.25
Other	2.87 (0.70–11.75)	0.14	1.25 (0.29–5.42)	0.76
Year of first isolation				
2010/2011	(reference)		(reference)	
2012	0.91 (0.15–5.47)	0.92	1.96 (0.28–13.59)	0.49
2013	0.90 (0.17–4.64)	0.90	1.37 (0.23–8.21)	0.73
2014	0.55 (0.08–3.93)	0.55	0.64 (0.08–5.20)	0.68
2015	0.74 (0.14–3.80)	0.71	0.47 (0.08–2.72)	0.40
2016	1.05 (0.23–4.68)	0.95	0.85 (0.16–4.53)	0.85
2017	0.66 (0.14–3.09)	0.59	0.52 (0.09–2.89)	0.45
2018	0.75 (0.18–3.15)	0.69	0.92 (0.18–4.66)	0.92
2019	0.56 (0.14–2.32)	0.43	0.67 (0.13–3.36)	0.62

Model 2

	Univariate analysis		Multivariable analysis	
Risk factor	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age	1.03 (1.01–1.04)	< 0.001	1.00 (0.98–1.01)	0.56
Chronic kidney disease	1.50 (1.01–2.23)	0.04	1.46 (0.93–2.30)	0.10
Solid cancer	1.75 (1.21–2.53)	< 0.001	2.57 (1.70–3.89)	< 0.001
Solid organ transplantation	0.32 (0.17–0.58)	< 0.001	0.32 (0.17–0.63)	< 0.001
APACHE II score	1.12 (1.09–1.14)	< 0.001	1.11 (1.08–1.13)	< 0.001
Carbapenemase-producing organism				
NDM-producing Enterobacterales other than *K. pneumoniae*	(reference)		(reference)	
NDM-producing *K. pneumoniae*	2.43 (1.22–4.82)	0.01	2.45 (1.11–5.41)	0.03
KPC-producing Enterobacterales other than *K. pneumoniae*	5.07 (2.34–10.99)	< 0.001	2.42 (0.97–6.01)	0.06
KPC-producing *K. pneumoniae*	2.65 (1.58–4.45)	< 0.001	2.19 (1.21–3.95)	0.01
Previous carbapenem use	2.36 (1.63–3.41)	< 0.001	1.85 (1.25–2.73)	< 0.001
Indwelling device	1.66 (0.98–2.81)	0.06	1.17 (0.66–2.04)	0.59
Site of infection at the time of the first culture				
Colonization at baseline	(reference)		(reference)	< 0.001
Bloodstream infection	4.24 (2.55–7.07)	< 0.001	3.09 (1.75–5.46)	< 0.001
Urinary tract infection	3.07 (1.56–6.01)	< 0.001	2.42 (1.19–4.93)	0.01
Pneumonia	7.95 (4.76–13.25)	< 0.001	3.38 (1.89–6.05)	< 0.001
Abdominal infection	1.01 (0.40–2.52)	0.99	0.59 (0.23–1.52)	0.28
Other	2.87 (0.70–11.75)	0.14	1.13 (0.25–5.09)	0.87
Year of first isolation				
2010/2011	(reference)		(reference)	
2012	0.91 (0.15–5.47)	0.92	2.31 (0.33–16.28)	0.40
2013	0.90 (0.17–4.64)	0.90	2.14 (0.35–13.25)	0.41
2014	0.55 (0.08–3.93)	0.55	1.38 (0.15–12.36)	0.77
2015	0.74 (0.14–3.80)	0.71	0.98 (0.15–6.40)	0.99
2016	1.05 (0.23–4.68)	0.95	1.47 (0.26–8.21)	0.66
2017	0.66 (0.14–3.09)	0.59	0.93 (0.16–5.50)	0.94
2018	0.75 (0.18–3.15)	0.69	1.61 (0.30–8.75)	0.58
2019	0.56 (0.14–2.32)	0.43	1.20 (0.22–6.44)	0.83

Table 3. Risk factors for development of infection in patients with KPC- or NDM-producing Enterobacterales isolates within 30 days from initial colonization (n = 648)

	Univariate analysis		Multivariable analysis	
Risk factor	HR (95% CI)[a]	*P* value	Adjusted HR (95% CI)[b]	*P* value
Male sex	1.76 (1.04–2.95)	0.03	1.46 (0.86–2.48)	0.16
Charlson comorbidity index	1.16 (1.07–1.24)	< 0.001	1.10 (1.01–1.20)	0.03
Chronic kidney disease	1.53 (0.98–2.40)	0.06	1.09 (0.67–1.78)	0.72
Liver cirrhosis	2.06 (1.34–3.17)	< 0.001	1.59 (1.01–2.50)	0.047
Indwelling device	1.82 (1.01–3.28)	0.048	1.65 (0.91–3.00)	0.10
KPC-producing Enterobacterales	2.01 (1.27–3.19)	< 0.001	1.45 (0.90–2.32)	0.12
Previous antibiotics within 3 months	6.85 (0.95–49.09)	0.06	4.24 (0.58–30.93	0.15
Previous carbapenem use within 3 months	1.76 (1.14–2.69)	0.01	1.48 (0.96–2.29)	0.07

[a] HRs were obtained using the Fine and Gray proportional sub-distribution hazard model

[b] Significant univariate variables in the Fine and Gray proportional sub-distribution hazard model were included in the competing risk analysis. APACHE II score was excluded because it did not satisfy the proportional hazards assumption. We used male sex, Charlson comorbidity index, chronic kidney disease, liver cirrhosis, indwelling device, KPC-producing Enterobacterales, previous antibiotics within 3 months, and previous carbapenem use within 3 months in the competing risk analysis.

Figure A. Kaplan–Meier survival estimates of 30-day mortality from initial positive culture in patients with KPC- or NDM-producing Enterobacterales stratified by APACHE II score (log-rank test).

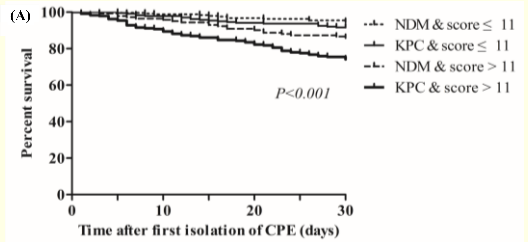
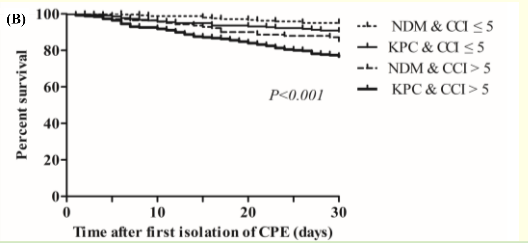


Figure B. Kaplan–Meier survival estimates of 30-day mortality from initial positive culture in patients with KPC- or NDM-producing Enterobacterales stratified by Charlson comorbidity index (log-rank test).



Conclusions

Our study suggests that KPC-producing Enterobacterales is significantly associated with poorer outcomes compared with NDM-producing Enterobacterales.