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Letter to the Editors – Brief papers about basic research or clinical experiences

Kidney transplant recipients infected with blaKPC-2-producing *Klebsiella pneumoniae*

Pacientes trasplantados renales con infección por *Klebsiella pneumoniae* productora de blaKPC-2

Dear Editor:

Gram-negative enterobacteria resistant to carbapenem pose a problem, as this antibiotic is usually used for infections caused by Enterobacteriaceae producing extended spectrum β-lactamases.[1] *Klebsiella pneumoniae* carbapenemase (KPC) enzymes are the most common class A carbapenemases.[2] We have reported the first cases of blaKPC-2-producing *K. pneumoniae* (KPC-Kp) in kidney transplant patients in our center.[3] We describe the treatment and outcomes of 13 new patients.

This retrospective cohort study was conducted at Hospital Alemán, Buenos Aires, Argentina. In the study period (1/2011–8/2013), 93 renal transplants were performed. Disk diffusion antimicrobial susceptibility tests were performed according to the Clinical and Laboratory Standards Institute guidelines. KPC was screened with double-disk diffusion synergy tests; a disk containing 300-μg phenyl boronic acid and a disk containing 10-μg imipenem, 10-μg meropenem, or 10-μg ertapenem. The modified phenotypic Hodge test was performed for isolates exhibiting reduced susceptibility to imipenem or meropenem on the disk diffusion test. blaKPC-2 was confirmed by PCR with primers KPC-F (5′-ATGTCACTGTATCGCCGTCT-3′) and KPC-R (5′-TTTTCAGAGCCTTACTGCCC-3′), heat-extracted DNA as template. Molecular typing was performed using pulsed-field gel electrophoresis, XbaI restriction enzyme; with strain sequence type 258 clone as reference. Tested antibiotics: ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, cephalothin, piperacillin/tazobactam, cefotaxime, ceftazidime, imipenem, meropenem, ertapenem, gentamicin, amikacin, ciprofloxacin, doxycycline, trimethoprim/sulfamethoxazole, nitrofurantoin, and fosfomycin. Tigecycline susceptibility was tested by disk diffusion (susceptible ≥19 mm, intermediate 15–18 mm, and resistant ≤14 mm). The isolates intermediate or resistant on disk testing were confirmed using MIC plates. Polymyxin B susceptibility was determined with Etest® (bioMérieux, Marcy l'Etoile).

Twenty-five KPC-Kp infectious episodes were documented in 13 renal transplant recipients. Mean age was 55.84 ± 13.84 years, 9 (62%) patients were female, and the most frequent primary kidney diseases were diabetes, polycystic kidney disease. All patients received antibiotic prophylactic therapy and induction therapy; 12/13 (92.3%) with thymoglobulin and 1/13 with basiliximab. Nine (69%) patients had been in the intensive care unit (ICU) within 30 days before their first infection, median time of stay was 4 days (0–66 days). Six (46%) patients showed surgical complications, 10/13 (77%) patients had delayed graft function, 9/13 (69%) patients had a central venous catheter and 8/13 (61%) had a urinary catheter for ≥5 days within 3 months before infection. The median time between transplant and the first infection was 79 (8–902) days. Six (46%) patients had more than two infections, totaling 25 infectious episodes (Table 1).

In all episodes, the site of infection was the urinary tract and some antibiotic had been administered within 30 days before diagnosis; however, in 10/25 (40%) episodes, the blood culture showed positive results. The most frequent antibiotics in which bacteria were susceptible were fosfomycin (68%), tigecycline (56%), and colistin (28%). In 1 case, the organism was not susceptible to any tested antibiotic, and in 3/25 (12%) cases, it was susceptible to one drug. Monotherapy was used in 9/25 (36%) episodes; two drugs were used in 10/25 (40%), three in 5/25 (20%), and four in 1/25 (4%) episodes. Table 2 shows the antibiotics used. Tigecycline, alone or combined, resulted in an unsuccessful outcome. The median treatment time was 21 (14–56) days. Four (31%) patients died as a result of infection.

Discussion: Transplant recipients share risk factors for infections with resistant bacteria.[4] In a report describing an outbreak of KPC-Kp in transplant patients, infection rates were 17%, 13%, and 26% in heart, liver, and kidney transplant recipients, respectively.[5] In our cases, the infection rate was 16% and strain sequence type 258.

The best treatment for KPC has not been established, and we could not identify a successful treatment. Before

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Table 1 – Patientsćharacteristics and outcomes.

Patient	Age, year	Sex	Base disease	Days between transplant and first infection	Agent used in induction therapy	Days in ICU (last 3 months prior to first infection)	Positive blood culture	Central venous catheter	Urinary catheter for ≥5 days	DGF	Complication	Number of infection episodes	Outcome
1	48	Male	Polycistic kidney disease	660	Thymoglobulin	0	No	No	No	Yes	None	1	Successful
2	46	Female	Unknown	902	Thymoglobulin	0	No	No	No	Yes	None	2	Successful
3	69	Female	Diabetes	295	Thymoglobulin	0	Yes	Yes	Yes	No	None	4	Successful
4	67	Female	Nephroangioscloris	127	Thymoglobulin	0	No	No	Yes	No	None	1	Successful
5	62	Male	Diabetes	21	Thymoglobulin	10	Yes	Yes	Yes	Yes	Urinary fistula	4	Successful
6	51	Female	Polycistic kidney disease	79	Thymoglobulin	10	Yes	Yes	Yes	Yes	Fistula and peritonitis	1	Died
7	50	Female	Unknown	20	Thymoglobulin	4	No	Yes	Yes	Yes	Fluid collection	1	Died
8	74	Male	Amyloidosis	22	Thymoglobulin	4	No	Yes	Yes	Yes	Urinary fistula	3	Successful
9	66	Male	Nephroangioesclorosis	66	Thymoglobulin	24	Yes	Yes	No	Yes	None	1	Died
10	68	Female	Diabetes	8	Basiliximab	7	No	Yes	Yes	Yes	Wound dehiscence	3	Successful
11	33	Female	Unknown	28	Thymoglobulin	4	No	Yes	No	No	None	2	Successful
12	31	Female	Systemic lupus erythematosus	100	Thymoglobulin	10	Yes	No	No	Yes	Hematoma	1	Successful
13	61	Female	Nephroangiosclorosis	626	Thymoglobulin	66	Yes	Yes	Yes	Yes	None	1	Died

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Table 2 – Infection episodes, susceptibility patterns, treatments and outcomes.

Patient	Infection episode	Colonization before infection	Time from transplant to infection	Susceptibility profile	Treatment	CST MIC (mg/l)	MEM MIC (mg/l)	Duration of treatment (days)	Time from isolation to drug administration (days)	Outcome
1	15	Yes	660	FOS TIG	FOS	32.0		21	3	Reinfection
2	16	No	902	FOS TIG CST	FOS	0.5		21	3	Reinfection
	17		949	FOS TIG AMK DOX	FOS DOX	16.0		21	0	Reinfection
3	18	Yes	295	TIG FOS CST	TIG FOS	0.25		14	3	Reinfection
	19		389	FOS DOX CST	DOX	0.12		14	8	Reinfection
	20		437	DOX FOS TIG CST	DOX	0.25	8	21	0	Reinfection
	21		522	DOX FOS CST	FOS DOX	0.25	2	21	0	Successful
4	22	No	127	FOS CST	FOS CST	0.25		15	3	Successful
5	23	Yes	21	FOS TIG CST	TIG CST	1.0		20	0	Reinfection
	24		57	TIG	FOS TIG CST	32.0		18	0	Reinfection
	25		85	FOS	FOS	>64		42	2	Reinfection
	26		288	DOX	DOX CST MEM	4	8	42	0	Successful
6	27	No	79	FOS DOX TIG GEN	MEM	0.12	0.5	43	0	Patient died
7	28	No	20	FOS TIG	TIG	0.12		28	2	Patient died
8	29	No	22	DOX FOS GEN TIG	DOX	16.0	4	15	0	Reinfection
	30		40	FOS GEN TIG	MEM FOS	8.0	8	25	0	Reinfection
	31		82	None	CST	4.0	8	15	0	Successful
9	32	Yes	230	GEN TIG T-S AMK FOS	MEM CST			20	0	Patient died
10	33	No	68	FOS AMK NFT TIG CST	MEM FOS	1.0	0.5	14	0	Reinfection
	34		103	FOS DOX CST	MEM FOS CST DOX	1.0	8	15	0	Reinfection
	35		143	AMK NFT	MEM FOS	>4	>8	21	0	Successful
11	36	NA	28	DOX FOS GA	MEM DOX		1	14	0	Reinfection
	37		98	DOX FOS GA	DOX MEM FOS	0.12		56	0	Successful
12	38	NA	100	TIG CST	TIG MEM CST	0.25	2	41	0	Reinfection
13	39	NA	626	FOS TIG DOX	FOS TIG DOX	8.0	16	40	2	Patient died

obtaining susceptibility, empirical treatment was administered; a frequent reported combination therapy is tigecycline plus colistin, but the empirical use of colistin could contribute to selection of resistant strains.[6] We avoided nephrotoxic agents, and took into consideration the drug concentration at the site of infection and potential adverse events. Carbapenem monotherapy has a higher rate of treatment failure compared to combination therapy; moreover, only the combination of meropenem, colistin, and tigecycline is associated with improved survival in patients with blood infections.[6] Colistine was successful when the isolate showed resistance to all tested antibiotics. The use of a triple-drug regimen including tigecycline, colistin, and meropenem was linked to a reduced risk of death.[7]

To prevent the spread of bacteria, measures such as perirectal surveillance swabs, susceptibility tests, use of gowns and gloves, and strict hand hygiene were followed. Also, recipients of kidneys from living donors were transferred from the operating room to a non-intensive setting, or underwent a reduced stay in the ICU. Despite its limitations, this report shows that UTIs caused by KPC-Kp pose a threat to kidney transplant patients.

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"Masked" renal disease in the elderly: Still "masked" after a 5-year follow-up?☆

Enfermedad renal "oculta" en ancianos: ¿continúa "oculta" a los 5 años de seguimiento?

Dear Editor,

"Hidden" renal disease (HRD) is defined by an UF <60 ml/min associated to normal range SCR. In Primary Care several trials have been performed in order to know HRD prevalence; Labrador et al. performed 13,784 SCR measurements in patients over the age of 18. Findings were the following: UF <60 ml/min/1.73 m^2 in 1042 patients, out of which 418 resulted

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