Does Thymoglobulin Induction Increase Susceptibility to Carbapenem-Resistant *Acinetobacter baumannii* Sepsis-related Death in Expanded Criteria Donors?

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ABSTRACT

Background. Solid organ transplant recipients are susceptible to antibiotic-resistant infections and carbapenem-resistant *Acinetobacter baumannii* (CRAB) has recently been recognized as a serious complication in solid organ recipients. High mortality rates have been described.

Methods. We retrospectively analyzed 807 transplantations and detected 10 patients who died 24 hours after the diagnosis of septicemia, all with CRAB-positive blood cultures. Recipients were followed up for at least 1 year and were stratified into the following groups: Group 1, patients alive; Group 2, patients that died due to other causes except *Acinetobacter* infection; and Group 3, patients who died within 24 hours of CRAB diagnosis.

Results. CRAB-positive patients died a median of 3.17 (range, 1.81–18.7) months after transplantation. In these patients, expanded criteria donors (ECDs) were more frequent ($P < .001$), as were the use of anti-thymocyte globulin (ATG) induction ($P = .02$) and delayed graft function ($P = .01$). For ECD recipients, death rate from any cause, whether induced with ATG or not, was 25% and 20.6%, respectively (odds ratio [OR], 1.28; confidence interval [CI] 95%, 0.56–2.91; $P = .68$). The death rate from CRAB-related sepsis was 10.3% and 0% whether receiving ATG or not, respectively (OR, 15.49; CI 95%, 0.87–277.16; $P = .014$). There was a 25.75-fold increase in the death rate in ECD kidney recipients induced with thymoglobulin and with CRAB-related sepsis.

Conclusion. Transplants from ECDs and induced with thymoglobulin may be at increased risk of CRAB death in 24 hours when compared with patients with standard donors and induced with thymoglobulin.

BACTERIAL infections are important causes of morbidity and mortality after organ transplantation, and the leading cause of death among transplant recipients [1]. Although solid organ transplant recipients are particularly susceptible to the development of drug-resistant bacterial infections due to their frequent and prolonged hospitalizations, interventions, and/or chronic immunosuppression [2], there are few data on the epidemiology of carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection among such patients. The impact on the survival of these patients has been extensively studied [2–5].

A baumannii is an opportunistic pathogen that persists in the hospital environment. It is intrinsically resistant to some beta-lactam antibiotics, but it is better known for its ability to acquire resistance to all commercially available antimicrobial agents [6]. Furthermore, high mortality rates have been described with CRAB infections in organ transplants recipients [2].

In the Organ Transplant Program at Hospital São Lucas, a University Hospital in southern Brazil, we have recently

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0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.06.015

had 10 patients who rapidly died due to *A baumannii*–related sepsis. They evolved to death within 24 hours of onset of symptoms, despite the use of polymyxin B.

In the present study, we sought to analyze variables that could potentially play a role in death due to *A baumannii*–related sepsis in kidney and kidney-pancreas recipients.

METHODS

From January 1, 2000 to April 31, 2013, 807 transplantations were performed at Hospital São Lucas, including 755 kidneys and 52 kidney-pancreas transplantations. We reviewed the medical records of these 807 recipients and enrolled all 10 patients who died 24 hours after the diagnosis of septicemia, and had CRAB-positive blood culture.

A 10-mL blood sample was drawn under sterile conditions and injected, at bedside, into 2 aerobic blood culture bottles. Samples were collected from more than 1 site for each patient. Blood samples were processed using the BACTEC 9120 blood culture system (Becton Dickinson, Cockeysville, Md, United States). Bacteria species identification was performed using the Vitek-2 system (bioMerieux, Marcy l'Etoile, France). Antimicrobial susceptibility was determined using the disk diffusion method and the results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria [7]. Carbapenen-resistant *Acinetobacter* species were characterized, in this study, as resistant to carbapenens with a minimum inhibitory concentration of imipenem $\geq$16 μg/mL.

Most patients enrolled were administered triple-drug immunosuppression consisting of calcineurin inhibitor, a mycophenolic acid, and corticosteroids. Thymoglobulin (ATG) was administered to sensitized patients (panel-reactive antibody [PRA] >50%) or to those with at least 1 of the following criteria: previous organ transplantation, 3 or more pregnancies, 3 or more blood transfusions, long-time in the waiting list, cold ischemia time >24 hours, and for those when a steroid-free regimen was planned.

Information on clinical characteristics, previous transplantations, donor characteristics, cold ischemia time, delayed graft function (DGF), acute rejection, mortality, and laboratory data was collected. Expanded criteria donors (ECDs) were defined according to The Brazilian Medical Association Guideline, as aged 60 years or older, history of diabetes or chronic kidney disease, or older than 50 years with at least two of the following conditions: hypertension, serum creatinine >1.5 mg/dL, or death due to cerebrovascular accidents [8].

Statistical Analysis

Continuous variables, with normal distribution, were presented as mean ± standard deviation. Variables with nonparametric distribution were expressed as median and interquartile range (25th-75th percentile). Chi-square analysis was used for comparison of categorical data, analysis of variance (ANOVA) for normal continuous variables, and Kruskal-Wallis test for nonparametric variables. Hazard ratios (HR; 95% confidence interval [CI]) were calculated. A 2-sided $P < .05$ was considered statistically significant. Data analyses were performed with IBM SPSS Statistics for Mac, version 22. The local hospital's ethics committee approved this study.

RESULTS

Of the 807 recipients, 438 (54.3%) were male, 705 (87.4%) were white, and the mean age was 41.72 ± 16.9 years old. Six hundred thirty-six patients (78.8%) received a kidney from a deceased donor. In the later population, 10 patients died within 24 hours of the diagnosis of septicemia with a CRAB-positive blood culture. One hundred sixty-two patients died due to other causes.

Recipients were followed up for at least 1 year until April 31, 2014 and were stratified into three groups: Group 1, with patients alive; Group 2, with patients who died due to other causes than *Acinetobacter* infection; and Group 3, patients who died with CRAB sepsis. The characteristics of each group are listed in Table 1.

Most were recipients of a first kidney graft, with no difference between groups. There were also no differences in gender or race, but patients who died due to CRAB-related sepsis were older than the others ($P < .001$).

Table 1. Characteristics of Study Population According 3 Groups (Group 1 Patients Alive, Group 2 Patients Who Died due to Other Causes, and Group 3 Patients Who Died due to CRAB)

Characteristics	Total (n = 807)	Group 1 (n = 635)	Group 2 (n = 162)	Group 3 (n = 10)	*P*
Age, mean y ± SD	41.72 ± 16.9	39.8 ± 17.1	48.7 ± 14.0	53.6 ± 12.8	<.001*
Race, white n (%)	711 (88.1%)	569 (89.6%)	134 (82.7%)	8 (80%)	.039†
Gender, male n (%)	438 (54.3%)	344 (54.2%)	87 (53.7%)	7 (70%)	.589†
Deceased donor, n (%)	636 (78.8%)	486 (76.5%)	140 (86.4%)	10 (100%)	.006†
CIT, mean h ± SD	17.7 ± 10.3	17.3 ± 10.7	18.6 ± 9.1	24.5 ± 7.8	.039*
PRA I, median (IQR)	0 (0–1)	0 (0–2)	0 (0–2)	7.5 (0–81.3)	.004‡
ATG use, n (%)	316 (39.2%)	250 (39.4%)	58 (35.8%)	8 (80%)	.02†
Rejection, n (%)	197 (24.4%)	164 (25.8%)	32 (19.8%)	1 (10%)	.156†
ECD, n (%)	131 (16.2%)	101 (15.9%)	23 (14.2%)	7 (70%)	<.001†
PreTx HD time, median mo (IQR)	25 (11–51)	23 (9–48)	33 (18–66)	33 (17.3–51.3)	<.001‡
DGF, n (%)	382 (47.3%)	284 (44.7%)	91 (56.2%)	7 (70%)	.01†
First Tx, n (%)	717 (88.8%)	571 (89.9%)	138 (85.2%)	8 (80%)	.156†
Length of stay, median d (IQR)	17.0 (11–27)	17.0 (11–26)	20.0 (14–33)	18.0 (10.5–31)	.002‡

Abbreviations: CIT, cold ischemic time; IQR, interquartile ranges; PreTx, pretransplantation; HD, hemodialysis.
*ANOVA, date as means and standard deviation.
†Chi-square, date as n (%).
‡Nonparametric Kruskal-Wallis Test, date as medians and IQR.

Table 2. Global and CRAB Death Rate Among Patients With SCDs and ECDs

	Global Death Rate		OR (CI) *P*	CRAB Death Rate		OR *P*
	ATG Induction	Without ATG		ATG Induction	Without ATG	
SCD group	19.8% (49/248)	21.7% (93/428)	OR = 0.89 (0.60–1.31) *P* = .62	0.4% (1/248)	0.5% (2/428)	OR = 0.86 (0.08–9.56) *P* = .99
ECD group	25.0% (17/68)	20.6% (13/63)	OR = 1.28 (0.56–2.91) *P* = .68	10.3% (7/68)	0% (0/63)	OR = 15.49* (0.87–277.16) *P* = .014

*Using Agresti's method.

CRAB-related deaths occurred a median of 3.17 (range, 1.81–18.7) months after transplantation. In 60% of cases, it occurred in the first 4 months post-transplantation. All patients who died of CRAB-related sepsis underwent transplantation with kidneys from deceased donors. This was significantly higher compared with those who died due to other causes and with recipients who are still alive.

Of the 807 patients, 131 received kidneys from ECDs. In the CRAB-positive group, ECDs were more frequent ($P < .001$), as well as use of ATG induction ($P = .02$) and occurrence of DGF ($P = .01$). CRAB-positive recipients also had significantly higher HLA class I PRA compared with patients who died due to other causes as well as with patients who are still alive ($P = .004$).

Death rate was evaluated in kidney recipients from either standard criteria donors (SCD) or ECDs. Recipients of ECD grafts had a death rate due to any cause, whether induced with ATG or not, of 25% and 20.6%, respectively (odds ratio [OR], 1.28; CI 95%, 0.56–2.91; $P = .68$). When we consider the death rates due to CRAB, transplants from ECDs showed 10.3% rates when induced by ATG and 0% without ATG. We used the Agresti's method (OR 15.49; CI 95%, 0.87–277.16; $P = .014$; Table 2).

The death rate for CRAB-related sepsis in patients who were induced with thymoglobulin and were recipients of ECD grafts was 25.75-fold higher compared with those receiving thymoglobulin but SCD grafts (Fig 1).

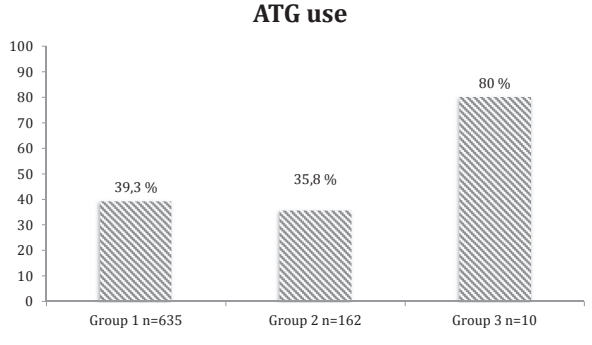

Fig 1. Thymoglobulin induction (Group 1 patients alive, Group 2 patients died from other causes and Group 3 patients died from CRAB).

DISCUSSION

Although solid organ transplant (SOT) recipients are particularly susceptible to CRAB infections, studies in this population are still limited. Shields et al, in a retrospective study of 69 SOT recipients who were colonized (41%) or infected (59%) with CRAB, reported that infections were significantly more common among cardiothoracic than abdominal transplant recipients ($P = .0004$) and 98% had respiratory tract infections, most commonly ventilator-associated pneumonia (88%). Survival rates at 28 and 90 days were 54% and 46%, respectively [9]. Our study found that most patients had respiratory sepsis, with pneumonia presenting in 8/10 cases and most deaths (60%) occurring in the first 4 months after transplantation.

In none of the CRAB-related deaths in the present study, infection was transmitted by the donor. Sikora et al described a case of possible *A baumannii* transmission from the donor to the recipient through analysis of amplified polymorphic DNA [10]. Martins et al, in a case report from University of Rio de Janeiro, described a severe CRAB infection in a lung transplant recipient who died on the 65th postoperative day [11].

Despite the fact that CRAB infection is associated with higher mortality, CRAB-related deaths in our study occurred within the first 24 hours after the onset of infectious symptoms. There was a high prevalence of death from CRAB in 24 hours of sepsis, with 5.8% of all causes of deaths.

Because of the shortage of organs for transplantation, in recent years, we have increased the use of ECDs [12]. However, 5-year graft and patient survival is shorter when donors are ECDs, compared with SCDs. Annual adjusted death rate is lower for ECD graft recipients compared with wait-listed and on dialysis patients [13].

The Organ Procurement and Transplantation Network database (http://optn.transplant.hrsa.gov) demonstrates an increase in ECD incidence for deceased donor transplants during the last decade, with a rate of 14.3% in 2002 to 16.6% in 2012. In a 5-year retrospective study in Seoul an 11.6% incidence of ECDs was disclosed and, in a Brazilian 15-year retrospective study with 582 deceased donor transplants, 25.4% of ECDs were reported [14]. Despite our low prevalence compared with the Brazilian report, a 25.7-fold increase in CRAB-related death was observed in recipients of ECD grafts compared with recipients of SCD grafts.

The present study was conducted retrospectively, from database analysis, and, therefore, has limitations. Patients who received ATG induction had greater immunologic risk and/or more prolonged cold ischemia time. When assessing ischemia time, there was a small significant difference between the groups, but the class I PRA was higher in patients who died and was especially higher in the CRAB group. This suggests that patients with CRAB infection received ATG induction for high immunologic risk.

We found that ECD transplant recipients and those induced with thymoglobulin have a high risk of CRAB-related death. Importantly, in such patients, death occurs in the first 24 hours of the sepsis diagnosis. Because our study was retrospective, a prospective analysis, assessing donors type, exposure to thymoglobulin, immunologic risk factors of the recipient, DGF, length of stay, and other confounding factors, could confirm our results that suggest that thymoglobulin induction increases susceptibility to CRAB death in ECD graft recipients.

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