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Research Article

Peri-transplant Treatment with Ceftaroline in Kidney Transplant Recipients at Risk of Donor-derived MRSA Infections: A Case Series

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Abstract

The rising prevalence of MDR pathogens has a significant impact on the recipients' outcome, as this increases the risk of graft complications and makes the management of the peri-transplant phase more difficult. Among the different MDR germs, Methicillin-resistant Staphylococcus aureus (MRSA) represents one of the most frequently isolated pathogens. We report for the first time the off-label use of Ceftaroline in six kidney transplant recipients with donor peritransplantation MRSA bacteremia at the Division of Kidney Transplant Unit of

Federico II University Hospital of Naples, Italy, between September and December 2022. Each patient was followed up for the next three months after transplantation, monitoring the clinical and laboratory outcome, the risk of infection, and the efficacy and safety profile of the treatment performed. In the subsequent three months of follow-up to the transplant, none of the six patients showed donor-related infections. In particular, none of the six patients showed MRSA bacteremia or other related MRSA infections. In conclusion, our real-life experience shows that Ceftaroline could represent a valid therapeutic option in the management of solid organ transplant patients with a risk of donor-derived MRSA infection. However, despite the few cases considered, this approach deserves further investigation in ad hoc studies or clinical trials due to our positive results.

Keywords
Ceftaroline; kidney transplantation; peri-transplant treatment; MRSA; donor-derived infection

1. Introduction

The burden of antimicrobial resistance is increasingly impacting the management of solid organ transplants. Transplants from donors with colonization or infection by Multidrug-Resistant (MDR) germs have been more and more commonly performed [1]. The rising prevalence of MDR pathogens has a significant impact on the recipients' outcome, as this increases the risk of graft complications and makes the management of the peri-transplant phase more difficult [2].

Donors are often critically ill patients, admitted to Intensive Care Units (ICUs), and, for this reason, maybe colonized by MDR germs [3]. It is estimated that about 5% of patients are affected by bacteremia at the time of organ retrieval. This creates a significant issue in managing this situation as the results of ongoing microbiological investigations at the time of transplantation are often lacking [4].

There is currently little data regarding the risk and management of Donor-Derived Infections (DDI) caused by MDR pathogens [5, 6]. Moreover, it is unclear if a prophylaxis or preemptive therapy strategy may work.

Among the different MDR germs, Methicillin-resistant Staphylococcus aureus (MRSA) represents one of the most frequently isolated pathogens. In fact, as high as 30% of donors have a colonization or an infection due to MRSA [7-9]. It is noteworthy that most MRSA infections typically occur in the first month after the transplant and are associated with a mortality between 15% and 30% [10, 11].

In this context, although therapeutic options such as Vancomycin and Daptomycin are already available, the advent of the 5th generation cephalosporins Ceftaroline and Ceftobiprole could constitute helpful weapons in the management of peritransplantation treatment of MRSA bacteremia, due the optimal tolerability and low potential for drug-drug-interaction typical of betalactams together with the high activity against MRSA [12, 13].

However, there is currently no data in the literature regarding this aspect and this use.

2. Methods

We report for the first time the off-label use of Ceftaroline in six kidney transplant recipients with donor peritransplantation MRSA bacteremia at the Division of Kidney Transplant Unit of Federico II University Hospital of Naples, Italy, between September and December 2022.

The donor-derived MRSA infections were all MRSA-related bacteremia and were defined by blood cultures positive for MRSA.

No patient had a history of allergy to β-lactams. Each patient received Ceftaroline at 200 mg as a loading dose one hour before transplantation, followed by Ceftaroline every 12 hours post-transplantation. Subsequently, the dosage was re-evaluated according to the evolution and recovery of renal function. In particular, for an eGFR (estimated Glomerular Filtration Rate) <15 ml/min, 200 mg iv q12 h was administered. For an eGFR between 15 and 30 ml/min, a dosage of 300 mg iv q12 h was administered. For an eGFR between 30 and 50 ml/min, a dosage of 400 mg iv q12 h, and for an eGFR >50 ml/min, 600 mg iv q12 h.

Each patient was followed up for the next three months after transplantation, monitoring the clinical and laboratory outcome, the risk of infection, and the efficacy and safety profile of the treatment performed.

3. Results

We summarize demographic and clinical variables in Table 1. All transplant recipients underwent therapy with Ceftaroline (see Table 2). In addition to Ceftaroline, each patient received another antibiotic based on strains isolated from the donor. In detail, three patients received Piperacillin/Tazobactam, two received Meropenem, and one received Daptomycin (see Table 2). The median duration of therapy was 14.5 days (9-16) (see Table 2).

Table 1 Characteristics of enrolled patients.

Age (median, IQR)	*50 (47-61)*
Gender	
M	*2 (33%)*
F	*4 (67%)*
Comorbidities:	
Hypertension	*4 (67%)*
COPD	*1 (17%)*
Obesity	*1 (17%)*
Cardiovascular disease	*1 (17%)*
Type of transplant	
Kidney transplant	*6 (100%)*
Indication for the transplant	
ADPKD	*4 (67%)*
IgA nephropathy	*1 (17%)*
VUR	*1 (17%)*
Induction Immunosuppressive therapy	
Basiliximab + Methylprednisolone	*6 (100%)*
Maintenance Immunosuppressive therapy	

Tacrolimus-Mycophenolate-Steroids	*4 (67%)*
Cyclosporine-Mycophenolate-Steroids	*2 (33%)*
Length of post-transplant hospital stay (median, IQR)	*16 (11-31)*
Post-transplant infection DDIs-related	*0*
Post-transplant infection no DDIs-related (3 months after transplantation)	*4 (67%)*
UTI caused by Escherichia coli	*2 (33%)*
UTI caused by Enterococcus faecium	*1 (17%)*
Urosepsis caused by Escherichia coli	*1 (17%)*
Timing of post-transplant infection (median, IQR)	*35 (14-70)*

IQR: InterQuartile Range, COPD: Chronic Obstructive Pulmonary Disease, ADPKD: Autosomal Dominant Polycystic Kidney Disease, VUR: Vesicoureteral Reflux, DDIs: Donor-Derived Infections, UTI: Urinary Tract Infection, WBC: White Blood Cells, PLT: Platelets, CRP: C-Reactive Protein, LDH: lactic dehydrogenase

Table 2 Donor-Derived Infections and treatments/3-months post-transplant follow-up of recipients.

Donor			Recipient			
			Recipient's Organ: Kidney			
Patient	**Donor Infection**	**Strains**	**Preemptive therapy**	**Duration (days)**	**Post-transplant infection DDIs-related**	**Outcome**
1	Bloodstream Infection/ Pneumonia	MRSA*/ Serratia marcescens**	Ceftaroline + Piperacillin/Tazobactam	14	No	Alive
2	Bloodstream Infection/ Pneumonia	MRSA*/ MRSA-Serratia marcescens**	Ceftaroline + Piperacillin/Tazobactam	9	No	Alive
3	Bloodstream Infection/ Pneumonia	MRSA*/ Pseudomonas aeruginosa**	Ceftaroline + Meropenem	15	No	Alive
4	Bloodstream Infection catheter-related	MRSA* – Enterococcus faecalis*	Ceftaroline + Daptomycin	13	No	Alive
5	Bloodstream Infection/ UTI	MRSA*/ Escherichia coli***	Ceftaroline + Piperacillin/Tazobactam	16	No	Died 65 d after transplant[ǂ]
6	Bloodstream Infection/ UTI	MRSA*/ Proteus mirabilis***	Ceftaroline + Meropenem	12	No	Alive

UTI: Urinary Tract Infection, MRSA: Methicillin-Resistant Staphylococcus Aureus, DDIs: Donor-Derived Infections

* isolated from blood cultures, ** isolated from bronchoaspiration, *** isolated from urine culture

[ǂ] died of gastrointestinal perforation

In the subsequent three months of follow-up to the transplant, none of the six patients showed donor-related infections. In particular, none of the six patients showed MRSA bacteremia or other related MRSA infections.

In the follow-up period, three infectious events occurred in three patients: two presented an episode of urinary tract infection, and one underwent sepsis due to urinary tract infection. In all three cases, the infectious etiology was unrelated to donor infections (see Table 1).

Of the six transplanted patients, 5 survived the follow-up period, and one patient died. However, the cause of death was considered unrelated to the infection, as she died following an episode of gastrointestinal perforation.

We also observed the impact of therapy with Ceftaroline on renal function in the follow-up period; no patients showed abnormalities in renal function recovery.

Regarding potential pharmacological interactions with immunosuppressants, no particular pharmacological interactions were observed between immunosuppressive therapies and Ceftaroline, as already known in the literature.

None of the six patients showed adverse drug reactions.

4. Discussion

Currently, there is no data regarding Ceftaroline use in the peritransplant treatment for donor-derived MRSA infections. However, it is well known that Ceftaroline is a new fifth-generation cephalosporin that has activity against MRSA [12, 13].

As part of managing donor-derived MRSA infections, the use of Vancomycin or Daptomycin is currently envisaged [1, 2]. However, proven effectiveness in the management of these infections consolidates the use of Vancomycin and Daptomycin. However, the advent of Ceftaroline could represent a new and valid therapeutic option in this area. In fact, with Ceftaroline, there would be the possibility of using a β-lactam with its bactericidal activity and pharmacokinetic and pharmacodynamic characteristics [12]. At the same time, there would be an additional benefit in particular settings, such as that of kidney transplant recipients or in patients with renal insufficiency, where due to significant alterations in eGFR in the initial post-transplant phases, the use of Vancomycin could be challenging to implement due to a greater risk of side effects and nephrotoxicity related to drug accumulation [10, 11].

In conclusion, our real-life experience shows that Ceftaroline could represent a valid therapeutic option in the management of solid organ transplant patients with a risk of donor-derived MRSA infection. However, despite the few cases considered, this approach deserves further investigation in ad hoc studies or clinical trials due to our positive results.

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Author Contributions

P.B. participated in substantial contributions to the conception, design of the work, the acquisition, analysis and interpretation of data for the work. R.C. conceived idea with analysis and participated in interpretation of the literature, drafting the article, approving the final version to be

published and is accountable for the accuracy/integrity of the content. T.E. participated in revising the initial draft of the article and approving the final version to be. D.A. participated in drafting the article, and approving the final version to be published. S.F. participated in analysis and interpretation of data for the work. S.A. participated in the acquisition and analysis of data for the work. M.S. participated in design of the work and interpretation of data for the work. S.F. participated in approving the final version to be published and is accountable for the accuracy/integrity of the content. P.A. participated in analysis and interpretation of the literature, drafting the article, and approving the final version to be published. S.E. participated in revising the initial draft of the article and approving the final version to be published. R.P. participated in the acquisition and analysis of data for the work. R.G. participated in drafting the article, approving the final version to be published and is accountable for the accuracy/integrity of the content. T.R.I participated in revising the initial draft of the article and approving the final version to be published. G.I. participated in substantial contributions to the conception, design of the work, the acquisition, analysis and interpretation of data for the work, approving the final version to be published.

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Competing Interests

The authors declare no conflicts of interest.

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