

## Research Article

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

Biagio Pinchera <sup>1,\*</sup>, Rosa Carrano <sup>2</sup>, Emilia Trucillo <sup>1</sup>, Alessia D'Agostino <sup>1</sup>, Alessia Sardanelli <sup>1</sup>, Simona Mercinelli <sup>1</sup>, Fabrizio Salemi <sup>2</sup>, Amerigo Piccione <sup>2</sup>, Elisa Schettino <sup>2</sup>, Paolo Romano <sup>2</sup>, Gianluca Rompianesi <sup>3</sup>, Roberto Ivan Troisi <sup>3</sup>, Ivan Gentile <sup>1</sup>

1. Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy; E-Mails: [biapin89@virgilio.it](mailto:biapin89@virgilio.it); [emiliatrucillo@libero.it](mailto:emiliatrucillo@libero.it); [alessiadagostino53@gmail.com](mailto:alessiadagostino53@gmail.com); [ale\\_sardanelli@hotmail.com](mailto:ale_sardanelli@hotmail.com); [simona.mercinelli@gmail.com](mailto:simona.mercinelli@gmail.com); [ivan.gentile@unina.it](mailto:ivan.gentile@unina.it)
2. Section of Nephrology, Department of Public Health, University of Naples "Federico II", Naples, Italy; E-Mails: [rosa.carrano@alice.it](mailto:rosa.carrano@alice.it); [fabriziosalemi@yahoo.it](mailto:fabriziosalemi@yahoo.it); [amerigopiccione@libero.it](mailto:amerigopiccione@libero.it); [elisa.schettino94@gmail.com](mailto:elisa.schettino94@gmail.com); [paolo.romano.92@alice.it](mailto:paolo.romano.92@alice.it)
3. Division of Hepato-Bilio-Pancreatic, Minimally Invasive, Robotic and Transplant Surgery, Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy; E-Mails: [gianluca.rompianesi@unina.it](mailto:gianluca.rompianesi@unina.it); [roberto.trosi@gmail.com](mailto:roberto.trosi@gmail.com)

\* **Correspondence:** Pinchera Biagio; E-Mail: [biapin89@virgilio.it](mailto:biapin89@virgilio.it)

**Academic Editor:** Abbas Ghazanfar

**Special Issue:** [Kidney Transplantation - Clinical and Surgical Challenges](#)

*OBM Transplantation*

2023, volume 7, issue 4

doi:10.21926/obm.transplant.2304200

**Received:** July 19, 2023

**Accepted:** October 29, 2023

**Published:** November 01, 2023

**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



© 2023 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

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 5<sup>th</sup> 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  $\beta$ -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.

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

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

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			
Patient	Donor Infection	Strains	Preemptive therapy	Recipient's Organ: Kidney		
				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 <sup>†</sup>
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

<sup>†</sup> 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  $\beta$ -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.

#### **Acknowledgments**

The authors declare no funding was received for this study.

#### **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 published. 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.

## **Funding**

The authors declare no funding was received for this study.

## **Competing Interests**

The authors declare no conflicts of interest.

## **References**

1. Bartoletti M, Giannella M, Tedeschi S, Viale P. Multidrug-resistant bacterial infections in solid organ transplant candidates and recipients. *Infect Dis Clin*. 2018; 32: 551-580.
2. Cervera C, Van Delden C, Gavalda J, Welte T, Akova M, Carratalà J, et al. Multidrug-resistant bacteria in solid organ transplant recipients. *Clin Microbiol Infect*. 2014; 20: 49-73.
3. Garzoni C, Vergidis P. Methicillin-resistant, vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* infections in solid organ transplantation. *Am J Transplant*. 2013; 13: 50-58.
4. Lumbreras C, Sanz F, González A, Pérez G, Ramos MJ, Aguado JM, et al. Clinical significance of donor-unrecognized bacteremia in the outcome of solid-organ transplant recipients. *Clin Infect Dis*. 2001; 33: 722-726.
5. Miceli MH, Gonulalan M, Perri MB, Samuel L, Al Fares MA, Brown K, et al. Transmission of infection to liver transplant recipients from donors with infective endocarditis: Lessons learned. *Transpl Infect Dis*. 2015; 17: 140-146.
6. Wendt JM, Kaul D, Limbago BM, Ramesh M, Cohle S, Denison AM, et al. Transmission of methicillin-resistant *Staphylococcus aureus* infection through solid organ transplantation: Confirmation via whole genome sequencing. *Am J Transplant*. 2014; 14: 2633-2639.
7. Singh N, Paterson DL, Chang FY, Gayowski T, Squier C, Wagener MM, et al. Methicillin-resistant *Staphylococcus aureus*: The other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis*. 2000; 30: 322-327.

8. Florescu DF, McCartney AM, Qiu F, Langnas AN, Botha J, Mercer DF, et al. Staphylococcus aureus infections after liver transplantation. *Infection*. 2012; 40: 263-269.
9. Desai D, Desai N, Nightingale P, Elliott T, Neuberger J. Carriage of methicillin-resistant Staphylococcus aureus is associated with an increased risk of infection after liver transplantation. *Liver Transplant*. 2003; 9: 754-759.
10. Florescu DF, Qiu F, West SB, Richards S, Florescu MC, Stevens B, et al. Staphylococcus aureus infections in kidney transplantation: A matched case controlled study. *Scand J Infect Dis*. 2012; 44: 427-432.
11. Oliveira-Cunha M, Bowman V, Di Benedetto G, Mitu-Pretorian MO, Armstrong S, Forgacs B, et al. Outcomes of methicillin-resistant Staphylococcus aureus infection after kidney and/or pancreas transplantation. *Transplant Proc*. 2013; 45: 2207-2210.
12. Sotgiu G, Aliberti S, Gramegna A, Mantero M, Di Pasquale M, Trogu F, et al. Efficacy and effectiveness of Ceftaroline Fosamil in patients with pneumonia: A systematic review and meta-analysis. *Respir Res*. 2018; 19: 205.
13. Giurazza R, Mazza MC, Andini R, Sansone P, Pace MC, Durante-Mangoni E. Emerging treatment options for multi-drug-resistant bacterial infections. *Life*. 2021; 11: 519.