Colistin Sulfate for Decontamination of Preservation Fluid to Decrease Donor-derived Infections Caused by Multi-drug Resistant Gram-negative Pathogens

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Abstract

Background: Preservation fluid (PF) contamination, especially contamination with multi-drug resistant (MDR) Gram-negative pathogens, poses a high risk of donor-derived infections (DDIs) and severe clinical outcomes. We sought to determine whether the use of colistin sulfate to decontaminate PF in kidney transplantation can decrease probable DDIs (p-DDIs) caused by MDR Gram-negative pathogens.

Methods: In a retrospective study of 916 recipients who received deceased donation, 864 PF samples were collected and cultured, and microbiological contaminants were recorded with the recipients' clinical data and outcomes. From March 2016 to May 2019, 624 samples were decontaminated with ceftizoxime; from June 2019 to March 2021, colistin sulfate was administered for PF decontamination in 240 samples. Between-group comparisons were performed to assess the ability of the two decontamination regimens to decrease p-DDIs, especially MDR Gram-negative pathogen-related infections.

Results: The overall PF contamination rate was 53.36% (461/864), and 80 samples had MDR Gram-negative pathogen contamination. All p-DDIs occurred in the ceftizoxime group ($p < 0.001$), and 67.65% of p-DDIs were MDR Gram-negative pathogen-related. In the ceftizoxime group, 23 of 61 cases of MDR Gram-negative pathogen contamination led to related p-DDIs, while none occurred in the colistin sulfate group ($p = 0.002$). Among these 23 patients with p-DDIs, 5 died of severe infections, and 2 experienced graft loss.

Conclusions: The goal of decontamination should be decreasing MDR Gram-negative pathogen-related p-DDIs, and colistin sulfate could be an effective and feasible option.

Background

The risk of donor-derived infections (DDIs) could lead to in-hospital morbidity and mortality in the early posttransplantation period [1]. Contamination of preservation fluid (PF), including infection caused by pathogens transmitted directly from the donor organ or from the organ recovery process, has been identified as a potential cause of DDIs, and the reported incidence ranges from 9.5% to as high as 98.4% [2]. Contamination of PF has been reported to be associated with the impairment of graft function [3, 4], drug-resistant bacterial infection, and higher mortality rates [2]. Among all pathogens, multi-drug resistance (MDR) Gram-negative pathogens including *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. present inclination to potential lethal outcomes. There are limited options to treat MDR Gram-negative pathogens especially among the immunocompromised patients [5], thus it is essential to study pathogen transmission risk factors and preventive strategies.

To prevent DDIs transmitted by PF contamination, empirical allograft decontamination via the addition of antibiotics to the PF before transplantation is commonly practiced worldwide [6, 7]. However, in kidney transplantation, the mechanism of PF decontamination and its potential outcomes are still inadequately researched, leading to difficulty in decision making over the use of various antibiotic regimens.

The aim of this study was to report the epidemiology of PF contamination and probable DDIs (p-DDIs) at our center, to clarify the purpose of PF decontamination and to assess the ability of two different decontamination protocols to prevent p-DDIs caused by PF contamination, especially MDR Gram-negative pathogen-related infections.

Patients And Methods

Study Design and Population

Between March 2016 and March 2021, 916 patients underwent kidney transplantation at Changhai Hospital, Shanghai, China. We included cases with the following characteristics in this retrospective single-center study: (1) deceased donor kidney recipients provided informed consent for using their medical data before transplantation; (2) samples of PF were collected before decontamination for microbial assessment; (3) either ceftizoxime or colistin sulfate was administered for PF decontamination; and (4) the demographic and medical information of the donors and recipients was available, including immunosuppressive regimens, infections, clinical features, postoperative drainage fluids/catheter microbiological results, and outcomes.

Procedures for Sample Preservation and Culture

Hypertonic citrate adenine solution II (HC-A II, Shanghai Haini Pharmaceutical Co., Ltd., Shanghai, China) was used for donor perfusion and graft preservation, and no antibiotics were administered during organ procurement. Grafts were double-bagged in sterile plastic bags and preserved at 0-4°C. To record the authentic microbiological data, 2×20 ml samples of PF were obtained before decontamination and back-table dissection. After the collection of PF, 0.25 million units (MIU) of colistin sulfate or 250 mg of ceftizoxime were added to the HC-A II (500ml) in the operating basin where the grafts were placed for full immersion. Before the back-table operation finished, another 0.25 MIU of colistin sulfate or 250 mg of ceftizoxime were added to the perfusate solution (HC-A II, 500ml), 100 ml of which was utilized for further perfusion and decontamination of each graft. From March 2016 to May 2019, ceftizoxime sodium (Southwest Pharmaceutical Co., Ltd., Chongqing, China) was used for PF decontamination in 624 patients; from June 2019 to March 2021, colistin sulfate (Shanghai SPH New Asia Pharmaceutical Co., Ltd., Shanghai, China) was used in 240 patients. The drainage fluids from the retroperitoneum next to the kidney and blood samples of recipients were collected daily for the first 3 days posttransplantation. When there was a possibility of infection, monitoring was prolonged, and other bodily fluid samples were tested accordingly. The inoculated bottles were incubated at 35°C, and all microbiological findings were recorded. Microbial identification was performed using commercially available panels (Vitek [Biomérieux; Marcy-L'Étoile, France]). The Clinical and Laboratory Standards (CLSI) criteria were used to define susceptibility or resistance to antimicrobial agents. Antibiotic susceptibility was tested using the paper disc method following CLSI guidelines [8]. The culture results were recorded, including infection types, pathogens, and antibiotic susceptibility profiles.

Definition

The infection-related events referred to the positive culture results after transplantation, with or without clinical symptoms. These events consisted of graft-site infection, urinary tract infection, non-specific pneumonia, and bacteraemia, and the results were reviewed by the hospital infection control office. Specifically, in our study, a graft-site infection was defined as recipients having positive microbiological results in peri-renal allograft fluid collections obtained by drainage, puncture or surgery. Furthermore, a p-DDI was diagnosed when the pathogenic microorganisms from the infection site were the same as the microbial strains cultured in the PF and had the same antibiotic susceptibility profiles. These infections were diagnosed according to the CDC/NHSN guidelines[9]. The case-fatality rate was regarded as death by any cause within the first 30 days of the onset of infection [10]. MDR Gram-negative refers to extended-spectrum cephalosporin-resistant Enterobacterales, carbapenem-resistant Enterobacterales (CRE), MDR *Pseudomonas aeruginosa*, and MDR *Acinetobacter baumannii* [11].

Immunosuppressive Therapy and Infection Prophylaxis

The immunosuppressive protocol included induction with anti-thymocyte globulin/basiliximab and tapered steroids, and maintenance with tacrolimus/cyclosporin A and mycophenolate.

No changes in hospital practice, antibiotic use, perioperative antimicrobial prophylaxis occurred in the two study periods. If the donor had a low risk of infection without signs of infection, prophylaxis including ceftizoxime/quinolones and caspofungin was performed for 3-5 days. If the donor was at a high risk of infection or had a confirmed infection, the initial prophylaxis was changed to carbapenems and caspofungin, and was modified accordingly with the further knowledge of resistance profiles of the microorganisms identified. The anti-infection treatment could be discontinued only when the recipients presented no symptoms of infection, normal procalcitonin and C-reactive protein levels, and two consecutive negative blood/drainage fluid culture results.

Statistical Analysis

Statistical analysis was carried out using statistical software (SPSS program version 19.0, SPSS Inc., Chicago, IL, USA). Continuous variables are presented as the mean and standard deviation or median and range, as appropriate. Categorical variables are characterized as percentages and were compared with chi-square tests. Statistical analyses were performed using descriptive statistics. All statistical tests were two-tailed, and the threshold of statistical significance was <0.05.

Results

Results of Microbiological Evaluation of Preservation Fluid Cultures

In our study, among 916 kidney transplantation patients, 864 patients were included in our retrospective cohort study (Figure 1). These patients were divided into the ceftizoxime group (624 patients) and the colistin sulfate group (240 patients). The overall incidence rate of PF contamination was 53.36%

(461/864), among which 282 contaminated samples were mono-microbial and 179 samples had more than two strains of microorganisms. The microorganisms isolated are described in detail in Table 1. In the positive samples, coagulase-negative staphylococci, *Enterococcus* species, and *Klebsiella pneumoniae* were the most frequently detected microorganisms.

Table 1
Microorganisms isolated from preservation fluid samples.

Microorganisms	No.	(%)
Negative	403	46.64%
Positive	461	53.36%
mono-microbial	282	32.64%
multi-microbial	179	20.72%
Gram-positive cocci		
<i>Staphylococcus aureus</i>	9	1.04%
Coagulase-negative staphylococci	117	13.54%
Enterococcus species	88	10.19%
Streptococcus species	62	7.18%
Other gram-positive cocci	19	2.20%
Bacillus		
Corynebacterium species	10	1.16%
Bacillus species	8	0.93%
Gram-negative Enterobacteriaceae		
<i>Klebsiella pneumoniae</i>	86	9.95%
<i>Escherichia coli</i>	46	5.32%
<i>Enterobacter aerogenes</i>	4	0.46%
<i>Enterobacter cloacae</i>	6	0.69%
Other gram-negative Enterobacteriaceae	41	4.75%
Non-fermentative bacteria		
<i>Acinetobacter baumannii</i>	63	7.29%
Other Acinetobacter	8	0.93%
<i>Pseudomonas aeruginosa</i>	26	3.01%
<i>Pseudomonas fluorescens</i>	11	1.27%
<i>Stenotrophomonas maltophilia</i>	6	0.69%
Other Pseudomonas	8	0.93%
Other non-fermentative bacteria	9	1.04%

Microorganisms	No.	(%)
Candida		
<i>Candida albicans</i>	55	6.37%
<i>Candida tropicalis</i>	8	0.93%
<i>Candida parapsilosis</i>	5	0.58%
<i>Candida glabrata</i>	19	2.20%
<i>Candida krusei</i>	6	0.69%
Other <i>Candida</i> spp.	8	0.93%
Others	52	6.02%

Descriptions of Infection-Related Events and p-DDIs

The incidences of different infection-related events as well as p-DDIs in the posttransplant patients are described in Table 2. In total, 21.64% of the recipients (187/864) presented infection-related events after transplantation, but only 34 p-DDI cases (3.94%) were confirmed by finding the same pathogen isolated from the PF, moreover, all these events occurred in the ceftizoxime group ($p < 0.001$).

Table 2
Frequencies and incidences of infection-related events and p-DDIs.

	Ceftizoxime group (n=624)	Colistin sulfate group (n=240)	p-value
Patients with infection-related events	141 (22.60%)	46 (19.17%)	0.273
Graft-site infection	117 (18.75%)	19 (7.92%)	<0.001
Urinary tract infection	35 (5.61%)	12 (5%)	0.724
Non-specific pneumonia	29 (4.65%)	7 (2.92%)	0.254
Bacteraemia	38 (6.09%)	5 (2.08%)	0.015
Patients with p-DDIs	34 (5.45%)	0	<0.001
Graft-site p-DDIs	34 (5.45%)	0	<0.001
Bacteraemia p-DDIs	10 (1.60%)	0	0.07
Abbreviations: p-DDIs, probable donor-derived infections.			

Effect of the Decontamination Regimens on the Occurrence of p-DDIs Caused by Gram-negative Pathogens

As shown in Table 3, there was no significant difference in PF contamination between the two groups (349/624 vs 122/240, $p=0.195$). In addition, 80 cases of MDR Gram-negative pathogen contamination in the PF were confirmed, and no significant difference was found between the two groups (61/624 vs 19/240, $p=0.398$). These 349 cases of PF contamination in the ceftizoxime group accounted for the all 34 p-DDI events, which was significantly higher than that in colistin sulfate group ($p<0.001$). Among the 61 patients with MDR Gram-negative contamination in the ceftizoxime group, 23 patients had MDR Gram-negative pathogen-related p-DDIs, while none of the 19 patients with MDR Gram-negative contamination in the colistin sulfate group developed p-DDIs ($p=0.002$). All of the 23 patients with MDR Gram-negative infection suffered from frequent tests and procedures, long hospitalization, and high overall costs (Supplementary Table 1). Even worse, 5 of the patients died of severe complications related to p-DDIs, 1 patient experienced graft loss and 1 graft was removed due to graft rupture attributable to infection (Supplementary Table 1).

Table 3
Incidences of PF contamination and p-DDIs.

	Ceftizoxime group (n=624)	Colistin sulfate group (n=240)	p-value
PF contamination	349	122	0.195
MDR Gram-negative pathogens in PF	61	19	0.398
p-DDIs caused by PF contamination	34	0	<0.001
p-DDIs caused by MDR Gram-negative pathogens in PF	23	0	0.002
Abbreviations: PF, preservation fluid; p-DDIs, probable donor-derived infections; MDR, multi-drug resistant.			

Discussion

The PF contamination rate was 53.36% in our study, and the incidence of p-DDIs was 3.94%, which was consistent with the rates reported in most studies [12]. In most cases, PF contamination seems manageable and harmless and would not lead to severe DDIs[13, 14]. However, when reported, the mortality rate of such infections is high[14, 15].

We remained vigilant about the monitoring and decontamination of PF, and ceftizoxime was previously used for PF decontamination because of its relatively broad-spectrum activity against commonly seen Gram-positive and Gram-negative bacteria[16]. We found that MDR Gram-negative pathogens accounted for a nonnegligible percentage of the contaminating pathogens (80/461, 17.35%) in the PF, and of all 34 patients with p-DDIs, 23 patients were confirmed to have MDR Gram-negative pathogen-related p-DDIs,

suggesting that MDR Gram-negative pathogens were likely to escape the ceftizoxime decontamination and prophylaxis and contribute to pernicious infectious consequences. Hence, we adjusted the goal of decontamination from untargeted generic prevention to targeted prevention of MDR Gram-negative pathogen transmission.

Therefore, the focus is on the selection of an effective antibiotic for decontamination regimen against MDR Gram-negative pathogens and how to balance the benefits and potential risks, such as toxicity and increasing resistance. For tissue preservation, a widely implemented regimen includes cefmetazole, vancomycin, lincomycin, and polymyxin B[6, 7]. However, there is still a lack of clinical practice guidelines currently on the decontamination regimen.

To be suitable for PF decontamination, an antibiotic needs to exhibit valid performance and stability in PF at a temperature of 0-4°C, low toxicity, and most importantly, antibacterial activity targeted to MDR Gram-negative pathogens. Polymyxins are a class of cyclic polypeptide antibiotics[17] that are active against *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, etc.[18], and may also possess broad-spectrum antifungal properties[19, 20]. In clinical practice, polymyxins represent some of the last treatment options for MDR bacterial infections. Of the different isolated polymyxins, polymyxin B sulfate, colistin sulfate and colistin sulfomethate sodium are commercially available. Colistin sulfomethate sodium is an inactive pro-drug and was ruled out [21]. Both colistin sulfate and polymyxin B sulfate exhibited antimicrobial activity in vitro and exerted similarly high bactericidal activity when administered topically [21, 22]. While colistin sulfate showed less nephrotoxicity, little has been reported on the bactericidal effect of colistin sulfate under allograft preservation conditions [23, 24]. After the relaunch of colistin sulfate in May 2019 in China, we quickly changed our decontamination regimen from ceftizoxime to colistin sulfate for the purpose of preventing MDR Gram-negative pathogen-related p-DDIs.

In our study, 240 grafts were decontaminated using colistin sulfate. The contamination rate of PF in this group was similar to that in the ceftizoxime group, but the incidence of p-DDIs in the colistin sulfate group decreased to zero under the same empirical prophylaxis regimen. Colistin sulfate demonstrated a stronger capacity to stop the MDR Gram-negative pathogens in PF from causing related p-DDIs than ceftizoxime ($p=0.002$). Based on these results, colistin sulfate has become a routine PF decontamination regimen at our center.

Overall, although the relationship between PF contamination and DDIs has not been fully elucidated, we still recommend routine PF collection and culture. The goal of decontamination should be targeted at MDR Gram-negative pathogens, and colistin sulfate is recommended as the decontamination regimen for PF. However, there are several concerns and limitations of our study. It was difficult to fully determine the relationship between PF contamination and postoperative infection, as the surgical and medical data regarding organ procurement were incomplete (e.g. intestine/lung injury and donor antibiotic administration). Additionally, we did not study fungal contamination and infection. Some studies claimed that prophylactic antibiotics could increase drug resistance, especially in the setting of colistin-resistant

bacteria emerging worldwide [17, 25, 26]. However, in this study, colistin sulfate was utilized in vitro in PF at a very high dose with a single administration, which could minimize the negative impact on the trend in drug resistance. Further evidence-based research needs to be performed to better assess the benefits and risks of colistin sulfate as a decontamination treatment for PF.

List Of Abbreviations

CLSI, Clinical and Laboratory Standard; CRE, carbapenem-resistant Enterobacterales; DDI, donor-derived infection; MDR, multi-drug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; p-DDIs, probable donor-derived infections; PF, preservation fluid; VRE, vancomycin-resistant Enterococcus species.

Declarations

Ethics approval and consent to participate

The study had approval from the Clinical Research Ethics Committee of Changhai Hospital. None of these graft donors were from prisoners or a vulnerable population, and written informed consent for the publication of data was obtained from the patients or their guardians. The graft procurement and transplantation procedures complied with related national laws, statutes, and ethical guidelines.

Consent for publication

This manuscript was approved for publication by the Clinical Research Ethics Committee of Changhai Hospital.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing Interests

The authors of this manuscript have no conflicts of interest to disclose.

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Authors' contributions

MS and LZeng designed the study and performed the experiments. YL, DX and NZ collected and analysed the data, and MS, HL and NZ wrote the initial draft. LZhang, WZ, and LZeng revised this manuscript; YZ

and LZeng refined the decontamination protocol; All authors read and approved the final manuscript.

MS, NZ, and HL contributed equally to this manuscript.

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Figures

Figure 1

Incidences of PF contamination and p-DDIs caused by MDR Gram-negative pathogens (extended-spectrum cephalosporin-resistant Enterobacterales, carbapenem-resistant Enterobacterales, MDR Pseudomonas species, and MDR Acinetobacter species) in the ceftizoxime group and the colistin sulfate group. Abbreviations: PF, preservation fluid; MDR, multi-drug resistant; p-DDIs, probable donor-derived infection

Supplementary Files

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- [SupplementaryTable1.doc](#)