



Assessing the impact of positive cultures in preservation fluid on renal transplant outcomes: a scoping review

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Abstract

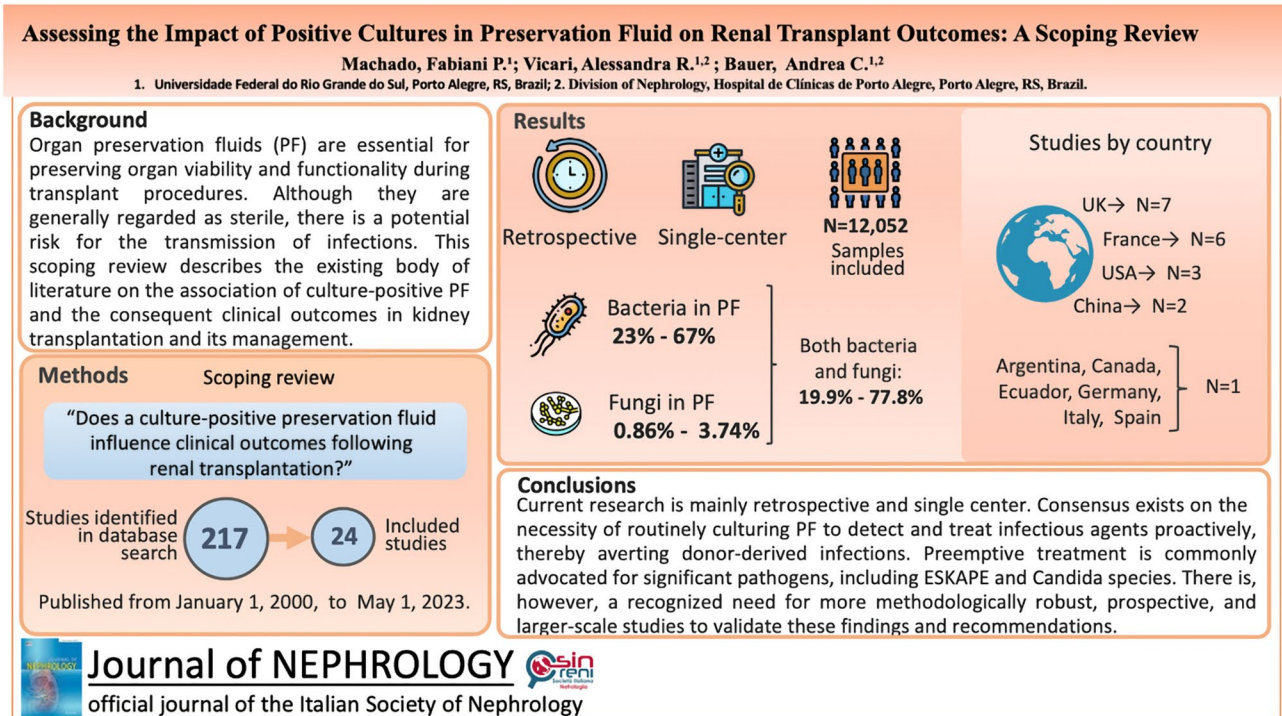
Background Infection following kidney transplantation is a significant risk factor for adverse outcomes. While the donor may be a source of infection, microbiological assessment of the preservation fluid (PF) can mitigate potential recipient contamination and help curb unnecessary antibiotic use. This scoping review aimed to describe the available literature on the association between culture-positive preservation fluid, its clinically relevant outcomes, and management.

Methods Following the Joanna Briggs Institute's scoping review recommendations, a comprehensive search in databases (EMBASE, MEDLINE, and gray literature) was conducted, with data independently extracted by two researchers from selected studies.

Results We analysed 24 articles involving 12,052 samples, predominantly published post-2000, 91% of which retrospective. The prevalence of culture-positive preservation fluid varied from 0.86 to 77.8%. *Coagulase-negative staphylococci* emerged as the most frequently isolated pathogen in 14 studies. The presence of ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), observed in two studies involving 1074 donors, was significantly associated with an increased risk of probable donor-derived infections (p-DDI). Of the reviewed articles, 14 reported on probable donor-derived infections, while 19 addressed the topic of preemptive antibiotic therapy.

Conclusions Routine culturing of preservation fluid is crucial for the identification of pathogenic organisms, facilitates targeted treatment and prevents probable donor-derived infections. Furthermore, this approach helps avoid the treatment of low-virulence contaminants, thereby reducing unnecessary antimicrobial use and the risk of antibiotic resistance. In cases where ESKAPE or *Candida* species are detected, preemptive therapy appears to be an important strategy. Given that the current evidence primarily stems from retrospective studies, there is a pressing need for large-scale, prospective trials to corroborate these recommendations. This scoping review currently represents the most thorough compilation of evidence on how contamination of preservation fluids affects kidney transplant management.

Graphical abstract



Keywords Kidney transplant · Infection · Preservation fluid · Preemptive treatment

Abbreviations

DBD	Donor after brain death
DCD	Donor after cardiac death
DDI	Donor-derived infections
DGF	Delayed graft function
ESBL-PE	Enterobacteriaceae producing extended-spectrum β -lactamases
ESKAPE	<i>Enterococcus faecium</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i> and <i>Enterobacter spp</i>
HLA	Human leukocyte antigens
ICU	Intensive care unit
KT	Kidney transplant
P-DDI	Probable donor-derived infection
PE-T	Preemptive treatment
PF	Preservation fluid
SOT	Solid organ transplantation

Introduction

Effective control over potential complications arising during the post-transplantation period, including infectious processes, is crucial for the success of the therapy. Among patients with known infections, the mortality rate can reach 50% during the first year post-transplantation [1]. Hence, the prevention, diagnosis, and adequate clinical management of infectious episodes are crucial for satisfactory transplant outcomes [2]. The potential pathogens that may infect the immunocompromised host are diverse, with clinical manifestations often nondescript [3, 4].

In recent years, while immunosuppressive agents have reduced the incidence of graft rejection, they have concurrently increased the risk of infections. Hence, comprehensive control of infectious sources and possible transmission methods are of paramount importance [5]. Evaluating the donor for potential infections and gathering information on ongoing infection treatments are crucial to determining organ acceptance and the viability of the donation process. Additionally, latent infections in the recipient can become active, posing significant risks [6].

Organ preservation fluids were developed to maintain the viability and functionality of organs during transplant procedures. Their primary objective is to sustain organ function during cold ischemia, ensuring graft functionality post-perfusion [7, 8]. However, despite being considered sterile, preservation fluid (PF) can potentially transmit infections to organ recipients, with pathogens like gram-negative, gram-positive, anaerobic bacteria, and fungi isolated in 7–24% of the cases [9].

Pathogens from the donor, surgical manipulation, and the bench, as well as organ storage prior to implantation, can be sources of infection. Consequently, many transplant centers routinely perform microbiological examinations of preservation fluid samples to track potential infectious processes in the recipient. Although existing literature addresses this subject, gaps remain concerning the best management strategy for culture-positive preservation fluid and how to avoid complications in kidney transplant (KT) recipients. Therefore, this scoping review is necessary to describe the available literature on the relationship between culture-positive preservation fluid and related clinical outcomes in kidney transplantation.

Aims

This scoping review aimed to describe the available literature on the association between culture-positive preservation fluid in kidney transplantation, its clinically relevant outcomes, and management.

Methods

We employed a scoping review approach in alignment with the steps detailed in the PRISMA-ScR reporting guidelines. This method was chosen due to the comprehensive nature of the review questions and the imperative to map the existing evidence comprehensively. A protocol was developed to direct the review process, encompassing the search, categorization, data extraction, and synthesis phases. This protocol has been registered at OSFHOME under <https://doi.org/10.17605/OSF.IO/W5A6B> (supplementary material 1).

Review question

The review question was formulated using the PCC (Population, Concept, Context) strategy:

- Population: Kidney transplant recipients
- Concept: Evaluation of outcomes
- Context: Culture-positive preservation fluid

Consequently, the review question is: “Does culture-positive preservation fluid influence clinical outcomes following renal transplantation?”

Information sources

Studies were identified through a search in the following databases: Excerpta Medica DataBase (EMBASE) and Medical Literature Analysis and Retrieval System Online (MEDLINE). In addition, the gray literature was explored through Google Scholar. A citation search of included studies was conducted manually to identify any additional publications of relevance that could have been missed while searching the main database.

Search strategy

The search strategy was developed using a combination of controlled descriptors and/or keywords relevant to the topic. Additional potentially eligible studies were identified through manual searches in the reference lists of the initially selected articles. The search was conducted by combining the following significant concepts via appropriate Boolean operators: renal transplantation, kidney transplantation, perfusion fluid, perfusion solution, organ preservation solution, preservation fluid, and infection.

Search: ((Renal transplantation) OR (Kidney transplantation)) AND ((perfusion fluid) OR (perfusion solution) OR (organ preservation solution) OR (preservation fluid)) AND (infection) AND (2000/01/01: 2023/05/01)).

Eligibility criteria

The inclusion criteria for this scoping review were developed using the Population, Concept, and Context framework provided by the JBI Manual [10]. This review encompasses literature from various study designs, including clinical trials, retrospective database reviews, systematic reviews, meta-analyses, scoping reviews, literature reviews, cross-sectional analyses, cohort studies, and case–control studies. Case reports, editorials, commentaries, and correspondences were excluded as they do not typically report original research. There was no exclusion of articles by language. Studies were limited to those published from January 1, 2000, to May 1, 2023, when the use of current immunosuppression started, i.e. induction immunosuppression with thymoglobulin or basiliximab and maintenance with corticosteroids, mycophenolic acid and calcineurin inhibitor.

Data extraction

Data from the selected studies were analyzed and collected by two independent and blinded reviewers (FPM and ACB) by completing a characterization table in Microsoft Word software, which contains:

- Study characteristics: identification (citation), study design, evaluation period, follow-up time, country in which it was developed, language, year, and number of centers included.
- Characteristics of the population: sample size, demographic characteristics (sex, age), characteristics of the donor (type, length of intensive care unit stay, cause of death, culture methods), number of samples, results of cultures and use of antibiotics, number of polymicrobial results, characteristics of the recipient (cause of chronic kidney disease, pre-transplantation diabetes, human leukocyte antigen (HLA) mismatches, cold ischemia time, use of perioperative antibiotics, preemptive antibiotics used to treat culture-positive preservation fluid, antibiotics to treat infection, duration of treatment).
- Main result: the result of the microbiological analysis of the preservation fluid, identified microorganisms, number of infections in the recipient by the same microorganism in the preservation fluid (probable donor-derived infection), complications such as nephrectomy, rupture of anastomoses, rejection, delay in graft function, emergence of multidrug-resistant pathogens, and patient and graft survival.

A third reviewer resolved disagreements when necessary.

Data synthesis

A qualitative (narrative) synthesis of data from the selected studies is presented, outlining the main findings of the microbiological analysis of the preservation fluid and its correlation with outcomes in the recipients.

Results

Literature search and study characteristics

A total of 217 articles were identified from the initial database search. After removing 44 duplicates, 173 articles remained. Of these, 110 were excluded during title and abstract screening due to irrelevance to the review's focus, leaving 63 articles for full-text screening. Subsequent evaluation resulted in the exclusion of 39 articles, mainly due to non-eligibility regarding population ($n = 13$), study design

($n = 14$), the outcome of interest ($n = 7$), or repetition not previously flagged as duplicates ($n = 5$). The detailed screening process is illustrated in Fig. 1. Ultimately, 24 studies were included, 18 were journal articles, and 6 were conference abstracts.

Study characteristics

Most of the included studies were retrospective ($n = 19$) [11–29]. Additionally, there were two prospective studies [30, 31], one cross-sectional study [32], and two case series [33, 34]. The Wakelin et al. study, which accounted for 4.2% of the total, involved four centers, while Corbel et al., a study also representing 4.2% of the total, utilized a national database [15, 27]. The remaining 22 studies (91.6%) were presumed to be from single-center sources [11–14, 16–26, 28–34].

Publications were from 2005 to 2022, with 23 (95.8%) published in English, [11–34] and 1 (4.2%) in Spanish [32]. Geographically, the research was predominantly conducted in the UK ($n = 7$) [11, 14, 17, 19, 23, 25, 27], followed by France ($n = 6$) [12, 15, 16, 30, 33, 34] the USA ($n = 3$) [13, 22, 31], China ($n = 2$) [18, 29], and one study each from Argentina [24], Canada [28], Ecuador [32], Germany [26], Italy [21], and Spain [20] (Fig. 2A). Regarding the data collection timeframe, one study covered the period from 1999 to 2002 [27], and all other studies collected data post-2000 up to 2020. A detailed breakdown of the included studies is provided in Table 1.

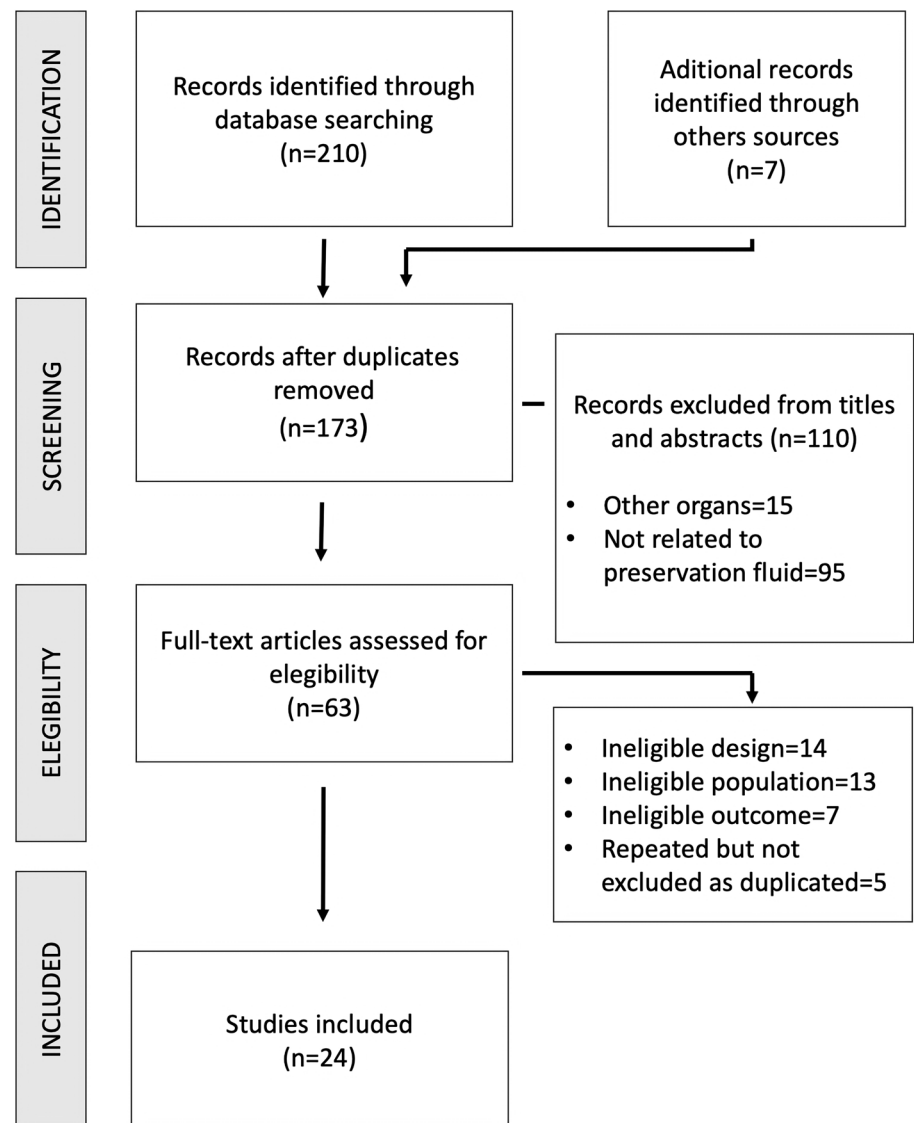
Characteristics of the included subjects

Altogether, 12,052 samples were included. Preservation fluid samples, recipients, and kidney transplants were included in respectively 12 [11, 12, 16, 19, 21, 25–27, 29, 31, 32, 34], 8 [14, 16, 18, 20, 22–24, 29] and 10 [13, 15, 17, 19, 26–28, 30, 33, 34] studies. The distribution across these categories is shown in Fig. 2B.

The follow-up period ranged from 9 to 3763 days [13, 16, 21, 25, 26, 30, 31, 34]. In 19 (79.2%) studies [11–14, 16–18, 20–26, 29, 31–34] only deceased donors were included. Living donors represented 7.3–31.1% of the samples [15, 19, 27, 28, 30]. In 2 studies (8.4%), other organs were also analyzed: liver, pancreas, and heart [28] and liver and heart [30], the remaining 22 (91.6%) were exclusively from kidneys. Studies that did not offer this distinction when analyzing the results were excluded.

In the studies reviewed, 6 (25%) focused solely on bacteria identification [14, 17, 19, 22, 24, 25], 4 (16.7%) exclusively on fungi [26, 30, 33, 34] while both bacteria and fungi were the subject of 14 (58.3%) studies [11–13, 15, 16, 18, 20, 21, 23, 27–29, 31, 32]. The positivity rate

Fig. 1 PRISMA flow diagram



of preservation fluid cultures varied between studies: 23 [17]–67% [22] for bacteria, 0.86 [26]–3.74% [34] for fungi, and 19.9 [27]–77.8% [29] when both fungi and bacteria were considered together.

Recipient characteristics

The age of the recipients ranged from 5 to 71 years [12, 13, 15, 16, 18, 19, 21, 22, 24–26, 29–31, 34], and male gender was the most prevalent, ranging from 37–69% [12, 16, 18, 21, 22, 26, 28–30, 34]. Two studies reported first transplant as making up most of the cases [12, 16], varying from 76.5% [12] to 87.2% [16]. Length of hospital stay [11, 25, 31] was consistent between recipients with treated preservation fluid and those not treated ($p=0.37$) [22].

Several recipient characteristics have been investigated as potential predictors of infection. Female recipients were

associated with a higher prevalence of pyelonephritis in the study of Encatassamy et al. [16]. Other characteristics evaluated across various articles as potential risk factors for probable donor-derived infection (p-DDI) included the etiology of kidney disease, type of dialysis, body mass index, and the presence of diabetes [35]. Underlying renal disease was reported in three studies [16, 26, 29] with glomerulonephritis (18.2–84%), diabetic nephropathy (2–27.3%), and polycystic kidney disease (3.9–13.6%) being the most common conditions. Furthermore, hemodialysis was the predominant renal replacement therapy, being adopted in 51.4% [18] to 66.2% [29] of the cases. Neither the positivity of the preservation fluid nor the risk of transmitting infections to the recipient through the preservation fluid could be associated with body mass index [22, 29], type of kidney disease, or choice of renal replacement therapy [18, 29].

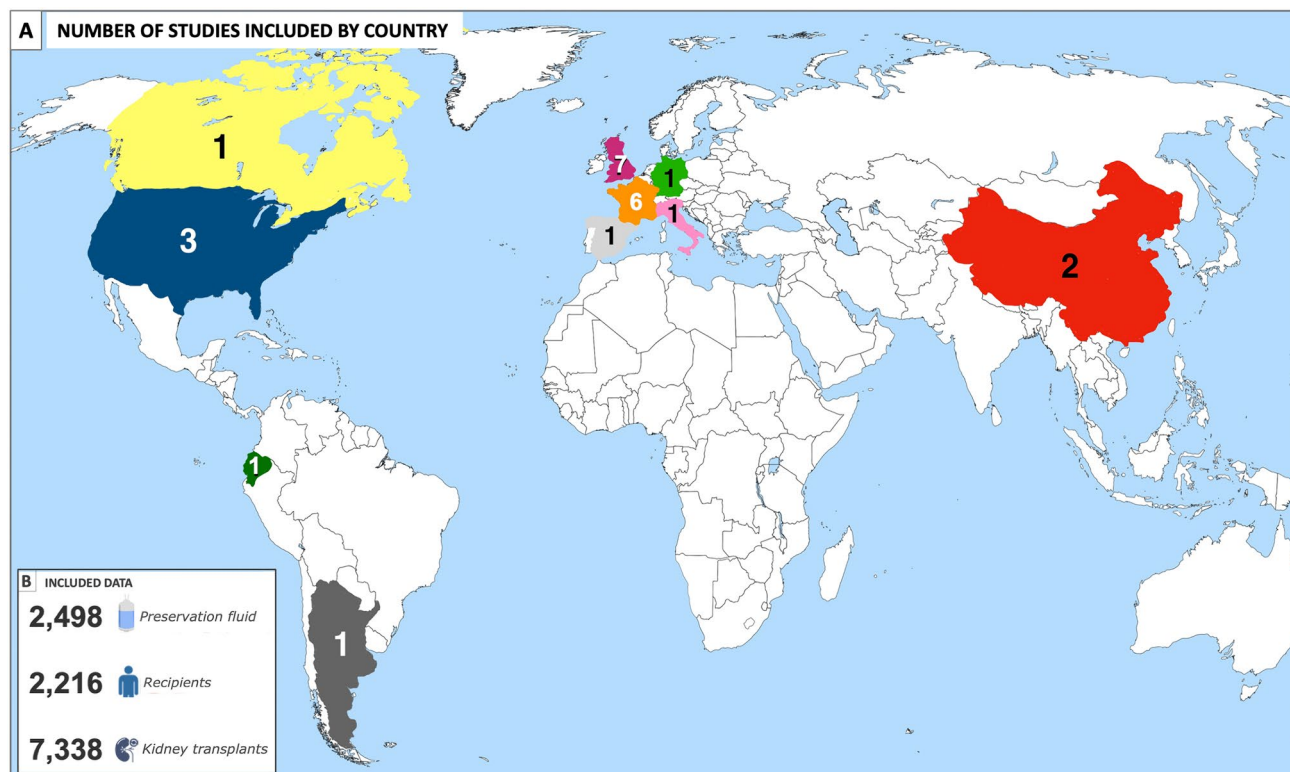


Fig. 2 Geographical distribution and number of included studies by country (A). Total number of preservation fluid samples, recipients, and kidney transplants included (B)

The prevalence of diabetes mellitus among recipients was reported in only two studies. Bertrand et al. indicated a prevalence of 14% [12], while Black et al. noted a 21% prevalence and reported a higher incidence of infections among these patients [14]. Post-transplant diabetes mellitus (PTDM) was observed in 7.5% and 4.3% of recipients, according to Bertrand and Black, respectively [12, 14]. This condition was associated with an increased incidence of Enterobacteriaceae-producing extended-spectrum β -lactamases (ESBL-PE) ($p=0.006$). Other factors related to the development of Enterobacteriaceae-producing extended-spectrum β -lactamases included length of hospital stay, use of urethral catheterization, and urinary tract obstruction. Also, post-transplant therapies such as plasmapheresis and rituximab and the use of antibiotics to treat preservation fluid were associated with Enterobacteriaceae-producing extended-spectrum β -lactamases in the study by Bertrand et al. [12].

Donor characteristics

Age and Gender: Donor age ranged from 0 to 75 years [15, 16, 18, 19, 21, 26, 29, 31, 33, 34] and male gender was the most prevalent among the donors [18, 26, 29, 31, 33, 34].

Length of stay in intensive care unit (ICU): Donor length of ICU stay varied, with reports ranging from 1 to 69 days across various studies [13, 15, 18, 26, 29, 33]. Among these, only Li et al. identified a significant association between the length of ICU stay and culture-positive preservation fluid [18]. Conversely, Yu et al. found no correlation with potential probable donor-derived infections [29].

Deceased Donor Types: Donor after brain death (DBD) and donor after cardiac death (DCD) were described in five (20.8%) studies [11, 14, 18, 19, 25], of which only one including living donors [19]. These studies describe the proportion of each type of donor included, but only Al Midani et al. analyzed outcomes related to this topic [11]. In the latter study, it was found that among culture-positive preservation fluid for *Candida albicans* ($n=15$), a majority (93.3%, $n=14$) were from donor after brain death [11]. No further associations were reported between donor type and culture-positive preservation fluid.

Cause of death: Studies reported that stroke was the cause of death in 27% to 66.7% of the donors, while traumatic brain injury accounted for 9.1% to 60% [18, 26, 29, 31, 33, 34]. No significant differences were observed when analyzing the cause of death concerning culture-positive preservation fluid or the incidence of probable donor-derived infections [18, 29].

Table 1 Data extraction

Author	Publication	Study design/ Evaluation period	Samples/ Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Schiavelli et al., 2018[24]	Conference abstract	Retrospective 2015–2016	72 (R) Deceased	To describe the incidence and consequences of PF in kidney transplantation	43 (59.7%)	Yes	2 (2.8%)	Performing routine PF cultures has increased the detection of contaminants and increased the prescription of early antibiotic treatments. However, the question remains whether the low incidence of p-DDI is due to the low transmissibility of the agents recovered from PFs or early antibiotic treatments and the risk of developing multi-resistant bacteria in those treated early
Yansouni et al., 2012[28]	Journal article	Retrospective 2006–2009	185 (Tx) Mixed	To describe the microbiology and define the clinical impact of culture-positive PF	106 (57.3%)	Yes	53 (28.6%)	Culture-positive PF predicts postoperative infections in solid organ transplantation recipients
Yu et al., 2019[29]	Journal article	Retrospective 2010–2018	1002 (R) Deceased	To determine whether microbial contamination of PF in kidney transplantation is associated with DDI	402/517 (77.8%)	Yes	29 (2.9%)	The prevalence of p-DDI was significantly higher in patients with contamination by the ESKAPE group

Table 1 (continued)

Author	Publication	Study design/ Evaluation period	Samples/ Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Li et al., 2022[18]	Journal article	Retrospective 2015–2020	808 (R) Deceased	To examine the microbiological profile of PF and its association with early events related to infection after kid- ney transplantation and identify related pathogens, resist- ance profile, and the effects of using PE-T	329 (40.7%)	Yes	12 (1.49%)	The incidence of bloodstream and graft site infections was significantly higher in culture-positive PF recipients. Further- more, recipients with ESKAPE pathogens or Candida species had a higher rate of blood- stream ($p=0.033$) and graft site infections ($p<0.01$) than those with other positive pathogens ESKAPE pathogens or Candida species in PF and their antimicrobial resistance properties and non-preventive antibiotic therapy may cause risks of early infection-related events. PE-T should always be used when ESKAPE or Candida pathogens are detected in PF, particularly if they are determined to be resistant to antiimi- crobial treatments
Garrido et al., 2019[32]	Journal article	Transversal 2014–2019	59 (PF) Deceased	To present the avail- able information on contamination of PF and its complications	20 (28.17%)	NA	No clinical complica- tions associated with this contamination were identified in any of the cases	Contamination by Can- dida sp, despite not having a high preva- lence, is clinically the most relevant
Encatassamy et al., 2017[16]	Journal article	Retrospective 2010–2013	424 (R) Deceased	To determine the impact of bacte- rial colonization of PF samples on the development of graft pyelonephritis in KT	195 (46%)	Yes	2 (0.47%)	There was no relation- ship between contami- nation of PF and acute graft pyelonephritis

Table 1 (continued)

Author	Publication	Study design/ Evaluation period	Samples/ Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Bertrand et al., 2013[12]	Journal article	Retrospective 2009–2011	165 (PF) Deceased	To determine the prevalence of PF contamination using systematic, high- sensitivity culture methods and discuss the clinical character- istics and bacterio- logical significance of positive cultures	62 (37.6%)	Yes	The incidence of the clinical complica- tions of PF contami- nation is negligible	The use of more sensi- tive culture methods increased the rate of bacterial contamina- tion of PF and was associated with increased antibiotic prescriptions and increased carriage of ESBL-PE and related infections
Botterel et al., 2010[30]	Journal article	Prospective 2004–2008	397 (Tx) Mixed	To assess the preva- lence of yeast con- tamination on PF	11 (3.1%)	Yes	2 (0.50%)	Fungal contamination in kidney transplanta- tion occurred in 3.1% of cases. The author suggests that a stand- ardized procedure, including systematic screening of PF for fungal contamination, may help determine the extent of the prob- lem and potentially prevent subsequent infectious complica- tions
Matignon et al., 2008[34]	Journal article	Case series 2004–2006	214 (Tx) Deceased	To report the clinical characteristics and results of eight patients undergoing KT in which the PF tested positive for <i>Candida</i> sp.	8 (3.74%)	Yes	No clinical signs of fungal infection were observed in any patient during follow-up	This case series reported the occurrence of a favorable outcome in eight patients, despite very different thera- peutic approaches. He considered that nephrectomy should not be proposed sys- tematically, and that clinical management should be determined on a case-by-case basis

Table 1 (continued)

Author	Publication	Study design/ Evaluation period	Samples/Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Corbel et al., 2019[15]	Journal article	Retrospective 2015–2016	4487 (Tx) Mixed	To determine the epidemiology of bacterial and fungal agents in kidney transplant PF cultures and identify risk factors associated with these positive cultures	920 (20.5%)	NA	NA	PF culture positivity due to the same bacteria found in the donor culture was a rare event (1% of cases), mainly involving Enterobacteriaceae isolated from donor urine samples. The infectious agents in PF appear to be related to contamination that occurred during capture procedures. The study reinforces the urgent need to standardize processes to limit this contamination
Canaud et al., 2009[33]	Journal article	Case series 2004–2007	474 (Tx) Deceased	To describe 8 cases managed with a conservative strategy based on early antifungal therapy, strict morphological monitoring of the graft artery, and surgical second look	8 (1.69%)	Yes	2 (0.42%)	The conservative strategy offered safe management in patients with KT whose PF was contaminated with <i>Candida</i> . The study concludes that early initiation of antifungal therapy, together with rigorous microbiological and morphological monitoring, should be carried out as soon as PF contamination with <i>Candida</i> is detected

Table 1 (continued)

Author	Publication	Study design/ Evaluation period	Samples/ Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Stern et al., 2021 [26]	Journal article	Retrospective 2008–2019	1273 (PF) Deceased	To evaluate the incidence of fungal contamination of PF and determine whether there is an association with infectious complications in KT	11 (0.86%)	Yes	2 (0.16%)	The study suggested that PF should always be evaluated for fungal growth. Two cases were reported which developed a mycotic aneurysm at the anastomosis site, with severe bleeding and the 1-year mortality rate was 18%. Although the incidence of fungal contamination of PF is low, it is associated with high mortality
Ranghino et al., 2016 [21]	Journal article	Retrospective 2010–2012	290 (PF) Deceased	To evaluate the incidence of bacterial contamination by PF and the impact of PE-T on clinical outcomes	101 (34.8%)	Yes	1 (0.34%)	This was the first study designed to evaluate the clinical impact of PE-T in culture-positive PF. Although there is evidence that contamination can occur, the rate of p-DDI is negligible. However, strict clinical and microbiological monitoring of the recipient in case of PF contamination is highly recommended to establish a diagnosis as quickly as possible and promptly initiate appropriate antibiotic therapy

Table 1 (continued)

Author	Publication	Study design/ Evaluation period	Samples/ Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Picola Brau et al., 2018[20]	Conference abstract	Retrospective 2015–2016	191 (R) Deceased	To evaluate the incidence and microbiological etiology of PF contamination in cadaveric renal transplants, analyze its clinical consequences and assess the need for a PE-T	70 (36.7%)	Yes	No patient had a urinary tract infection, surgical site infection, or graft loss caused by the transmission of the microorganism grown in the PF during a 6-month follow-up	It showed that contamination during KT is commonly caused by saprophytic skin bacteria and that less than 9% of kidney transplants required antibiotic or antifungal therapy. This finding may be related to the early initiation of antimicrobial treatment after the isolation of a pathogen in the PF. However, more extensive, and prospective studies must be carried out to confirm these findings
Wakelin et al., 2005[27]	Journal article	Retrospective 1999–2002	269 (Tx) Mixed	To determine the incidence and clinical relevance of bacterial contamination of PF	61 (19.9%)	NA	Infective complications were not seen in the allograft recipients	Even though no infectious complications were found, the author recommends routine microbiological analysis of the PF to ensure that potentially significant microorganisms are identified and treated appropriately
Sran et al., 2013[25]	Conference abstract	Retrospective 2012–2013	41 (PF) Deceased	To evaluate the impact of culture-positive PF following deceased donor KT	10 (24.4%)	NA	4 (9.76%)	The study associated the positive result of PF cultures with an increase in the incidence of infections, suggesting proactive verification of these results and establishing appropriate treatment at the beginning of the post-transplant period

Table 1 (continued)

Author	Publication	Study design/ Evaluation period	Samples/ Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Robati et al., 2013[23]	Journal article	Retrospective 2000–2006	237 (R) Deceased	To determine the prevalence and assess the clinical significance of culture-positive PF	66 (21%)	Yes	3 (1.27%)	The study concluded that early identification of microorganisms may allow targeted treatment of culture-positive PF from symptomatic recipients
Al Midani et al., 2021[11]	Journal article	Retrospective 2009–2018	661 (PF) Deceased	To assess the incidence of PF contamination and to review the organisms identified and the impact of this routine analysis	168 (25.4%)	Yes	1 (0.15%)	The study identified a patient with Enterococcus faecalis isolated in the PF and urine two weeks after transplantation and advocates routine culture of the PF for early initiation of treatment when virulent microorganisms are identified
Black et al., 2018[14]	Conference abstract	Retrospective 2014–2016	173 (R) Deceased	To evaluate the significance of PF in deceased donor KT	79 (45.7%)	Yes	NA	In this study, the use of prophylactic antibiotics did not reduce hospitalization time and the author suggests that the decision to administer antibiotics is based on the patient's clinical status and the virulence of the pathogens found
Haq et al., 2022[17]	Conference abstract	Retrospective 2017–2020	100 (R) Deceased	To assess whether cold ischemia time is a risk factor for infection	22 (23%)	NA	NA	According to the results presented by the study, there is a possible correlation between increased cold ischemia time and bacterial growth in PF, however, more research is needed

Table 1 (continued)

Author	Publication	Study design/ Evaluation period	Samples/ Type of donor	Aim	Positive PF (%)	Preemptive antibiotic	Infection with the same germ as PF (%)	Conclusion
Paraskeva et al., 2015[19]	Conference abstract	Retrospective 2012–2014	158 (Tx) Mixed	To evaluate the micro- biological results of culture of PF and ureter from kidney donors	55 (43.3%)	Yes	NA	The author identified high-risk pathogens in 19% of the samples, and was able to treat recipients promptly, avoiding further com- plications
Billault et al., 2009[13]	Journal article	Retrospective 2004–2006	150 (Tx) Deceased	To assess risk and determine whether a patient should receive PE-T	93 (62%)	Yes	3 (2%)	The author used not only on the PF, but also on graft artery, vein, ureter, and perirenal fat. When multiple results were positive for the same pathogen, preemptive treatment was initiated
Rodrigues et al., 2013[31]	Journal article	Prospective 2010–2011	70 (PF) Deceased	To determine the incidence of PF contamination by fungi and its clinical consequences	53 (75%) = 67.1% bacterial + 8.6% fungal	Yes	1 (1.43%)	In this prospective study, the outcomes of recipi- ents whose PF was positive for fungi were analyzed, showing that they may vary from the need for nephrec- tomy due to serious vascular complications to good results, with- out complications
Reticker et al., 2021[22]	Journal article	Retrospective 2015–2017	152 (R) Deceased	To define the incidence of postoperative infection related to PF and examine the negative results and sequelae of culture- positive PF	102 (67%)	Yes	No cases of infec- tion related to PF, regardless of whether culture-positive PF was treated or untreated	This study did not identify a difference in the incidence of infections between patients with a positive PF culture compared to those with a negative culture and further suggested that antimicrobial treatment may not be necessary for pathogens that are common contaminants and of low virulence

ESBL-PE: Enterobacteriaceae producing extended-spectrum β -lactamases; ESKAPE: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species; KT: kidney transplant; NA: Not available; P-DDI: probable donor-derived infection; PE-T: preemptive treatment; PF: preservation fluid; R: receptor; Tx: transplant

Donor microbiological cultures: Only two studies assessed donor cultures, mainly blood and urine cultures, observing positivity rates of 9% [13] to 20.3% [15]. The administration of antibiotics to donors, as reported in studies by Corbel, Stern, Billault, and Canaud, varied between 65 and 100% [13, 15, 26, 33]. No other association with probable donor-derived infections was identified.

Transplantation characteristics

Induction immunosuppressive therapy: As reported in several studies, induction therapy was administered in 62.5% to 100% of the recipients. Basiliximab was the preferred agent in 52.6% to 98.6% of cases, whereas thymoglobulin was used in 3.44% to 47.9%. No studies identified a direct correlation between the administration of induction immunosuppressive therapy and an increased incidence of probable donor-derived infections [29]. However, an association between thymoglobulin and urinary tract infections (UTIs) was noted in two separate studies [16, 21].

HLA mismatches: Three studies referenced the number of HLA mismatches [29, 31, 34]. Only Yu et al. evaluated the association between HLA mismatches with probable donor-derived infections, with negative results [29].

Cold ischemia time: The time ranged from 3.6 to 28.5 h across studies. No notable differences were linked to either preservation fluid positivity or the occurrence of probable donor-derived infections [13, 15–18, 21, 29, 31, 33, 34].

Delayed graft function (DGF) was reported in 15.2% to 50% of recipients, as documented in multiple studies [14, 18, 29, 34]. Black et al. observed no significant difference in infection rates in relation to delayed graft function. Similarly, Li et al. found no differences in the prevalence of culture-positive preservation fluid samples [14, 18]. However, a trend toward an increased incidence of probable donor-derived infections was noted [29].

Bacterial culture-positive preservation fluid

In the preservation fluid, the most commonly occurring microorganisms were reported in 16 studies, representing 66.7% of the total. Figure 3 illustrates the primary pathogens identified in these studies, indicated by their prevalence, study design, and the number of samples analyzed.

In 13 (54.2%) studies [12–18, 20, 22, 24, 27, 28, 35] *coagulase-negative Staphylococcus* was the most prevalent microorganism, followed by *Staphylococcus epidermidis* in 2 (8.4%) studies [11, 21], and *Enterococcus spp* in 1 study (4.2%) [29], with 22.4% positivity. In 3 (12.5%) studies, this information was not included [19, 23, 25].

In three (12.5%) studies [18, 28, 29], the authors defined a severity profile to classify the pathogens isolated in the preservation fluid. In Yansouni et al., cultures were classified as

"high risk" if they were identified as *Staphylococcus aureus*, beta-hemolytic *Streptococcus* species, *Streptococcus pneumoniae*, *Enterococcus* species, gram-negative bacteria, any spore-forming anaerobic gram-positive bacteria, or fungi. The most identified high-risk pathogens were Enterobacteriaceae. All other positive cultures were defined as "low risk," including normal skin flora such as *coagulase-negative Staphylococcus* species and *Corynebacterium* species [28].

Yu et al. and Li et al., in 2019 and 2022, respectively, introduced the concept of the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*) as the most drug-resistant microorganisms [18, 29]. Further details are discussed in a subsequent paragraph [29]

Li et al., comparing positive and negative preservation fluid results, identified differences in bloodstream infection ($p=0.006$) and surgical site infection ($p=0.004$), as not being significant for pneumonia ($p=0.386$), surgical wound ($p=0.070$), urinary tract infection ($p=0.265$) or infectious diarrhea ($p=0.188$) [18].

Antimicrobial therapy: surgical prophylaxis and preemptive use

Antimicrobial therapies employed to prevent infections can be categorized into two main types: surgical prophylaxis, initiated during surgery, and preemptive treatment. The latter is initiated when a pathogen is detected in the preservation fluid, leading to targeted treatment even without overt signs of infection in the recipient [36].

The use of perioperative prophylactic antibiotics was described in 15 (62.5%) studies [11–13, 16, 18, 21–23, 25–29, 31, 34]. The duration of therapy ranged from a single dose [13, 23, 26, 27, 31] to 9 [21] days. The use of preemptive antibiotics was described in 19 (66.7%) studies [11–14, 16, 18–24, 26, 28–31, 33, 34]. However, the duration of use was reported in eight [11, 21, 22, 26, 30, 33, 34]. In the Matignon et al. study, it ranged from 14 days to 3 months, whereas in Reticker's study, the average duration was five days [22, 34]. The treatment of choice was detailed in only 6 (25%) studies [22, 24, 26, 30, 33, 34], most of which described antifungal therapy. Fluconazole was used in 5 (20.8%) studies [24, 26, 30, 33, 34], caspofungin in 3 (12.5%) [26, 30, 34], voriconazole in 2 (8.4%) [30, 34] and vancomycin in 2 (8.4%) [22, 24]. Amphotericin [24], 5-fluorocytosine [33], imipenem [24], trimethoprim-sulfamethoxazole [24], and cephalosporin [22] in 1 (4.2%) study.

Bertrand et al. found that patients with culture-positive preservation fluid who received preemptive antibiotics

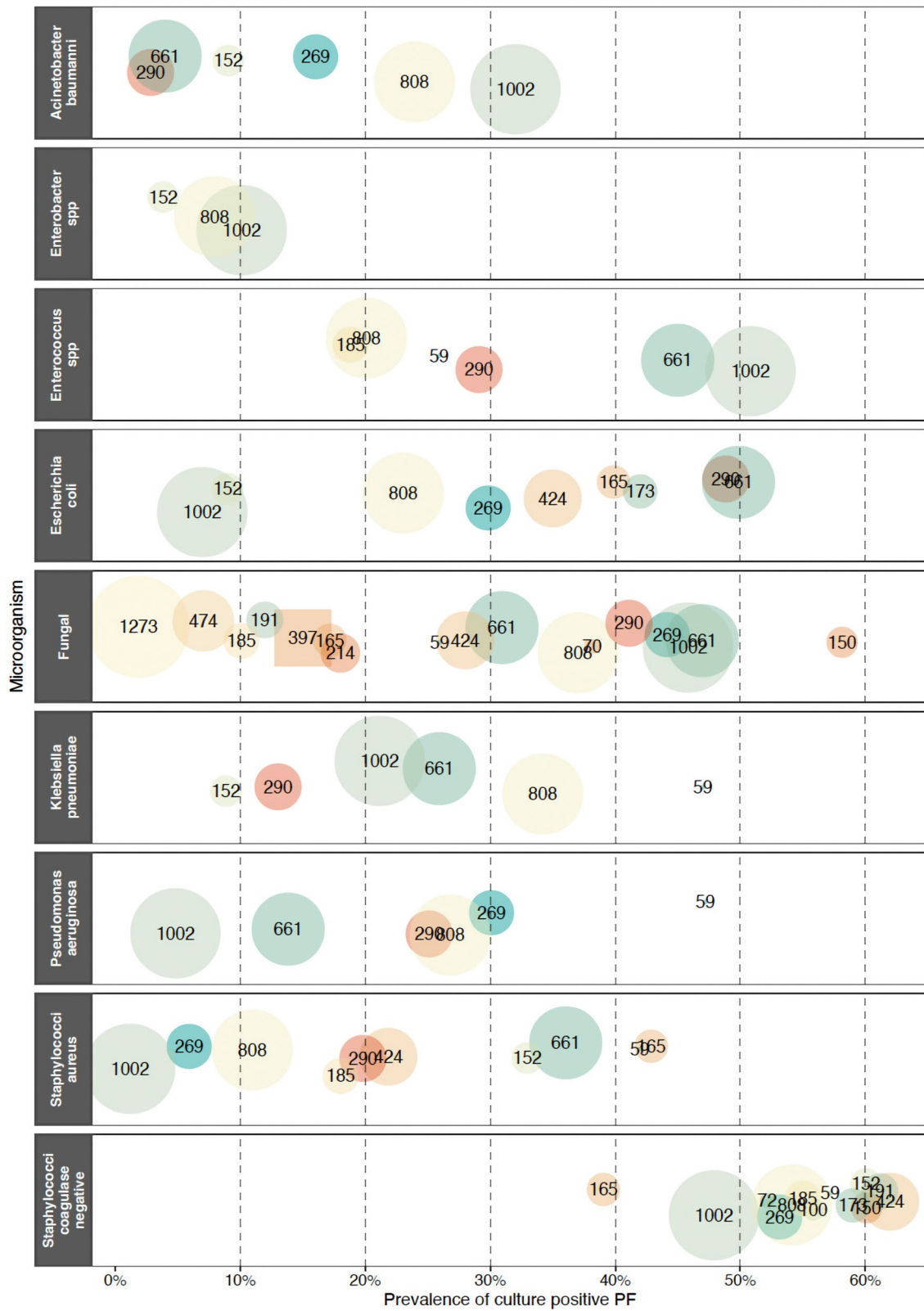


Fig. 3 Bubble chart of the primary pathogens identified in the included studies, indicated by their prevalence. The size of each bubble is proportional to the number of samples evaluated in each

study, with distinct colors representing different studies. The shape of the bubbles indicates the study design: circles for retrospective and squares for prospective studies

had a significantly higher risk of colonization by Enterobacteriaceae-producing extended-spectrum β -lactamases, with the majority developing urinary infections. The study concluded that preemptive antibiotic use is an independent risk factor for acquiring Enterobacteriaceae-producing extended-spectrum β -lactamases. Furthermore, there was no increased rate of invasive infections among those not receiving preemptive antibiotics [12].

Probable donor-derived infection

Infection in recipients with the same microorganism found in the preservation fluid was reported in 14 (58.3%) studies [11, 13, 16, 18, 21, 23–26, 28–31, 33] and the prevalence ranged from 0.15% [11] to 28.6% [28]. Commonly observed infection sites included the graft site, mycotic aneurysm leading to infectious rupture of the graft renal artery, urinary tract infections, pneumonia, and superficial abscesses. The primary therapeutic agents employed were meropenem, ciprofloxacin, fluconazole, amphotericin, and voriconazole, with treatment durations spanning from 1 to 94 days [26, 30, 33].

Aiming to identify predictors for probable donor-derived infections in recipients, Raghino et al. assessed clinical and laboratory variables, including body temperature, white blood cell count, and C-reactive protein levels, whenever positive cultures from preservation fluid were reported. However, no significant differences were observed in these markers between the groups analyzed in the study [21].

In Billault's study, graft components, including the artery, vein, ureter, and perirenal fat and preservation fluid, were analyzed. Sixty-nine percent of the grafts had negative results, while 31% were positive: 51% had one positive sample, 22% had two, 23% had three, and 4% had four. The most commonly positive sample was the preservation fluid at 62%. Direct pathogen transmission from graft to recipient was confirmed in three cases, leading to specific antibiotic treatment based on the identified pathogens [13].

Yansouni et al. found that recipients with grafts from culture-positive preservation fluid were at increased risk of infection by the same pathogen in the first 90 days post-transplant (RR 2.2; 95% CI, 1.28; 3.90), but no difference in bloodstream infections or mortality was observed [28]. Encatassamy et al. investigated the link between culture-positive preservation fluid and acute post-transplant pyelonephritis, finding two cases (4.4%) with matching *E. coli* in the preservation fluid and urine but differing antibiogram results [16].

ESKAPE group

The ESKAPE group significantly elevates the risk of early post-transplant probable donor-derived infections when detected in preservation fluid, according to Yu et al. [29].

The authors evaluated the recipients of 1077 deceased kidney transplants coming from 560 donors and reported a higher incidence of probable donor-derived infections in cases of ESKAPE contamination compared to other bacteria [7.2% (18/251) vs. 1.0% (4/405), $p=0.000$]. The ESKAPE pathogen group was also the only independent risk factor for probable donor-derived infections, conferring a three-fold increase in risk (OR: 3.4; 95% CI: 1.58–7.39, $p=0.002$) [29].

Another study evaluated data from 514 KT donors and 808 recipients and showed an increased rate of bloodstream infection (14.1% versus 6.9%, $p=0.033$) and graft-site infection (16.7% versus 3.5%, $p<0.01$) among recipients with culture-positive preservation fluid for ESKAPE. In this group, preemptive antibiotic therapy was associated with a reduction in bloodstream infection (11.8% versus 35.7%, $p=0.047$) [18].

Additionally, Li et al., found that recipients with culture-positive ESKAPE pathogens or *Candida* experienced higher probable donor-derived infection rates (6.4% versus 1.2%, $p=0.011$) along with an increase in bloodstream and graft-site infections [18].

Fungal culture-positive preservation fluid

Among the included studies, four exclusively reported the presence of fungal culture-positive preservation fluid, as indicated by Stern, Botterel, Matignon, and Canaud [26, 30, 33, 34]. Concurrently, Rodrigues et al. described bacterial positivity but also provided detailed results on fungal culture positivity [31]. *Candida albicans* was the most common, with 59% (26/44), followed by *Candida glabrata* 25% (11/44), *Candida tropicalis* 9.1% (4/44), *Candida krusei* 4.5% (2/44) and *Candida parapsilosis* 4.5% (2/44). The prevalence of fungal positivity in these studies varies from 0.86 [26] to 8.6% [31].

Botterel et al. and Stern et al. identified 11 patients, each of whom received fungal-positive kidneys, while Canaud et al. and Matignon et al. described 8 cases, and Rodrigues et al. 6 cases [26, 30, 31, 33, 34].

In the study of Stern et al., eleven recipients (11/1273, 0.86%) received kidneys stored in preservation fluid contaminated by *Candida* species. Five underwent fungal treatment due to infection suspicions. Two experienced *Candida*-linked infections in arterial anastomosis, one of whom succumbed to hemorrhagic shock on the ninth post-operative day, and the other faced complications leading to death 225 days post-transplantation [26].

Rodrigues et al. reported an 8.6% incidence of fungi in preservation fluid. Of the six patients receiving kidneys from culture-positive preservation fluid, two developed vascular complications. One was readmitted 37 days after

transplantation with renal artery aneurysm and hemoperitoneum. The other patient was readmitted one week after transplantation with asymptomatic graft dysfunction, and aneurysmal dilation in one of the graft arteries was identified. Both required nephrectomies [31].

Canaud et al. observed *Candida* in 1.7% of preservation fluid samples. Six patients had intra-abdominal collections suggestive of surgical site infections and were treated conservatively with antifungal therapy [33].

Another study found *Candida* in 3.7% (8/214) of kidney graft preservation fluid. None of the eight recipients showed *Candida* in urine or blood. They underwent antifungal treatment, ranging from 14 days to 3 months. After an average 18.5-month follow-up, no fungal infection signs were evident, and no aneurysms were detected in the ultrasound and magnetic resonance angiography evaluations, with all grafts remaining functional [34].

Botterel et al. identified yeast in 3.1% (11/356) of kidney preservation fluid samples; *C. albicans* in 6 cases, *C. glabrata* in 3, *C. tropicalis* in 1, and *C. krusei* in 1. Regular ultrasonography and magnetic resonance angiography post-transplantation did not detect any aneurysms or vascular complications [30].

Discussion

Prevention, diagnosis, and treatment of infectious diseases in transplantation are essential contributors to better outcomes. The risk of serious infections is determined in part by interactions between the patient, epidemiological exposures, and their immunosuppression status [6]. Therefore, every effort must be made to establish specific microbiological diagnoses and prevent unexpected transmission of infections from donor to recipient, which, although rare, is associated with significant morbidity and mortality [2, 37]. This scoping review was motivated by the insufficient evidence in the literature guiding the clinical management of positive results of preservation fluid in kidney grafts. Given the considerable variability in study designs, descriptions, and outcome measurements, we opted for a scoping review. This approach permitted the inclusion of articles with diverse designs and outcome measures, ensuring a comprehensive collection of available evidence.

Oriol et al. published, in 2017, the first systematic review and meta-analysis on the impact of culture-positive preservation fluid on solid organ transplantation, and included liver, kidney, heart, and lung transplant studies. This review incorporated 17 studies in which the incidence rate of culture-positive preservation fluid was 27% for retrospective and 85% for prospective studies. Within this systematic review, only eight studies focused on KT, four exclusively evaluated kidney transplant preservation fluid, and 4 were multi-organ

studies. No differences in the incidence of culture-positive preservation fluid were found when stratifying by organ type [38].

Most of the existing studies are retrospective and single-center. Only two prospective studies were found, and they evaluated preservation fluid positivity solely for fungi [30, 31]. Wide variability in the prevalence of culture-positive preservation fluid across the studies was observed, ranging from 19.9% [27] to 77.8% [29]. *Coagulase-negative Staphylococci* emerged as the predominant microorganisms in preservation fluid and were generally considered to pose a low risk for probable donor-derived infections in the recipients [28]. Although the positivity of the preservation fluid is elevated among the studies, the incidence of infections in the recipients attributable to this finding is proportionally low [21].

In this review, we have identified two specific scenarios wherein preemptive antibiotic therapy is deemed necessary by the majority of researchers. Firstly, when the microorganisms isolated in the preservation fluid were considered highly drug-resistant, more recently referred to as the ESKAPE group [18, 29, 39]. Secondly, the emergence of fungal growth in preservation fluid calls for intervention, a stance supported universally by studies reporting such contamination independent of the presence of clinical infection symptoms [26, 30, 31, 33, 34]. Regarding indications for preemptive antibiotic therapy in donor after brain death and donor after cardiac death, the limited data concerning probable donor-derived infections preclude the recommendation of preemptive antibiotic therapy based solely on the type of donor. Nonetheless, Wan et al. and Ravaioli et al. reported a heightened incidence of infections in donor after cardiac death kidney transplant recipients, potentially linked to the procedures of vascular cannulation and the associated risk of mycotic aneurysm [40, 41].

While consensus is yet to be reached on the timing or duration of preemptive antibiotic therapy, its application in targeting pathogens from the ESKAPE group and *Candida* species is recognized for providing protection against early infections post-transplant [18, 29]. Moreover, donor extended ICU stays have been correlated with increased positivity in preservation fluid [18].

Although culture-positive preservation fluid for high-risk microorganisms is linked to a higher incidence of post-operative bacterial infections, mortality as a direct outcome remains infrequent [28]. In contrast, infections attributed to *Candida* species in the context of preservation fluid are associated with more severe consequences, including the potential need for graft nephrectomy [26, 31], vascular complications [42, 43], and a heightened mortality risk [26]. Notably, donors who succumb to trauma, especially those with digestive tract injuries, appear to be at significant risk

Table 2 Suggestions for managing preservation fluid contamination in kidney transplantation

- 1- Preservation fluid from kidney donations should always be collected for microbiological analysis, regardless of donor's infection status or specific characteristics [11, 19, 23, 25, 27]
- 2- The presence of microorganisms from the ESKAPE group in the preservation fluid demands immediate attention. We **suggest** starting preemptive treatment, irrespective of symptoms or signs of infection in the recipient [18, 29]
- 3- For microorganisms other than those from the ESKAPE group, we **advise against** preemptive treatment. Instead, adopting a vigilant surveillance approach to promptly detect initial signs of infection in the recipient, followed by the timely initiation of antimicrobial treatment, seems to be a suitable and reliable strategy [12, 14, 21, 22]
- 4- Detection of fungi in preservation fluid is a **life-threatening situation**. A prompt antifungal preemptive therapy must be initiated. Fluconazole is the first-line recommended treatment [26, 30–34]

for fungal contamination and warrant meticulous monitoring [26, 44].

In 2012, the American Society of Transplantation, Infectious Diseases Community of Practice released a guideline addressing Donor-Derived Fungal Infections in Organ Transplant Recipients. The guideline underscores the need for more comprehensive studies to determine the risk factors associated with *Candida* transmission and to evaluate the cost-effectiveness of routinely culturing preservation fluid. Based on their observations, it is recommended that, in instances where the preservation fluid tests positive for *Candida* or when there is a historical record of damage to the donor's gastrointestinal tract, cultures from blood, urine, and other clinically significant sites be obtained, followed by the commencement of antifungal treatment. Fluconazole is the recommended first-line treatment. Echinocandins are suggested as alternatives, especially when the *Candida* species is not identifiable or when non-albicans *Candida* is suspected. The guideline advises that, barring any documented infection, empirical antifungal therapy can be halted after a 2-week course. However, treatment should be prolonged to between 4 and 6 weeks for patients exhibiting clinical or microbiological signs of infection. In cases where vascular involvement is noted, antifungal therapy should be administered for at least 6 weeks [44].

Careless use of preemptive antibiotics in preservation fluid can inadvertently promote resistance, particularly the emergence of Enterobacteriaceae-producing extended-spectrum β -lactamases. This risk is heightened in recipients with predisposing factors for Enterobacteriaceae-producing extended-spectrum β -lactamases, including diabetes mellitus, recent urinary tract procedures, treatment with additional immunotherapies (such as plasmapheresis and rituximab), and extended hospital stays [12].

The primary strength of this review is that it is the first scoping review to evaluate outcomes related to culture-positive preservation fluid in kidney transplantation. However, a significant limitation is data heterogeneity. Not all studies consistently detailed the characteristics of donors, recipients, transplants, immunological data, or aspects pertinent to the

surgical process. This inconsistency complicates efforts to extrapolate indications on optimal decision-making. It is evident that preservation fluid positivity in kidney transplantation is a global concern, given that the included articles hail from diversely resourced countries. A limitation of the included studies is their retrospective nature and being predominantly single-center.

Based on the findings of this scoping review, we propose recommendations concerning organ preservation fluid in kidney transplantation, described in Table 2.

In conclusion, routine culture of preservation fluid is indicated to identify pathogenic organisms and provide targeted treatment, preventing the development of donor-derived infections. A considerable proportion of contamination is attributed to non-pathogenic or low-virulence microorganisms, with a minimal risk of developing relevant infection, thus, antimicrobial treatment for these pathogens can be avoided, reducing the excessive use of antibiotics and the induction of resistance. For ESKAPE pathogens or *Candida* species, considered highly pathogenic, preemptive therapy may allow protection against infections. Therefore, we suggest that preemptive antibiotic therapy should always be used when ESKAPE or *Candida* pathogens are detected in preservation fluids.

Prospective clinical trials and larger-scale studies need to be conducted to validate these assumptions and recommendations drawn from retrospective analyses. As of now, this scoping review represents the most comprehensive summary of evidence regarding outcomes associated with contamination of preservation fluids in kidney transplantation and suggestions on its management.

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Data availability This study was a scoping review and did not involve recruiting participants or collecting primary data; therefore, ethical

approval was unnecessary. The data analyzed in this scoping review primarily consist of articles and reports that are publicly accessible. These were retrieved from various databases, including PubMed, Scopus, Web of Science, as well as directly from the websites of the journals where these articles are published. Hyperlinks to the articles analyzed have been included within the references section of this article for ease of access.

Declarations

Conflict of interest The authors of this submission have no conflict of interest or financial ties to disclose.

Ethical approval The study was carried out in accordance with the Declaration of Helsinki in human research.

Human and animal rights This study does not contain animal studies performed by any of the authors.

Informed consent Informed Consent is not required for this type of study.

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