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Review article

# Clinical impact of culture-positive preservation fluid on solid organ transplantation: A systematic review and meta-analysis

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ABSTRACT

Contamination of the preservation fluid (PF) used for donated organs is a potential source of post-transplant infection. However, the information on this issue is scarce. We therefore conducted a systematic review and meta-analysis to assess the incidence of culture-positive PF and its impact on solid organ transplant (SOT) recipients. Seventeen studies were identified and included. The overall incidence of culture-positive PF was 37% (95% CI: 27% to 49%), and the incidence of PF-related infections among SOT recipients with PF cultures that grew pathogenic microorganisms was 10% (95% CI: 7% to 15%). There were differences in the rates of infections due to pathogenic microorganisms between SOT recipients who received pre-emptive treatment and those who did not, but without statistical significance. The mortality rate among SOT recipients with PF-related infection was 35% (95% CI: 21% to 53%). In conclusion, although contamination of the PF of donated organs is frequent, the incidence of PF-related infection is relatively low. A closely clinical and microbiologic monitoring of the SOT recipient in case of culture-positive PF, regardless of the type of microorganism isolated might be do in order to establish a prompt diagnosis of PF-related infection.



## 1. Introduction

Solid organ transplantation (SOT) has become the treatment of choice to improve life expectancy and quality for patients with end organ failure [1–3]. Regrettably, due to the need for immunosuppressive therapy in order to avoid graft rejection, infection in the post-transplant period represents a major cause of in-hospital morbidity and mortality among SOT recipients, especially in the first month post-transplant [4,5]. Immediately post-transplant, infections are usually derived from the donor, recipient, or technical complications of surgery [6].

In this sense, the presence of microorganisms on the organ preservation fluid (PF) culture has been pointed out as related with post-transplant infections. Although PF contamination has been reported via the donated organ, it is speculated that the most frequent mechanism of PF contamination is exogenous contamination during the processes between organ explantation from the donor to implantation in the recipient [7–10]. In addition it must be taking into account that the PF not only keeps the microorganisms alive but also facilitates their growth, providing a direct route of transmission of infection to the recipient [6,11].

Our current understanding of PF contamination and subsequent recipient infection derives mainly from only a few retrospective studies and case reports that offer discordant results [7,12,13]. To detect allograft contamination and improve the early diagnosis and management of infection-related complications, some transplant centers now routinely take intra-operative cultures from the organ PF. Importantly, however, there are no widely accepted guidelines for the evaluation of PF or for the use of prophylactic antibiotics [14]. In fact, the usefulness of routinely performing PF cultures, and their impact on the prognosis of SOT recipients, has not been established. This systematic review aimed to address this knowledge gap to summarize the current state of the evidence on this issue.

## 2. Materials and methods

The systematic review protocol was registered with PROSPERO (CRD 42017064017), and the study was conducted according to the Preferred Reported Items for Systematic Reviews and Meta-Analysis guidelines [15]. Two independent investigators performed a systematic literature review of the Ovid MEDLINE, Web of Knowledge, Cochrane Library,

*Abbreviations:* CI, confidence interval; CNS, *Coagulase-negative staphylococci*; N, non; PE-T, pre-emptive antibiotic therapy; PF, preservation fluid; SOT, solid organ transplantation; UTI, urinary tract infection; Y, yes.

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SCOPUS, and Science Direct databases for full-text articles that assessed the etiology, incidence, and clinical impact of PF contamination in SOT recipients. The search strategy included the following search terms: (preservation fluid OR preservation solution OR perfusion fluid OR perfusion solution) AND (transplantation) AND (contamination OR culture-positive OR infection). We searched the databases from inception to September 2016, and included only publications written in English, Spanish, or French. In addition, we excluded studies evaluating animal models or composite outcomes, reviews, abstracts from congresses/conferences, letters, editorials, and cases reports. To ensure saturation, the references lists of any included articles were also checked.

Observational cohort studies, both prospective and retrospective, were included in the meta-analysis if they reported the rate of culture-positive PF, which was defined as growth of any microorganism in the PF culture. Additionally, we collected information on the rate of culture-positive PF both by pathogenic microorganisms and saprophytic flora. Saprophytic flora was considered: *Coagulase-negative staphylococci*, *Corynebacteria*, *Streptococcus viridans* group. The following microorganisms were considered pathogens: *Gram-negative bacilli*, *Staphylococcus aureus*, *Streptococci* other than *Streptococcus viridans* group, *Enterococci* and *Candida* spp. Data regarding antibiotic prophylaxis for transplantation, pre-emptive antimicrobial treatment, and PF-related infections (microorganism isolated, source of infection, days of antimicrobial treatment, and outcomes) were also collected. PF-related infections were the main outcome measure of this meta-analysis.

### 2.1. Procedures

After performing the searches, non-relevant studies were excluded by abstract review and the potentially relevant studies were retrieved as full-text reports and assessed for compliance with the inclusion criteria. Two reviewers carried out the data extraction and quality assessment in a blinded fashion, and performed the search and screening independently. The reasons for excluding studies were recorded.

The main characteristics of the identified articles were extracted using a standardized form; relevant data included the author, year and journal of publication, country, type of study design, number of culture-positive PF cases, and number of culture-positive PF cases caused by pathogenic microorganisms or saprophytic flora. Raw data concerning the number of recipients with and without PF-related infection, stratified by the presence or absence of pre-emptive antibiotic treatment (PE-T) were extracted from original reports or by contacting the corresponding author directly. Information about individually cases of PF-related infection (isolate, source of infection, and outcomes) was also recorded if available. Discrepancies regarding eligibility or quality assessment were resolved by consensus. The risk of bias within individual studies was evaluated using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies [16].

### 2.2. Statistical analysis

The incidences of culture-positive PF and of PF-related infection, in both treated and untreated SOT recipients, as well as the difference in infection rates between treated and untreated SOT recipients, were estimated for the isolated microorganisms, pathogenic isolates, and saprophytic flora. We pooled the point estimates from each study using the generic inverse-variance method of DerSimonian and Laird. A random effects model or a fixed effects model was used depending on the grade of heterogeneity. We used the Cochran's Q test and the $I^2$ statistic to assess statistical heterogeneity, which was considered relevant when $I^2$ was >50% and the p-value for heterogeneity was <0.1. We conducted a sensitivity analysis stratifying the results by the study type (retrospective and prospective). Publication bias was assessed graphically and analytically by Egger's test [17], based on examining the asymmetry of the funnel plot by weighted linear regression. All statistical analyses were done with R (R Core Team, 2015) and Version 3.3.3 of the General Package for Meta-Analysis ("meta").

## 3. Results

A total of 882 abstracts were reviewed, from which we identified 56 articles for in-depth evaluation. After full-text review, we excluded a further 39 articles and identified 17 that were suitable for inclusion in the present meta-analysis [7–14,18–26]. Fig. 1 summarizes the literature review process. All included studies had an observational design. The Newcastle–Ottawa scale revealed the absence of comparability among the study groups due to the observational nature of the studies (Supplementary Table 1). In some cases, the follow-up period was not specified. Apart from these limitations, the reports fulfilled all other criteria. The included studies yielded 3788 analyzed PF cultures corresponding to SOT of the liver, kidney, pancreas, and lung. The number of PF cultures analyzed in the studies varied from 46 to 610. The main characteristics of the studies are summarized in Table 1.

### 3.1. Incidence of culture-positive PF

All 17 studies reported the number and percentage of culture-positive PF. The overall incidence of culture-positive PF estimated by random effects was 37.0% (95% CI: 27.0% to 49.0%; $I^2 = 97\%$, $p < 0.001$). Stratifying by type of study, the estimated incidence rates of culture-positive PF were 27.0% (95% CI: 18.0% to 38.0%) and 85.0% (95% CI: 39.0% to 98.0%) among the retrospective and prospective studies respectively (Fig. 2). No significant differences were detected when stratifying by type of organ transplant.

### 3.2. Incidence of culture-positive PF by pathogenic microorganisms or saprophytic flora

Eleven studies involving 2594 PF cultures were included in these analyses. The overall incidence of culture-positive PF by pathogenic microorganisms, estimated by random effects, was 13.0% (95% CI: 9.0% to 17.0%; $I^2 = 89\%$, $p < 0.01$). Stratifying by type of study, we observed that the incidences of pathogenic contamination of the PF culture were 21.0% (95% CI: 15.0% to 28.0%) in the prospective studies and 10.0% (95% CI: 6.0% to 15.0%) in the retrospective studies (Supplementary Fig. 1a). Regarding the incidence of culture-positive PF by saprophytic flora, overall it was estimated at 19.0% (95% CI: 9.0% to 36.0%; $I^2 = 98\%$, $p < 0.01$), but it varied from 53.0% (95% CI: 20.0% to 83.0%) in prospective studies to 9.0% (95% CI: 3.0% to 21.0%) in retrospective studies (Supplementary Fig. 1b).

### 3.3. Incidence of PF-related infection

Sixteen studies comprising 907 SOT recipients whose PF cultures were contaminated were included in these analyses. Table 2 summarizes the main characteristics of the 36 SOT recipients that suffered a PF-related infection. The overall incidence of PF-related infection, estimated by random effects, was 4.0% (95% CI: 2.0% to 7.0%; $I^2 = 60\%$, $p < 0.01$). There was moderate heterogeneity between the studies (Fig. 3a).

When we analyzed only the studies that evaluated PF-related infections by pathogenic microorganisms and saprophytic flora separately, the incidence of infection among SOT recipients with pathogenic contamination of PF cultures was 10.0% (95% CI: 7.0% to 15.0%; $I^2 = 0\%$, $p = 0.46$) (Fig. 3b). No related infection was found in the analysis of SOT recipients with contamination by commensal flora.

### 3.4. Incidence rate of PF-related infections among SOT recipients receiving PE-T

Nine studies involving 326 SOT recipients were analyzed for PF-related infections among SOT recipients receiving PE-T. The overall

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