

# Predictive risk factors of postoperative pneumonia after heart transplantation

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## Research article

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# Abstract

**Background** Pneumonia is a frequent complication in patients undergoing heart transplantation (HTx) which increases morbidity and mortality in this population. Nevertheless, risk factors of postoperative pneumonia (POP) are still unknown. The aim of this study was to investigate the predictive risk factors of POP in HTx recipients. **Materials and methods** In this retrospective study, all patients undergoing HTx between January 2014 and December 2015 were included. All POP occurring until hospital discharge were investigated. The primary end point was the risk factors of POP determined by a Cox model in uni- and multivariate analysis. Data are expressed in OR [95% CI].  $P < 0.05$  was necessary to reject the null hypothesis. **Results** At all, 175 patients were included without any loss of follow-up and 89 POP were diagnosed in 59 (34%) patients. Enterobacteriaceae and *Pseudomonas aeruginosa* were mainly involved. In multivariate analysis, main risk factors were preoperative mechanical ventilation (OR 1.42[1.12-1.80],  $P < 0.01$ ) and perioperative blood transfusion (OR 1.42[1.20-1.70],  $P < 0.01$ ). Duration of mechanical ventilation, time of veno-arterial extracorporeal membrane oxygenation weaning and length of stay in intensive care unit consistently increased the risk of POP which impacted the mortality at 30 days (Odd Ratio: 4[1.3 - 12.4],  $P = 0.01$ ) and 1 year (OR: 6.8[2.5-8.4],  $P < 0.01$ ). In sensitized recipients (53%), plasmapheresis exchanges and intravenous immunoglobulins did not increase the risk of POP. **Conclusion** After HTx, preoperative mechanical ventilation and blood transfusion appear as the main risk factors of POP, enterobacteriaceae and *Pseudomonas aeruginosa* being mainly involved.

## Background

Heart transplantation (HTx) is still the gold standard for the treatment of chronic heart failure, improving the survival but also the quality of life of these patients.(1) The administration of immunosuppressive treatment is essential to prevent rejection, but these therapies expose the HTx recipient to bacterial, viral and fungal infectious complications.(2) Thus, during the first year following HTx, postoperative infections represent the main cause of death in HTx recipients.(3) In cardiac surgery, POP is still the most common infectious complication(4)and is known to be associated with an increased mortality.<sup>5,6</sup> After HTx, the incidence and the risk factors of POP remain poorly investigated.(7–10) In addition, plasmapheresis and intravenous immunoglobulins (IVIg) used to prevent antibody mediated rejection in sensitized recipients may also influence the occurrence of POP after HTx.(11–13) The aim of this study was to investigate the risk factor of POP in HTx recipients, with or without preformed donor-specific anti-HLA antibodies (pfDSA).

## Materials And Methods

### Inclusion criteria

This is a retrospective study conducted in the academic center Pitié-Salpêtrière in Paris, France. All patients undergoing HTx, with or without pfDSA, between January 1<sup>st</sup>, 2014 and December 31<sup>th</sup>, 2015

were included in the study. This work complies with the Declaration of Helsinki, and the institutional review board approved the protocol (IRB 00010254-2018-26).

## Immunosuppression protocol and anti-infective treatment.

All recipients benefited from a standard immunosuppression protocol after HTx (13) based on an induction therapy with rabbit antithymocyte globulin (rATG; Thymoglobuline; Genzyme, Lyon, France;  $1.5 \text{ mg.kg}^{-1} \cdot \text{day}^{-1}$  for 5 days) or basiliximab (Simulect, Novartis, Basel, Switzerland) in case of an infectious context. Prophylactic immunosuppressive therapy included calcineurin inhibitors, mycophenolate mofetil and corticosteroids with posology recommended by ISHLT guidelines.(14) In cases of pfDSA, a prophylactic protocol including perioperative management of pfDSA and systematic treatment of subsequent antibody mediated rejection was applied to patients transplanted with pfDSA. Perioperative management was adapted to the results of the virtual cross-match and to the level of pfDSA, as evaluated by the mean fluorescence intensity (MFI) of the immunodominant pfDSA (ie, DSA with the highest MFI): (1) patients with MFI 500–1000 were treated with IVIg ( $0.5 \text{ g.kg}^{-1}$  over 4 consecutive days, total dose of  $2 \text{ g.kg}^{-1}$ ; Privigen; CSL Behring AG, Bern, Switzerland), (2) patients with MFI >1000 were treated with perioperative plasmapheresis sessions (1 immediately before HTx, then 4 sessions over 4 consecutive days; 2/3 fresh frozen plasma and 1/3 albumin, fibrinogen substitution if serum fibrinogen <  $2 \text{ g.L}^{-1}$ ) and IVIg. Initiation of the protocol was based on detection of pfDSA in historical sera. The treatment was readjusted 2 to 3 days after HTx according to the MFI results at the time of HT. (13)

## Prevention and diagnosis of pneumonia after HTx

POP was defined as pneumonia occurring between the transplantation and hospital discharge and was the combination of clinical criteria ( $\geq$  two criteria including fever  $> 38.5^\circ\text{C}$ , hyperleukocytosis  $> 10^9 \cdot \text{L}^{-1}$  or leucopenia  $< 4 \cdot 10^8 \cdot \text{L}^{-1}$ , occurrence of purulent secretions and the occurrence or persistence of a radiological focus) and microbiological criteria with a positive quantitative culture obtained by bronchial aspiration (threshold  $\geq 10^6 \text{ CFU.mL}^{-1}$ ), bronchoalveolar lavage (threshold  $\geq 10^4 \text{ CFU.mL}^{-1}$ ) or protected distal sampling (PDP, threshold  $\geq 10^3 \text{ CFU.mL}^{-1}$ ).(4,15) The diagnosis of Herpes virus pneumonia was based on the presence of more than  $10,000 \text{ copies.mL}^{-1}$  and the evidence of a cytopathogenic effect on anatomopathological investigation obtained by the bronchoalveolar lavage. The presence of Candida was considered as pathological only if it was associated with lung abscesses. POP diagnosis was retrospectively confirmed by 2 independent investigators (CV, RP) following analysis of the complete medical file, as previously reported.(4)

Prevention of POP in ICU was based on a combination of oro-tracheal intubation, tracheal balloon pressure maintained between 20 and 30 mmHg, repetitive mouth washing with chlorhexidine every 4 hours (Sandoz, Levallois Perret, France) and semirecumbent position. The sedation level was evaluated using the RASS score (Richmond Agitation-sedation Scale), and adapted in order to obtain a RASS score

0-1. Patients were extubated as soon as possible even if they received postcardiotomy circulatory support by Venous-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) for primary graft dysfunction.

## Statistical analyses

Quantitative variables were expressed as mean (SD) or median (IQR) in non-normally distributed variables. Comparisons between the two groups were performed using the Student's t-test or the Wilcoxon rank sum test when appropriate. Mean difference between the two groups with 95% CI was reported for normally distributed variables. Qualitative variables were expressed in numbers (percentage). Comparisons between the two groups were performed using the Chi-2 Pearson test or the Fisher test when appropriate. Absolute risk difference (with 95%CI) was also reported. A Kaplan Meier survival analysis was used. Log Rank tests were then performed on the assumed infection risk factor variables, followed by a univariate Cox model on variables with a  $P < 0.05$  value. Finally, a multivariate model was used for the significant variables.

All  $P$  values were two-tailed, and a  $P < 0.05$  was considered significant. Statistical analysis was performed using SAS software (Statistical Analysis System, SAS Institute, Cary, USA) with GraphPad Prism® software (GraphPad Software, Inc., La Jolla, USA) and XLSTAT® software (Addinsoft, Microsoft, Washington, USA).

## Results

In total, 175 patients were transplanted and consecutively included without any lost-of-follow-up. The recipients were mainly men (129, 73.3%) and the average age was  $50 \pm 13$  years old (Table 1). Indication for HTx was non-ischemic dilated cardiomyopathy in 53% (93/175) and coronary artery disease in 30% (53/175). Overall, 56 patients (32%) were assisted with VA-ECMO until the HTx and were transplanted in salvage conditions, 25 patients (14.2%) were assisted with mechanical circulatory support (MCS) and 15 patients (8.6%) were assisted with mechanical ventilation (Table 1).

Prior to the hospital discharge, 89 POP occurred in 59 (33.7%) HTx recipients (Table 2). The mean time between HTx and POP was 4 (IQR:3-6) days. The main pathogen involved were Enterobacteriaceae (53%), mainly *Klebsiella pneumoniae* (21%) and *Pseudomonas aeruginosa* (36%). In 25% of cases, POP was polymicrobial (Table 2). Bacterial pathogens classically associated with early POP such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* were responsible for a small proportion (10%) of POP in this cohort and cefotaxime was effective in only 36% of the cases (36% of *Pseudomonas aeruginosa* and 69% of Enterobacteriaceae produced extended-spectrum or AmpC beta-lactamases).. In the specific case of the 93 sensitized recipients (53%), 69 patients (74%) were transplanted despite pfDSA higher than 1000 MFI (Table 1). Thirty-seven sensitized recipients developed POP compared to the 22 other recipients (40% vs 27% respectively,  $P=0.08$ )

The multivariate analysis showed that mechanical ventilation at the time of HTx (OR 1.42, 95% CI [1.12 - 1.80],  $P<0.01$ ) and postoperative blood transfusion (OR 1.42, 95% CI [1.20-1.70],  $P<0.01$ ) were the main risk factors for POP. Plasma exchanges and IVIg were not associated with an increased risk of POP.

In HTx group with POP, mechanical ventilation duration, postoperative VA-ECMO support and ICU hospital length of stay increased in comparison with the HTx group without POP. In case of POP, the mortality increased significantly at 30 days (OR:4[1.3-12.4],  $P=0.01$ ) and at 1 year (OR:6.8[2.5-18.4],  $P<0.01$ ). In contrast, POP does not increase rejection rate at 1 year (Table 3).

In postoperative period, 114 (65.5%) primary graft dysfunctions occurred, requiring VA-ECMO support for 5 (4-8) days. The median of mechanical ventilation duration was 2 (1-7) days. Overall survival rate was 92% at 30 days and 87% at 1 year (Table 1). The main cause of death was septic complications (57%) followed by neurological complications (17%).

## Discussion

In this cohort of HTx recipients, a POP occurred in 33.7% of patients, mainly caused by *Enterobacteriaceae* or *Pseudomonas aeruginosa*, and increased consistently the mortality at 30 days and 1 year. Preoperative mechanical ventilation and postoperative blood transfusion, indirectly linked to the postoperative bleeding, were identified as the main risk factors for POP after HTx.

In a Californian cohort of 620 HTx recipients, infections were the main cause of morbidity and mortality while bacterial pathogenesis was involved in only 43% of cases.(8)In addition,most of pneumonia occurring later after HTx were due to *Cytomegalovirus*, *Aspergillus fumigatus* and *Pneumocystis carinii*. (7) However, authors did not investigate infections within the perioperative period but only infectious events at distance of the HTx in immunocompromised patients. Actually, in the postoperative period immunosuppressive therapy has just begun while the frequent intra and postoperative low cardiac output syndrome and hemodynamic instability are at the forefront, as shown by the increased incidence of primary graft dysfunction and postoperative VA-ECMO support in POP group. Hence, postoperative VA-ECMO circulatory support appears as a risk factor for infections.(3,10) <sup>24</sup> Nosocomial infections, especially ventilator associated pneumonia (55%), are frequent in patients assisted by VA-ECMO(17), and HTx recipients assisted by VA-ECMO are known to develop nosocomial infections and pneumonia.(10) Moreover, the low cardiac output syndrome may explain the increased incidence of POP after HTx in comparison with in conventional cardiac surgery, respectively 33.7% vs 5.7%,(4) in which the incidence of intra and postoperative hemodynamic instability is less important.(4) Nevertheless, the early use of VA-ECMO is an efficient support to prevent from organ failure and peripheral tissue hypoperfusion in HTx recipients with severe primary graft dysfunction. In our cohort, the incidence of VA-ECMO support following HTx was very high (66%) because a large proportion of recipients presented risk factors of primary graft dysfunction such as allosensitization (54%), preoperative VA-ECMO support (32%) or mechanical ventilation at the time of transplantation (9%).(18–20) Preoperative VA-ECMO support does not increase the rate of POP while postoperative hemodynamic instability requesting VA-ECMO support

are more frequent in POP group. Altogether, these findings suggest that tissue hypoperfusion occurring during low cardiac output syndrome could contribute to digestive bacterial translocation and may influence the kind of pathogens involved in early POP in HTx. This point should be considered to choose the appropriate empirical antimicrobial therapy of pneumonia in HTx recipients within the perioperative period. The association of increased incidence POP and transfusion or reoperation for bleeding are additional arguments to explain the blood-forming origin of POP(10) and this unusual high rate of *Enterobacteriaceae* and *Pseudomonas aeruginosa* in POP after HTx. Actually, transfusion *per se* is an additional process which is known to increase postoperative infections as soon as the first transfusion of packed red blood cells,(21,22) and to increase 28-day mortality.(23) The modulation of the immune response by transfusion may promote the development of postoperative infectious complications.(24,25) The transfusion in patients supported with VA-ECMO is known also to increase infectious complications.(26) In the present study, beyond the risk associated with low cardiac output and surgical reoperation by itself, 34% of HTx recipients received a postoperative transfusion, increasing the risk of postoperative pneumonia.

In this work, preoperative mechanical ventilation also appears as a major risk factor for POP after HTx, and is already known to be a risk factor for healthcare-related pneumonia and for mortality regardless of the context of HTx. (3,27) The bacterial colonization of the tracheobronchial tree and the alteration of fluid clearance are well known and have been reported to be the main pathophysiological mechanisms of pneumonia during mechanical ventilation.(28) Regarding the effect of mechanical ventilation on POP in HTx recipients, a more haematogenic mechanism is likely to be involved. Therefore, mechanical ventilation as a major risk factor, might be reflective of the HTx recipients' postoperative severity, given that Fast-track management is the priority in all HTx recipients including those with VA-ECMO support.

Plasmapheresis has been shown to prevent AMR in sensitized recipients.(11,12) Yet this more aggressive immunosuppression therapy should increase the recipients' exposure to infectious complications.(29) In kidney transplantation, Chung et al. showed that the administration of rituximab and plasma exchanges increased the risk of postoperative infectious complications.(29) In the present study, HTx recipients treated with plasmapheresis and/or IVIg treatment did not have more POP compared to the others HTx recipients suggesting that this therapy is not the main mechanism involved in sensitized HTx recipients.

Our work has several limitations. First, this is a retrospective and monocentric study with a relatively small sample size. Nevertheless, there was no loss of follow-up and no missing data in this cohort. Second, the population studied is relatively unusual with a high rate of HTx sensitized recipients. However, the proportion of sensitized recipients is increasing, possibly because the technological means to detect pfdSA are evolving. Third, the proportion of HTx recipients assisted with postoperative VA-ECMO support is coherent in this study. Due to the rarity of heart grafts and to the graft distribution prioritization program, the number of primary graft dysfunctions as well as the preoperative severity of recipients is increasing. Nevertheless, our study provides important information on this type of population.

## Conclusion

The occurrence of pneumonia after HTx is frequent and increases the mortality of these recipients. Most frequently pathogens are *Enterobacteriaceae* or *Pseudomonas aeruginosa*, which should be at the center of POP empirical treatment. In difference to Plasmapheresis and IVIg administration, mechanical ventilation prior to HTx and postoperative transfusion appear to be the main identified risk factors for POP.

## List Of Abbreviations

HTx : Heart Transplantation

POP : Post Operative Pneumonia

OR : Odd Ratio

IVIg : IntraVenous Immunoglobulins

pfDSA : preformed Donor-Specific anti-HLA Antibodies

rATG : rabbit AntiThymocyte Globulin

MFI : Mean Fluorescence Intensity

RASS : Richmond Agitation-sedation Scale

VA-ECMO : Veno-Arterial Extracorporeal Membrane Oxygenation

SD : Standard Deviation

IQR : Inter Quartile Range

CI : Confidence Interval

ICU : Intensive Care Unit

## Declarations

### Ethics approval and consent to participate

This work complies with the Declaration of Helsinki, and the institutional review board (Comité d’Ethique pour la Recherche en Anesthésie- Réanimation) approved the protocol (IRB 00010254-2018-26).

### Conflict of Interest Disclosures:

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Nodisclosure was reported and all authors confirmed that they have no financial relationships with companies or relevant entities that make products pertinent to the paper.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. Drs Amour and Vidal had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Competing interests

The authors declare that they have no competing interests

## Funding

The authors declare no source of funding for the research

## Authors' contributions

Drs Vidal, Pasqualotto, Bouglé, Leprince, Coutance, Varnous and Amour were involved in the concept and design of the study. All authors were involved in the acquisition of data. Drs Vidal, Pasqualotto, Varnous and Amour were responsible for the analysis and interpretation of data. Drs Vidal and Amour drafted the manuscript. All authors have read and approved submission of the manuscript.

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## Endnotes

Not applicated

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## Tables

Due to technical limitations, Tables 1-3 are only available as downloads in the supplemental file section

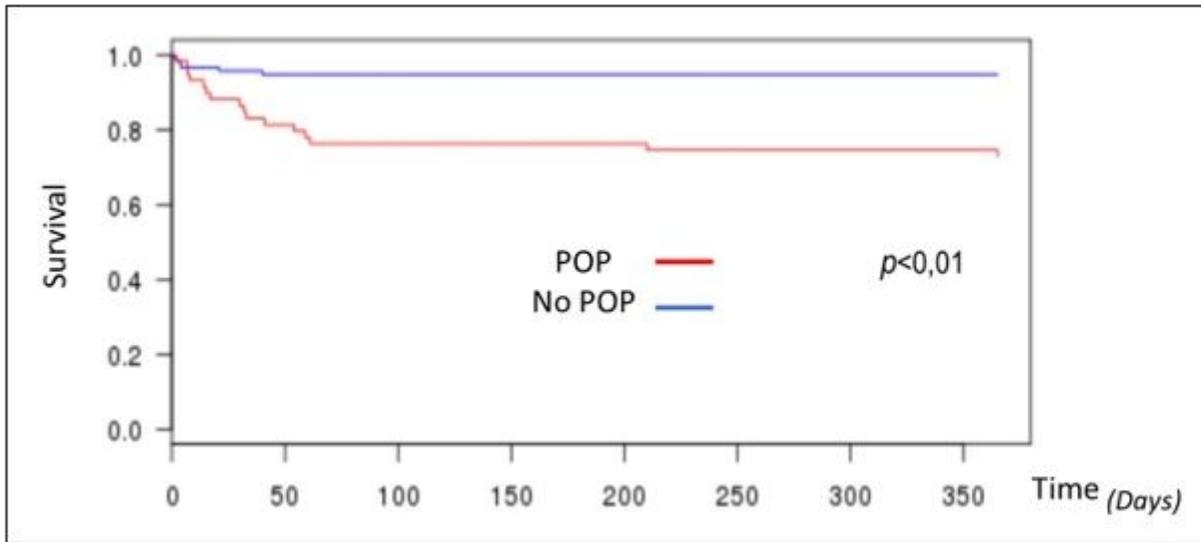
Table 1: Variables associated with postoperative pneumonia (POP) in HTx recipients.

Table 2: Pathogens associated with postoperative pneumonia in HTx recipients

Table 3: Comparison of secondary outcomes between HTx recipients with and without postoperative pneumonia

## Figures

**Figure 1.** One-year survival curve of HTx recipients with and without postoperative pneumonia (POP), respectively 95% versus 73%,  $p < 0.01$ .



**Figure 1**

One-year survival curve of HTx recipients with and without postoperative pneumonia (POP), respectively 95% versus 73%,  $p < 0.01$ .

## Supplementary Files

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