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Infections Management in the Lung Transplant Setting in Italy: A Web-Survey

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Received: 6 November 2024 | **Accepted:** 7 November 2024

Funding: This study was partially supported by the Ministero della Salute, Ricerca Corrente Funds 2023 to Alessandra Bandera.
This work was partially funded by the Italian Ministry of Health, Ricerca Corrente, and by EU funding within the NextGenerationEU - MUR - National Recovery and Resilience Plan, Mission 4, Component 2 Investment 1.3 – Extended Partnership initiative on Emerging Infectious Diseases INF-ACT (project nos. PE00000007 and CUP B73C22001230006) to Alessandra Mularoni.

Keywords: donor-derived infections | lung transplant | prophylaxis

ABSTRACT

Introduction: Infections significantly impact morbidity and mortality in lung transplant (LuTx) recipients. This survey focused on documenting current practices regarding the prevention and management of infections in LuTx in Italy.

Methods: A 52-question survey was administered online in the period from December 1, 2023, to January 31, 2024, assessing center characteristics, Tx team organization, microbiological investigations, infection prevention, and management. All Italian LuTx centers were invited to participate.

Results: Nine out of 10 Italian LuTx centers answered. Most centers (6/9, 67%) performed LuTx only on adults.

Chronic infection or colonization by *Mycobacterium abscessus* and *Burkholderia cenocepacia* is considered a contraindication to LuTx in five and two centers, respectively.

For cytomegalovirus D+/R- patients, prophylaxis is used in six centers (67%), with a variable duration from 3 to 12 months. Two centers also use IgG. Three centers (33%) use a pre-emptive strategy. Four centers (45%) screen for Human herpesvirus 8 infection.

Abbreviations: AmB, amphotericin B; CMV, cytomegalovirus; LuTx, lung transplant; MDRGNB, multidrug-resistant gram-negative bacteria; TEC, teicoplanin; Tx, transplant.

For a complete list of the LUNG-SITO study group Investigators, see the Acknowledgments section.

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Regarding antibiotic prophylaxis, most centers (6/9, 67%) utilise a dual regimen of anti-pseudomonal penicillin plus glycopeptide. The two most common durations of antibiotic prophylaxis were 72 h and 7 days, each reported by two centers (22%).
Targeted prophylaxis against fungal infections is employed by a minority of centers (4/9, 44%). Inhaled amphotericin B is the most common antifungal, used as targeted prophylaxis (2/4, 50%) and universal prophylaxis (2/5, 40%).
Almost all centers (8/9, 89%) involve the Tx infectious diseases specialist in the recipient management since the pre-listing period.
Conclusion: There is considerable heterogeneity in infection management among Italian LuTx centers. Establishing a shared platform for data collection and outcome evaluation is essential to improve infection management.

1 | Introduction

Infectious complications contribute substantially to morbidity and mortality following lung transplant (LuTx), accounting for over 25% of all post-Tx deaths [1].

Several factors contribute to infectious risk, including the surgical procedure, the administration of immunosuppressive drugs, pre-existing or latent infections in the donor, pre-existing or latent infections in the recipient, and the recipient's surrounding environment. Infections may present at different moments after transplantation, some becoming evident around surgery and others emerging years after the LuTx [2]. Furthermore, geographical differences also exist, owing to the presence of pathogens restricted to specific regions or the prevalence of certain microorganism variants in specific countries or regions. Despite the significant impact of infections on LuTx recipients' survival and quality of life, only a few uniform or standardized procedures are available to prevent and manage these complications. Each Tx center employs specific measures and algorithms, resulting in considerable variability within the same country [3].

Therefore, this field requires extensive efforts in documenting existing procedures, implementing new algorithms, and evaluating outcomes. We chose to address the first aspect of this triad on the national level, aiming to identify the procedures characterized by the highest heterogeneity.

2 | Methods

We developed a comprehensive survey of 52 questions, administered via an online platform (Google Form; Google Inc., USA) over a 2-month period (December 1, 2023–January 31, 2024). The detailed list of survey questions is available in File S1.

All the centers performing LuTx in Italy received an invitation to participate via e-mail prior to the commencement of data collection. Follow-up reminders were subsequently dispatched every 15 days until the survey's conclusion. We obtained a single response from each center; the centers were instructed to provide answers as a multidisciplinary team, with representatives from the various specialties involved in LuTx management.

The results are presented in tables illustrating frequencies and relative percentages. Multiple responses were permitted for specific questions, and the results are depicted accordingly to reflect this.

3 | Results

3.1 | Centres and Policies

Nine of the ten LuTx centers in Italy responded to our survey, as illustrated in Figure S1. The center reporting the highest annual number of LuTx is Padua, with over 50 Txs per year, followed by Milan and Turin, each reporting between 20 and 50 Txs annually.

Most centers perform only LuTx among adult recipients (6/9, 67%). In most centers (8/9, 89%) an infectious diseases specialist is involved in the recipient management since the pre-listing period. In one center (11%), a clinical microbiologist has been involved in the recipient management since the pre-listing period. Chronic infection or colonization by *Mycobacterium abscessus* and *Burkholderia cenocepacia* is considered a contraindication to LuTx in five and two centers, respectively.

The answers provided by the participating centers regarding rare infections and complex indications for transplantation are reported in Table 1.

3.2 | Viral Infections

Strategies for cytomegalovirus (CMV) prevention varied widely, with valganciclovir prophylaxis administered by 6/9 (66%) respondents in D+/R− LuTx recipients with or without CMV IgG and with variable duration. Instead, pre-emptive therapy was reported as the strategy against CMV infection for D+/R- and R+ recipients in three (33%) and four (44%) centers, respectively.

Almost half of centers (4/9, 44%) performed screening for Human herpesvirus 8 (HHV-8) infection, while five of nine centers (56%) experienced neoplastic or non-neoplastic complications due to HHV-8 infection in their LuTx recipients.

A complete overview of the answers provided by the centers regarding viral infections is presented in Table 2.

3.3 | Bacterial Infections

The most extensive section of the survey focused on managing infectious complications caused by bacteria. The nine

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TABLE 1 | Answers provided by the participating centers regarding rare infections and complex indications for transplantation.

Question	Answer	*n* (%)
Which type of donors are accepted?	Only DCD	0
	Only DBD	1 (11%)
	Both	8 (89%)
Which DCD donors are accepted according to the Maastricht classification? *	Class I	0
	Class II	5 (31%)
	Class III	7 (44%)
	Class IV	3 (19%
	NA	1 (6%)
Is EVLP available?	Yes	8 (89%)
	No	1 (11%)
Is it the recipient colonized by *B. cenocepacia*/genomavar III excluded from LuTx?	Yes	2 (22%)
	No	3 (33%)
	A case-by-case decision is performed	4 (44%)
Is it the recipient colonized by *M. abscessus* excluded from LuTx?	Yes	5 (56%)
	No	4 (44%)
Is it the recipient colonized (respiratory tract) by MDRGNB KPC-producing excluded from LuTx?	Yes	0
	No	9 (100%)
Is it the recipient colonized (respiratory tract) by MDRGNB MBLs-producing excluded from LuTx?	Yes	0
	No	9 (100%)
Is it *Ureaplasma* spp. presence usually assessed in respiratory samples (donor/recipient)?	Yes	0
	No	9 (100%)
Is LuTx performed in PLWH recipients?	Yes	4 (44%)
	No	5 (56%)

Abbreviations: DCD, donation after circulatory death; DBD, donation after brain death; NA, not answered; EVLP, ex-vivo lung perfusion; MDRGNB, multidrug-resistant gram-negative bacteria; KPC, *Klebsiella pneumoniae* carbapenemase; MBLs, metallo-beta-lactamases; PLWH, people living with HIV.
*Multiple choices allowed.

centers reported six distinct antibiotic perioperative prophylaxis regimens. Most of these (6/9, 67%) use a dual regimen with an anti-pseudomonal penicillin and a glycopeptide. Three centers (33%) reported single-agent prophylaxis, one employing piperacillin/tazobactam and the other two a first-generation cephalosporin.

Similarly, seven different durations of antibiotic prophylaxis were reported. The two most common durations were 72 hours and 7 days, each reported by two centers (2/9, 22%). Only one center (1/9, 11%) did not consider the chronic colonization or infection of the recipient's respiratory tract by multidrug-resistant gram-negative bacteria (MDRGNB) when deciding on antibiotic prophylaxis. In contrast, the other centers tailored these data, considering relevant specimens collected in a time frame ranging from 1 month before LuTx to an indefinite period before LuTx.

Specific answers on how to modify the antibiotic prophylaxis based on isolates responsible for chronic infection or colonization from the recipient's respiratory tract or isolates obtained from relevant donor material (blood cultures, respiratory samples, and perfusion fluid) are reported in Table 3.

3.4 | Fungal Infections

Regarding the prevention of fungal infections, five centers (56%) use universal prophylaxis, while targeted prophylaxis against fungal infections is employed by a minority of centers (4/9, 44%). Inhaled amphotericin B (AmB) is the most frequently chosen treatment, used as targeted prophylaxis (2/4, 50%) and as universal prophylaxis (2/5, 40%).

A more detailed description of the management of fungal infections is provided in Table 4.

4 | Discussion

Our survey represents the first systematic attempt to map the management of infections in the LuTx setting in Italy. We obtained detailed responses from nearly all the centers involved in this procedure, appraising the center and its characteristics, the organization of the Tx team, the management of infections caused by bacteria, viruses, fungi, and *Mollicutes*, and the significance of microbiological investigations on donors and recipients. Overall, substantial divergencies in preventing and managing infections are present across all centers.

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TABLE 2 | Answers provided by the participating centers regarding viral infections.

Question	Answer	*n* (%)
Which strategy is adopted for the prevention of CMV in D+/R-?	Antiviral prophylaxis for 3 months + anti-CMV Ig	1 (11%)
	Antiviral prophylaxis for 6 months + anti-CMV Ig	1 (11%)
	Antiviral prophylaxis for 3 months	1 (11%)
	Antiviral prophylaxis for 6 months	1 (11%)
	Antiviral prophylaxis for 12 months	2 (22%)
	Pre-emptive therapy	3 (33%)
Which strategy is employed to prevent CMV in R+?	Antiviral prophylaxis for 3 months + anti-CMV Ig	1 (11%)
	Antiviral prophylaxis for 6 months + anti-CMV Ig	2 (22%)
	Antiviral prophylaxis for 6 months	2 (22%)
	Pre-emptive therapy	4 (44%)
Is a resistance test performed in case of suspected CMV-resistant/refractory infection?	Yes, always	6 (67%)
	No, never	1 (11%)
	Sometimes	2 (22%)
Which treatment is employed in case of CMV-resistant/refractory infection?	Ganciclovir high-dose	5 (56%)
	Maribavir	3 (33%)
	Foscarnet	1 (11%)
Do you screen for HHV-8 infection?	Yes, donor and recipient	1 (11%)
	Yes, only recipient	3 (33%)
	No	5 (56%)
Which HHV-8 antibodies can be identified?	Lytic and latent	6 (67%)
	None	3 (33%)
Did HHV-8-related disease cases occur? *	Cutaneous KS	5 (38%)
	Visceral KS	2 (15%)
	KICS	1 (8%)
	Unspecified	1 (8%)
	None	4 (31%)

Abbreviations: CMV, cytomegalovirus; D, donor; R, recipient; HHV-8, human herpes virus 8; KICS, Kaposi sarcoma inflammatory cytokine syndrome; KS, Kaposi sarcoma.

*Multiple choices allowed.

Significant differences were evident in the definition of LuTx candidacy, with chronic infection or colonization by *M. abscessus* and *B. cenocepacia* serving as contraindications in five and two centers, respectively. Notable variability was also reported in the strategies adopted to prevent CMV infection regarding the choice of molecules and the duration of preventive regimens.

This variability is even more pronounced for the antibiotic prophylaxis administered at surgery, with six antibiotic regimens and seven different durations reported. The antifungal prophylaxis schemes are also heterogeneous, with more than half of the centers opting for universal prophylaxis. Interestingly, almost all centers involve the Tx infectious diseases specialist in the recipient management since the pre-listing period.

The answers collected mirror the global consensus regarding the conditions associated with recipient exclusion from LuTx. Colonization of the respiratory tract by MDRGNB is no longer deemed a sufficient reason, as it was in the past [4]. This shift is likely due to the availability of well-tolerated and effective therapies against these pathogens, which have diminished mortality and provided a reliable option for managing infections caused by MDRGNB [5, 6]. However, excluding recipients colonized with *B. cenocepacia* (genomovar III) and *M. abscessus* remains a more contentious issue. Non-tuberculous mycobacteria disease in solid-organ transplantation recipients is associated with a higher mortality risk, especially among LuTx recipients [7]. A recent Delphi study recommended a 12-month period of further treatment from the time of a culture-negative result before listing a patient with *M. abscessus* infection [8]. In the case of *B. cenocepacia* (genomavar III), this is considered a relative contraindication; LuTx may be considered if the infection is sufficiently treated preoperatively and there is a reasonable expectation of adequate control postoperatively. The complexity and debate surrounding these decisions are evident in our survey findings [9, 10].

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TABLE 3 | Answers provided by the participating centers regarding donor-derived infections and infections due to multi-drug-resistant bacteria.

Question	Answer	*n* (%)
Which antibiotic prophylaxis is employed?	TZP	1 (11%)
	TZP + TEC	1 (11%)
	TZP + VAN	2 (22%)
	FEP + VAN	2 (22%)
	CAZ + VAN	1 (11%)
	First generation cephalosporin	2 (22%)
What is the duration of the antibiotic prophylaxis?	24h	1 (11%)
	48h	1 (11%)
	72h	2 (22%)
	72 h except for cystic fibrosis patients	1 (11%)
	7 days	2 (22%)
	TEC 72 h – TZP 7 days	1 (11%)
	Until negative microbiology results in the recipient	1 (11%)
Is it the antibiotic prophylaxis modified according to the recipient's chronic colonization/infection of the respiratory tract by MDRGNB[§]?	Yes	4 (44%)
	No	1 (11%)
	Sometimes	4 (44%)
How long are previous isolates considered relevant from the recipient's respiratory tract in defining antibiotic prophylaxis?[*]	1 month	1 (9%)
	2 months	2 (18%)
	6 months	2 (18%)
	1 year	1 (9%)
	Indefinite	2 (18%)
	Case-by-case evaluation	2 (18%)
	Not considered	1 (9%)
How is the antibiotic prophylaxis adjusted according to the recipient's respiratory tract colonization status by *P. aeruginosa* DTR?	C/T	5 (%)
	BL/BLI + aminoglycoside	1 (%)
	BL/BLI + inhaled colistin	1 (%)
	According to the antimicrobial susceptibility test	1 (%)
	Not considered	1 (%)
How is antibiotic prophylaxis adjusted according to the recipient's respiratory tract colonization status by *S. maltophilia*?	Only with relevant clinical manifestations	5 (56%)
	SXT + quinolone	2 (22%)
	SXT	1 (11%)
	Not considered	1 (11%)
How is the antibiotic prophylaxis adjusted according to the recipient's respiratory tract colonization status by *A. xilosoxidans* MDR?	FDC	6 (67%)
	According to the antimicrobial susceptibility test	2 (22%)
	Not considered	1 (11%)
Do you perform a culture of preservation/perfusion fluid?	No	5 (56%)
	Yes, always	2 (22%)
	Yes, sometimes	2 (22%)
Do you perform bronchial swabs on donors and/or recipients at Tx?	Sometimes	2 (22%)
	Yes, for donor	2 (22%)
	Yes, always for both	4 (44%)
	No	1 (11%)

(Continues)

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TABLE 3 | (Continued)

Question	Answer	*n* (%)
How do you receive the results of microbiology tests performed on the donor?*	Internal microbiology laboratory	7 (39%)
	Donor manager platform	3 (17%)
	Telephone communication from OPO	1 (6%)
	E-mail communication from OPO	7 (39%)
Is it antibiotic prophylaxis modified according to donor results?	Yes, special conditions°	7 (78%)
	Yes, always	0
	No	2 (22%)
Which antibiotic is employed if a KPC-producing bacteria is isolated from the donor (special conditions°)?	CZA	5 (56%)
	MVB	3 (33%)
	None	1 (11%
Which antibiotic is employed if an MBL-producing bacteria is isolated from the donor (special conditions°)?	CZA + ATM	8 (89%)
	FDC	0
	None	1 (11%)

Abbreviations: ATM, aztreonam; BL/BLI, beta-lactam/beta-lactamase inhibitor; CAZ, ceftazidime; C/T, ceftolozane/tazobactam; CZA, ceftazidime/avibactam; FDC, cefiderocol; FEP, cefepime; KPC, Klebsiella pneumoniae carbapenemase; MBLs, metallo-beta-lactamases; MDRGNB, multidrug-resistant gram-negative bacteria; MVB, meropenem/vaborbactam; OPO, organ procurement organization; SXT, cotrimoxazole; TEC, teicoplanin; Tx, transplant; TZP, piperacillin/tazobactam; VAN, vancomycin.

*Multiple choices allowed.

§*P. aeruginosa* DTR/MDR, *S. maltophilia* MDR, and *A. xilosoxidans* MDR.

°Isolates from blood cultures, respiratory samples, and perfusion fluid.

Similarly, regarding antibiotic prophylaxis, our results follow data published by Coiffard and colleagues [3]. Italian centers do not differ from United States centers in terms of molecules employed in patients without a previous colonization/infection of the respiratory tract, with an anti-pseudomonal penicillin and a glycopeptide, to guarantee activity against methicillin-resistant *Staphylococcus aureus*, composing the most common regimen employed. Likewise, the duration of antibiotic prophylaxis in this setting is 7 days or less. The difficulty in defining the temporal relevance of previous respiratory tract isolates when tailoring antibiotic prophylaxis is another common point between the two experiences. In our survey, two centers stated that with this aim they consider samples collected at any time before transplantation. That mirrors what was detailed by Coiffard and colleagues, who stated that a sample collected more than a year before LuTx was considered in tailoring prophylaxis in around one-third of centers in their experience [3].

Screening for *Mollicutes* infection was not performed in the Italian centers. This was true until January 2024, when this survey was performed. After this date, a note from the Italian National Transplant Centre (CNT) made screening for this infection mandatory for the donor [11]. All centers are currently implementing the sampling and testing of donors, and we can expect an increase in the detection of these pathogens and the administration of antibiotic regimens against *Mollicutes* soon as a pre-emptive strategy in this population. This strategy will probably allow to avert a certain number of hyperammonaemia syndrome cases, which could be fatal [12].

Regarding antifungal prophylaxis, AmB, either inhaled or administered systemically in its liposomal form, is the most common antifungal drug used for universal and targeted prophylaxis. Targeted prophylaxis lasts an average of three months, whereas universal prophylaxis length ranges from discharge from hospitalization to at least 12 months after LuTx. The Italian scenario appears like the American one, where a recent survey has highlighted a widespread use of universal prophylaxis with nebulized AmB and a systemic triazole for six months or less post-LuTx [13].

Concerning the treatment of CMV-resistant/refractory infection, it should be noted that the survey was performed when maribavir was starting to be available on the market in Italy. Today all centers have access to this new drug, a condition that is probably leading to a more widespread use of the molecule.

Considering that almost all LuTx centers in Italy (9 out of 10) responded to the survey, our results can accurately depict the Italian context. Naturally, the survey could not exhaustively examine every facet of the intricate management of LuTx candidates and recipients; thus, specific issues have not been addressed, and some descriptions may be simplifications of the actual situation. Furthermore, each patient has unique characteristics that influence the decisions made. Consequently, the responses we collected represent a consensus on the strategies employed in each center, with likely variations to accommodate individual cases, reflecting the actual scenario.

The key message of our study is the significant granularity in the strategies adopted to manage infectious complications among LuTx candidates and recipients across Italy. Despite being a moderately sized country with a limited number of LuTx procedures performed annually, the approaches vary considerably from center to center. These discrepancies pertain to fundamental

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TABLE 4 | Answers provided by the participating centers regarding fungal infections.

Question	Answer	*n* (%)
Which approach is employed to prevent fungal infections?	Targeted prophylaxis	4 (44%)
	Universal prophylaxis	5 (56%)
How is targeted prophylaxis implemented?	Inhaled AmB	2 (50%)
	ISA	1 (25%)
	N/A	1 (25%)
How is universal prophylaxis implemented?	Inhaled AmB	2 (40%)
	VRC	1 (20%)
	VRC followed by ITC	1 (20%)
	Intravenous LAmB	1 (20%)
For how long is the targeted prophylaxis administered?	3 months	2 (50%)
	N/A	2 (50%)
For how long is administered the universal prophylaxis?	Inhaled AmB until discharge	1 (20%)
	Intravenous LAmB for 15 days, then inhaled AmB until discharge	1 (20%)
	At least 12 months	1 (20%)
	6 months	1 (20%)
	3 months (6–12 months if previous isolates)	1 (20%)
Is azoles TDM performed?	Yes, internally	6 (67%)
	Yes, externally	1 (11%)
	No	2 (22%)
Which therapy is employed in case of suspected fungal infection of the anastomosis?	VRC	1 (11%)
	VRC or ISA or POS	1 (11%)
	LAmB or VRC	1 (11%)
	LAmB or inhaled AmB or ISA	1 (11%)
	VRC or ISA	1 (11%)
	LAmB or ISA	1 (11%)
	LAmB	2 (22%)

Abbreviations: AmB, amphotericin B; ISA, isavuconazole; ITC, itraconazole; LAmB, liposomal amphotericin B; POS, posaconazole; TDM, therapeutic drug monitoring; VRC, voriconazole.

elements of infection prevention and management, such as antibiotic and CMV prophylaxis, indicating a lack of uniformity even in fundamental strategies. This variability is likely due to the limited evidence on the issues addressed in our survey and the scarcity of guidelines or recommendations from scientific societies and healthcare organizations.

Establishing or adopting standard and shared algorithms and guidelines is imperative to address the numerous issues arising from managing infectious complications among LuTx candidates and recipients. This is essential for the subsequent collection and evaluation of the outcomes of these approaches to assess their validity and make necessary adjustments. Without such standardization, ineffective strategies may persist unchallenged, adversely impacting the morbidity and mortality of this vulnerable population.

An immediate need highlighted by this study is establishing a platform to collect data on infectious complications among LuTx candidates and recipients. The results of this survey might influence the design of prospective multicentre studies and identify the educational needs of the Tx professional community to help improve infection management in LuTx recipients. Given the relatively small population and the limited number of centers managing these patients, it is feasible to implement such a tool, and efforts by our group are currently underway to develop it.

Author Contributions

Andrea Lombardi, Paolo Grossi, and Alessandra Mularoni conceived the study. Andrea Lombardi designed and performed the survey. Andrea Lombardi performed the statistical analyses. Andrea Lombardi, Paolo Grossi, Malgorzata Mikulska, Maddalena Giannella, Renato Pascale, Serena Marinello, Francesca Montagnani, Elena Seminari, Silvia Corcione, Alessandra Bandera, Alessandro Bertani, and Alessandra Mularoni evaluated the study results. Andrea Lombardi and Alessandra Mularoni wrote the first draft of the manuscript. All the authors reviewed the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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