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Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study

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ABSTRACT

Objectives Lung transplant (LT) recipients require multidisciplinary care because of the complexity of therapeutic management. Pharmacists are able to detect drug-related problems and provide recommendations to physicians through pharmacists' interventions (PIs). We aimed at assessing the clinical impact of PIs on therapeutic management in LT outpatients.

Design Data were collected prospectively from an LT recipients cohort during 7 years. A multidisciplinary committee assessed retrospectively the clinical impact of accepted PIs.

Setting French University Hospital.

Participants LT outpatients followed from 2009 to 2015.

Primary outcome measures Clinical impact of PIs performed by pharmacists using the CLEO tool and the Pareto chart.

Results 1449 PIs led to a change in patient therapeutic management and were mainly related to wrong dosage (39.6%) and untreated indication (19.6%). The clinical impact of PIs was 'avoids fatality', 'major' and 'moderate', in 0.1%, 7.0% and 57.9%, respectively. Immunosuppressants, antimycotics for systemic use and antithrombotic agents had the greatest clinical impact according to the Pareto chart. PIs related to drug–drug interactions (10%) mainly had a moderate and major clinical impact (82.3%, p<0.0001).

Conclusion Clinical pharmacists play a key role for detecting drug-related problems mostly leading to a change in therapeutic management among LT outpatients. Our study provides a new insight to analyse the clinical impact of PIs in order to target PIs which have most value and contribute to patient care through interdisciplinary approach.

Strengths and limitations of this study

► Very few studies highlighted the clinical pharmacists' key role for optimising therapeutic management in lung transplant outpatients.
► A strength of this study is the assessment of pharmacist's clinical impact through a new validated scale and the analysis according to the Pareto principle.
► Another strength is that pharmacist's added value is underlined through a collaborative practice model in lung transplantation over a 7-year period.
► The main limitation was the retrospective assessment of clinical impact in a single-centre study.
► Another limitation was not to be able to follow patients longitudinally through the anonymised database.

narrow therapeutic index, leading to potential severe adverse drug events and drug–drug interactions.[1–3] Involving pharmacists in a multidisciplinary transplant care teams may improve medication use[4] and some studies have highlighted the positive impact of the clinical pharmacist's involvement in solid organ transplantation since 1976.[5 6] Transplant pharmacists may reduce medication errors, improve patient's education and his drug knowledge as well as detect drug-related problems (DRPs)[7–10]; they decrease the average hospital length of stay[11] and improve transplant recipients medication's adherence by providing intensified pharmaceutical care during the first post-transplant year.[12] Clinical pharmacist is also an essential member of the transplant team for the prevention and treatment of transplant infectious diseases,[13] and for managing tacrolimus dosage.[14] However, pharmaceutical care in LT recipients is less studied than in renal or liver transplantation

INTRODUCTION

Lung transplantation is an established treatment for patients with end-stage lung disease. Lung transplant (LT) recipients require multidisciplinary care because of the complexity of long-term immunosuppressive therapy and other specific therapies with

and the impact of clinical pharmacists' interventions (PIs) is poorly studied in lung transplantation as only one study in Canada with a small sample size was reported.[15]

A Pharmacist Collaborative Care Programme (PCCP) has been initiated in the lung transplantation centre of Grenoble University Hospital (France) since 2008. There is no current accreditation for transplant pharmacist in our country but our lung transplantation centre is approved by the French Biomedicine Agency and involves pharmacists as experts in drug therapy.[16] This programme includes patient interviews and medication reviews during which pharmacists can detect DRPs and transmit PIs to physicians. DRP is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes,[17] whereas PI is defined as any action initiated by a pharmacist resulting in a change of patient's management or therapy by the physician.[18] In France, the work group 'Standardisation et valorisation des activités de pharmacie clinique' of the French Society of Clinical Pharmacy (SFPC) created and validated a tool for the standardisation of the documentation of PIs performed in healthcare facilities and the CLEO (CLinical, Economic and Organizational) tool for assessing PIs' impacts.[19 20] A free access website observatory named Act-IP was implemented in September 2006 allowing prospectively recording DRPs and PIs performed during daily practice, such as medication order review and multidisciplinary meetings.[20 21]

The objective of this study was to assess the clinical impact of PIs in lung transplantation management. Specific aims were: (1) to describe DRPs and PIs recorded on Act-IP website during LT outpatients' management over a 7-year period and (2) to evaluate their clinical impact.

METHODS
Study design and population
A retrospective observational study was performed on the PIs recorded on Act-IP website observatory from 1 January 2009 to 31 December 2015 and related to the 152 LT recipients followed at the 2200-bed Grenoble University Hospital over the 7-year period. Patients were eligible if they were lung transplanted before 1 January 2009 or between 1 January 2009 and 31 December 2015 according to our computerised hospital register of transplantation.

All patients gave written informed consent to use their data for research.

Patient and public involvement
Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

PCCP for LT outpatients
Overall, clinical pharmacy services are provided since 2008 by two senior and two resident pharmacists 5 days a week in our lung transplantation centre. They include validating computerised medication orders from medication

reconciliation and medical round attendance, implementing drug protocols, managing patient's education, improving medication use and optimising therapeutic management according to patient's pathophysiological context for LT inpatients and outpatients.

The lung transplantation PCCP is a collaborative care programme including physicians, nurses, dieticians, physiotherapists and pharmacists. LT outpatients come in the 15-bed Pneumology day hospital about every 1–3 months for monitoring according to medical appreciation. They are all individually interviewed for each medical visit by a clinical pharmacist or resident during 30–45 min in order to collect relevant data about drug handling, medication adherence, disease understanding and to provide them counselling on medication and lifestyle. Clinical pharmacists interview 10 LT outpatients per week on average, representing about 17% of the total number of outpatients visiting the day hospital. In this collaborative model, the pharmacist can detect DRPs according to medication reconciliation as well as clinical and biological data, and provide recommendations (PIs) to nurses and physicians on therapeutic management. These recommendations are mostly performed before medical rounds and also transmitted through shared computer files; therapeutic optimisations are discussed weekly collaboratively during lung transplantation group meetings. There is oversight by the senior clinical pharmacist over the resident's recommendations every week before data recording.

PIs data and Act-IP database
After registration on the Act-IP website, pharmacists can record and analyse their interventions. Entering an intervention in the database took 15 min on average. The type of DRP and PI was classified according to the SFPC criteria using the report forms developed and validated for routine documentation.[22] The pharmacist prospectively completed the anonymised online report form specifying the date, pharmacist rank (senior or resident), patient demographic characteristics (age, sex), drug(s) involved in the DRP coded according to the Anatomical Therapeutic Chemical classification,[23] DRP description, PI description and acceptance or not by the physician. Physician's acceptance was defined as prescription modification or change in medical care or therapeutic management. This tool was designed to record PIs through one-time actions and does not allow to follow patients longitudinally.

Potential significance of PIs
The impact of accepted PIs recorded on Act-IP database was assessed according to an SFPC validated tool adapted for the French clinical practice named CLEO. This tool includes a clinical dimension with several numeric levels including negative, null and positive impacts (Minor, Moderate, Major, Avoids fatality), and an open level 'undetermined', which evaluates patient's benefit according to the most likely case expected if no PI is performed[19 24]

(an additional file shows this in more detail (see online supplemental appendix 1)).

Clinical assessment was performed by an independent expert committee (a pharmacovigilance expert, a pulmonologist and a clinical pharmacist) from Grenoble University Hospital during a face-to-face meeting. After the presentation by the meeting moderator of each accepted intervention, each expert independently and blindly evaluated the clinical impact of each of these interventions prior to discussion to reach an expert consensus from available data: age, gender, patient's history, a description of the DRP and the PI according to the classification of the SFPC, drug(s) involved and clinical and biological information. No inter-rater agreement was measured as each PI was rated after expert consensus. In order to guarantee the quality of the interventions recording on Act-IP database, data management was performed by a pharmacist resident before expert assessment.

Statistical analysis

PI was the unit of analysis. Data were described as mean and SD for quantitative variables, and frequency and percentage for qualitative variables. PI description included all data and the clinical impact was assessed for accepted PI because of change in patient management from pharmacist's evaluation. The clinical impact of PI was presented using bar charts, a matrix assessing the relationship between it and DRP, and a Pareto chart. The Pareto chart using 'ABC analysis' is a useful tool for analysing what problems need attention first and is based on the 'Pareto principle', a theory maintaining that 80% of the output in a given situation or system is produced by 20% of the input (group A). The other inputs are categorised in group B (15% of the output) and group C (the last 5% of the output).[25 26] Fisher's exact test was used to compare the distribution of DRPs according to the clinical impact levels. Cochran-Armitage test for trend was used to test the association between different types of DRPs (drug–drug interaction, drug without indication and drug monitoring) and the clinical impact level as ordinal variable.

Data management and analysis were performed using EXCEL software and SAS V.9.4 statistical software, SAS Institute.

RESULTS

Characteristics of LT recipients

A description of the LT recipients' cohort is presented in table 1. PIs concerned male patients in 59.2% of cases and the mean age was 52 years old (range: 15–76 years old).

Characteristics of DRPs and PIs

During the 7-year study period, 1569 PIs were recorded by 23 clinical pharmacists (seniors and residents) on the Act-IP website observatory. These interventions were relied on 1751 drugs, as PIs involved two or three drugs in 176 cases (11.2%) (eg, 'drug–drug interaction' or

Table 1	Baseline patients' characteristics (n=152)
Characteristic	**n (%)**
Age *	
9–39 years old	46 (30.3)
40–59 years old	56 (36.8)
>60 years old	50 (32.9)
Sex	
Male	90 (59.2)
Female	62 (40.8)
Indication for lung transplantation	
Chronic obstructive pulmonary disease	79 (52.0)
Cystic fibrosis	39 (25.6)
Diffuse interstitial lung disease	22 (14.5)
Pulmonary hypertension	9 (5.9)
Other	3 (2.0)
Transplant procedure	
Double lung	94 (61.9)
Single lung	54 (35.5)
Heart/lung	4 (2.6)
Retransplantation	3 (2.0)
Death during the study period	39 (25.7)
No of lung transplantations during the study period	103 (67.8)

*Age at the time of the first lung transplantation

'drug duplication'). Overall, 92.4% (n=1449) of PIs were accepted by physicians (figure 1).

Therapeutic classes mostly involved in DRPs were 'antineoplastic and immunomodulating agents' (37.6%), 'anti-infectives for systemic use' (22.6%) and 'cardiovascular drugs' (9.2%) (table 2).

The types of the DRPs and PIs are summarised in table 3.

Overall, the most common types of DRPs identified by pharmacists were respectively 'subtherapeutic dosage' (20.5%), 'untreated indication' (19.6%) and 'supratherapeutic dosage' (19.1%). Subtherapeutic dosage mainly concerned immunosuppressants (n=226, 70.2%), lipid-modifying agents (n=18, 5.6%) and antivirals for systemic use (n=14, 4.3%). Untreated indication mostly concerned lipid-modifying agents (n=38, 12.3%) and antianaemic preparations (n=37, 12.0%). Supratherapeutic dosage mainly concerned immunosuppressants (n=205, 68.6%) and corticosteroids for systemic use (n=32, 10.7%).

Drug–drug interactions represented 8.4% (n=132) of DRPs. They mainly involved antimycotics for systemic use (n=99, 75.0%) and immunosuppressants (n=94, 71.2%). Among these drug–drug interactions, antimycotics for systemic use interacted with immunosuppressants in 76 cases (57.6%). Antimycotics for systemic use were mainly posaconazole (67.7%) and voriconazole (26.3%). Tacrolimus was the most implicated immunosuppressant in
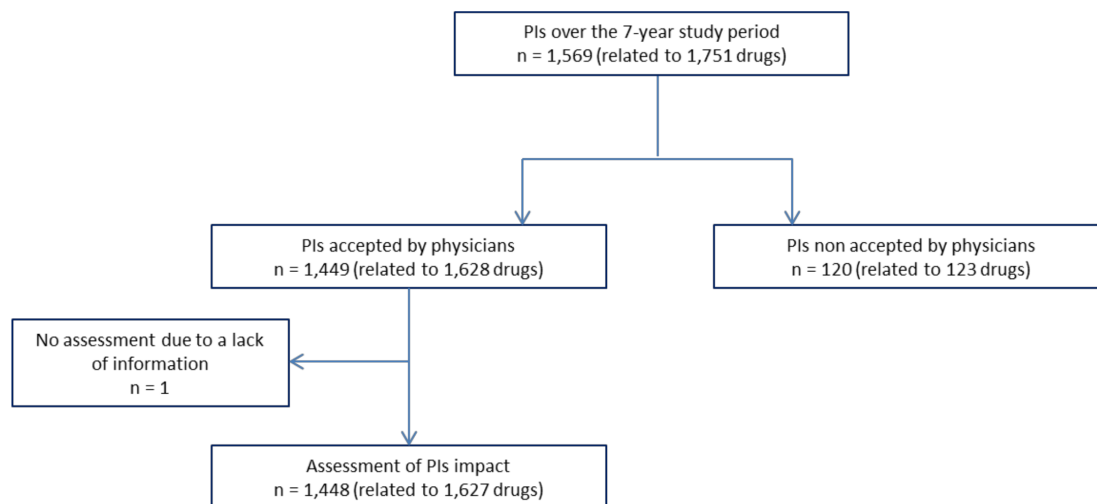
Figure 1 Flow chart of pharmacists' interventions (PIs) recorded on Act-IP database related to lung transplant outpatients followed at Grenoble university hospital from 1 January 2009 to 31 December 2015.

drug–drug interactions (87.2%). Only 11.4% (n=15) of the drug–drug interactions did not include neither immunosuppressant nor antimycotic for systemic use.

The PIs were mostly related to 'dose adjustment' (43.8%), 'addition of a new drug' (22.4%) and 'drug discontinuation' (13.4%).

Potential clinical impact of PIs

Clinical impact was assessed among the 1448 accepted PIs (one PI could not be assessed because of lack of information) (figure 1).

PIs had major (n=101, 7.0%), moderate (n=838, 57.9%) and minor (n=492, 34.0%) clinical impact (figure 2). Two PIs could prevent an accident that could cause a potentially fatal complication. One was related to a pregnant woman with cystic fibrosis treated with teratogenic vitamin A. The other was related to a patient with an untreated persistent severe hypokalaemia.

PIs with major clinical impact were mostly related to drug–drug interactions (n=40, 39.6%, p<0.0001), involving immunosuppressants and antimycotics for systemic use (n=36). Those with moderate clinical impact were mainly due to subtherapeutic dosage (n=242, 28.9%), untreated indication (n=173, 20.6%) or supratherapeutic dosage (n=170, 20.3%) and mostly leading to dose adjustment (52.9%). PIs with minor clinical impact were mainly related to supratherapeutic dosage (n=99, 20.1%) and drug without indication (n=97, 19.7%). There was a positive association between 'drug–drug interactions' DRPs and the clinical impact level (p<0,0001) whereas 'drug without indication' and 'drug monitoring' DRPs had a negative association with the clinical impact level (p<0,0001).

Subtherapeutic dosage problem with moderate clinical impact was the most common type of accepted PIs (n=242) (figure 3), involving tacrolimus in 40.9% of cases (n=99), followed by everolimus in 35.5% of cases (n=86). Among PIs with moderate clinical impact, supratherapeutic dosage (n=170) mainly involved tacrolimus

(n=134, 78.8%) and untreated indication (n=173) concerned lipid-modifying agents (n=31, 17.9%), anti-anaemic preparations (n=28, 16.2%) and vaccines (n=27, 15.6%). 82.3% of drug–drug interactions were related to a moderate or major clinical impact (n=107) (figure 3). Only 1.0% (n=15) of PIs had no clinical impact and was mainly related to drug without indication (figure 2).

According to the Pareto chart, concerning PIs with major or 'avoids fatality' clinical impact (n=103) related to 144 drugs, immunosuppressants, antimycotics for systemic use and antithrombotic agents had the greatest clinical impact (group A; figure 4).

DISCUSSION

Our study highlights a frequent intervention of clinical pharmacists in LT outpatient management with 1569 PIs over 7 years, representing about one intervention per day, as PIs have also an educational role decreasing DRPs rate over time. PIs were accepted by physicians almost all the time and mostly led to positive clinical impact for the patient.

To the best of our knowledge, only one other study described pharmaceutical care intervention among LT outpatients.[15] This Canadian study was also a retrospective single-centre study but performed over a short period of 7 months with senior clinical pharmacists providing patient care for only one-half day per week. Indeed, 55 DRPs were detected over 50 clinic visits concerning 43 patients mostly met only one time, during the early post-transplant period (<3 months). This study mainly discussed patient satisfaction with pharmacist care rather than the type of DRPs and the clinical impact of PIs.

In our study, the major causes of detected DRPs were an incorrect dose (39.6%), including both subtherapeutic and supratherapeutic dosages, and untreated indication (19.6%). These findings are in accordance to the literature in other solid organ transplantation.[7 27–29] Dosage

Table 2 Drugs involved in DRPs (n=1751 drugs)

Drug groups (ATC classification system)	N (%)	Most frequent drugs (N)
L-antineoplastic and immunomodulating agents	**659 (37.6)**	
Immunosuppressants (L04) 657	657 (37.5)	Tacrolimus (409), everolimus (190), mycophenolic acid (36)
J-anti-infectives for systemic use	**397 (22.6)**	
Antimycotics for systemic use (J02A) 175	175 (10.0)	Posaconazole (118), voriconazole (41), itraconazole (9)
Direct-acting antivirals (J05A) 87	87 (5.0)	Valganciclovir (80)
Immunoglobulins (J06B) 37	37 (2.1)	Human immunoglobulins (37)
Vaccines (J07) 33	33 (1.9)	Pneumococcal vaccines (18)
Sulfonamides and trimethoprim (J01E) 21	21 (1.2)	Sulfamethoxazole (21)
Macrolides, lincosamides and streptogramins (J01F) 17	17 (1.0)	Azithromycin (5), pristinamycin (4), clarithromycin (4)
Other antibacterials (J01X) 9	9 (0.5)	Colistin (8)
Aminoglycoside antibacterials (J01G) 5	5 (0.3)	Tobramycin (4)
Beta-lactam antibacterials (J01C+J01D) 5	5 (0.3)	Amoxicillin (2)
Quinolone antibacterials (J01M) 4	4 (0.2)	Ofloxacin (2)
C-cardiovascular system	**162 (9.2)**	
Lipid-modifying agents (C10) 90	90 (5.1)	Pravastatin (72), fenofibrat (10)
Calcium channel blockers (C08) 23	23 (1.3)	Lercanidipine (10), almodipine (10)
Agents acting on the renin–angiotensin system (C09) 20	20 (1.1)	Ramipril (9), perindopril (5), irbesartan (4)
Diuretics (C03) 11	11 (0.6)	Furosemide (8)
Cardiac therapy (C01) 8	8 (0.5)	Ivabradine (5)
Beta blocking agents (C07) 6	6 (0.3)	Atenolol (3)
A-alimentary tract and metabolism	**141 (8.1)**	
Calcium (A12A) 36	36 (2.1)	Calcium (36)
Drugs for peptic ulcer and GORD (A02B) 33	33 (1.9)	Esomeprazole (26)
Vitamins (A11) 29	29 (1.7)	Vitamin D (18), Vitamin A (8)
Potassium (A12B) 17	17 (1.0)	Potassium (17)
Drugs used in diabetes (A10) 8	8 (0.5)	Repaglinide (5)
B-blood and blood-forming organs	**120 (6.9)**	
Iron preparations (B03A) 71	71 (4.1)	Iron bivalent, oral preparations (62)
Antithrombotic agents (B01A) 22	22 (1.3)	Fluindione (7), warfarin (8)
H-systemic hormonal preparations	**60 (3.4)**	
Glucocorticoids (H02AB) 58	58 (3.3)	Prednisone (43), prednisolone (15)
N-nervous system	**59 (3.4)**	
Analgesics (N02) 28	28 (1.6)	Paracetamol plain and combinations (13), morphine (6)
Psycholeptics (N05) 11	11 (0.6)	Hydroxyzine (4)
Psychoanaleptics (N06) 10	10 (0.6)	Mianserine (3), clomipramine (2), paroxetine (2)
Antiepileptics (N03) 10	10 (0.6)	Pregabalin (10)
M-musculoskeletal system	**51 (2.9)**	
Bisphosphonates (M05BA) 44	44 (2.5)	Zoledronic acid (40)
Z-no ATC code	**35 (2.0)**	Magnesium (31)
P-antiparasitic products, insecticides and repellants	**28 (1.6)**	Pyrimethamine (25)
V-various	**22 (1.3)**	Calcium folinate (19)
R-respiratory system	**12 (0.7)**	
Drugs for obstructive airway diseases (R03) 8	8 (0.5)	Salbutamol (3), budesonide/formoterol (3)
G-genitourinary system and sex hormones	**3 (0.2)**	
D-dermatologicals	**2 (0.1)**	

DRPs relied on 1751 drugs, as each pharmacist's intervention involved two or three drugs in 176 cases (11.2%).
ATC, Anatomical Therapeutic Chemical; DRPs, drug-related problems.

Table 3 Characteristics of the DRPs and PIs

Characteristics	Total (n=1569) n (%)	Accepted (n=1449) n (%)
DRP		
Subtherapeutic dosage	322 (20.5)	284 (19.6)
Untreated indication	308 (19.6)	266 (18.4)
Supratherapeutic dosage	299 (19.1)	291 (20.1)
Adverse drug reaction	155 (9.9)	145 (10.0)
Drug without indication	148 (9.4)	132 (9.1)
Drug–drug interaction	132 (8.4)	130 (9.0)
Drug monitoring	85 (5.4)	83 (5.7)
Improper administration	42 (2.7)	42 (2.9)
Non conformity to guidelines/ contraindication	41 (2.6)	40 (2.7)
Failure to receive drug	37 (2.4)	36 (2.5)
PI		
Dose adjustment	687 (43.8)	635 (43.8)
Addition of a new drug	351 (22.4)	309 (21.3)
Drug discontinuation	210 (13.4)	191 (13.2)
Drug monitoring	180 (11.5)	175 (12.1)
Drug switch	102 (6.5)	100 (6.9)
Administration mode optimisation	37 (2.3)	37 (2.6)
Change of administration route	2 (0.1)	2 (0.1)

DRPs, drug-related problems; PIs, pharmacists' interventions.

problems are frequently detected because of the systematic pharmacist analysis of immunosuppressants and antimycotics blood trough concentrations before patient medication review and recommendations to physician, according to the routine therapeutic drug monitoring in our centre. Untreated indication was related to drug stopped for contraindication and not restarted (eg, everolimus after surgery), lack of premedication, necessary

drugs to correct drug side effects or non-prescribed drugs detected by medication reconciliation process. In Harrison *et al* study related to lung transplantation,[15] 'adverse drug effect' was the most common type of DRP. However, they defined 'adverse drug effect' as a 'patient who is experiencing or at risk of an adverse drug reaction', which can include 'supratherapeutic dosage' problem without any current adverse drug reaction. Immunosuppressants interacted with antifungal drugs in 57.6% of cases in our study. Of them, posaconazole and voriconazole are strong enzymatic inhibitors of cytochrome P450 3A4 which induce an increase of tacrolimus and everolimus elimination half-lives leading to potential toxicity. Multidisciplinary team should be also aware when antimycotics therapy is stopped, because of immunosuppressant trough concentration drop, and so potential graft rejection.

More than half of the PIs involved immunosuppressants (including glucocorticoids) and anti-infective drugs (63.4%). Immunosuppressants were the most concerned by PIs due to complex dosing regimens, high risk of drug–drug interactions and adverse drug events.[1–3] High intervention rate related to anti-infective drugs may be because of the high frequency of use of these drugs in LT outpatients since they are prone to fungal, viral and bacterial infections despite prevention measures.[30] More specific analysis showed that tacrolimus and posaconazole were involved in about 30% of all drugs. Thus, clinical pharmacists should particularly monitor prescriptions of these two drugs. Cardiovascular system drugs were also frequently involved in PIs (9.2%) because of post-transplant hypertension or hyperlipidaemia. Our results are in line with other previous studies in solid organ transplantation as immunosuppressants, cardiovascular drugs and antimicrobials were involved in most cases.[7 27 29 31] However, Harrison *et al*[15] reported that their interventions mainly involved gastrointestinal drugs without discussing this finding.
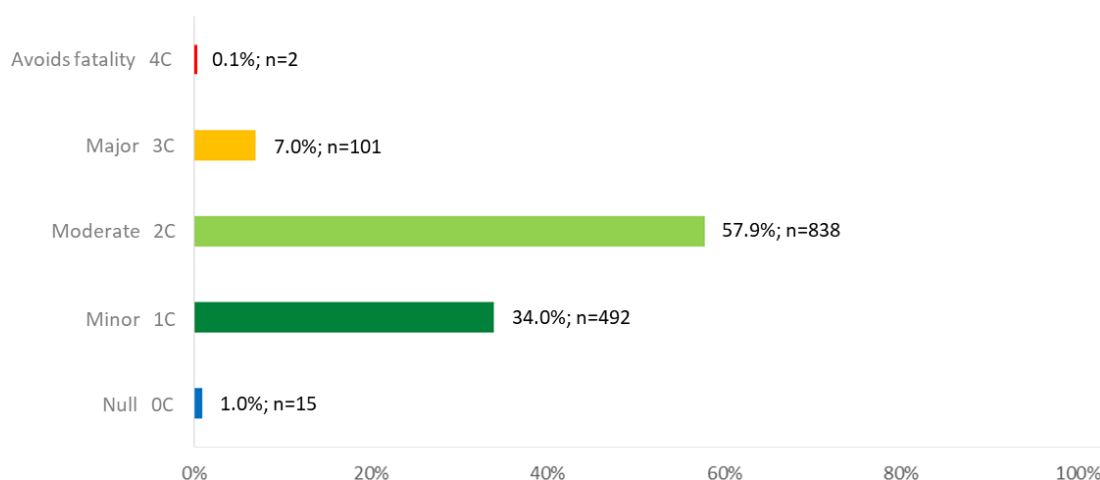

Figure 2 Clinical impact of accepted pharmacists' interventions (n=1448) recorded on Act-IP database related to lung transplant outpatients followed at Grenoble university hospital from 1 January 2009 to 31 December 2015.
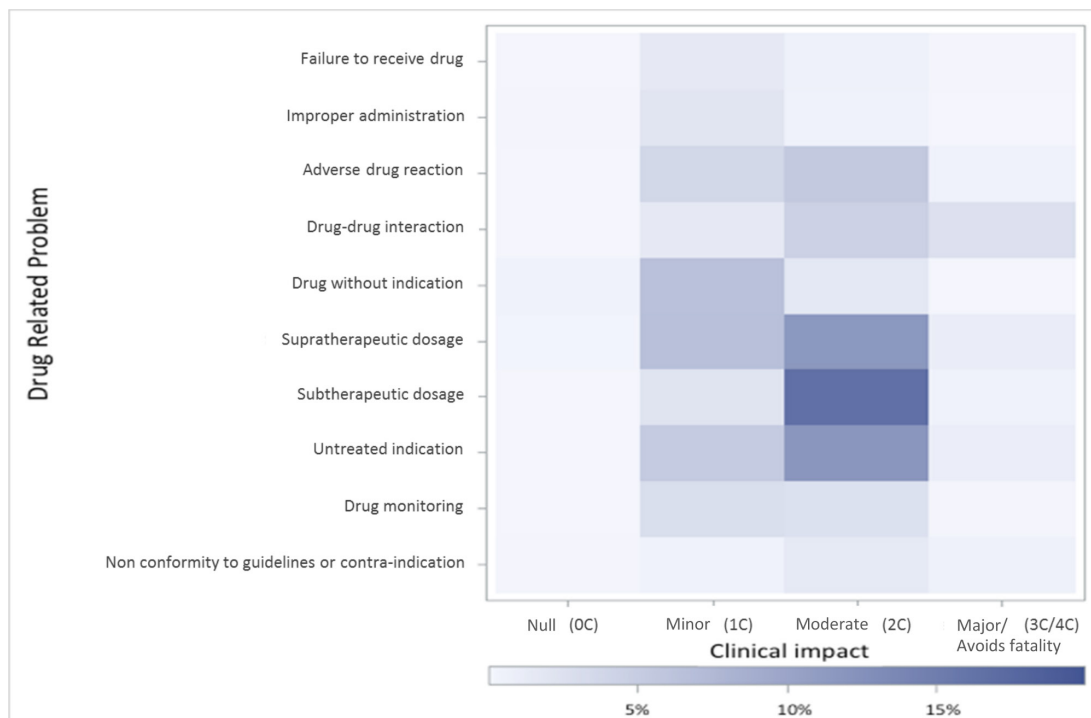
Figure 3 Clinical impact of accepted pharmacists' interventions (n=1448), according to drug-related problems, recorded on Act-IP database related to lung transplant outpatients followed at Grenoble university hospital from 1 January 2009 to 31 December 2015.

The high acceptance rate found in our study confirms the relevance of PIs. This finding is in line with previous studies in clinical pharmacy[32] and more specifically in solid organ transplantation.[7 15 27–29 31] Our rate was similar to Ah *et al*[7] study (92.3%) related to more than 1500 PIs in liver transplantation. It can be explained by the 'proactive approach' of PIs in our lung transplantation centre: clinical pharmacists interview outpatients before medical round and directly provide therapeutic suggestions to physicians during prescribing. Non-accepted
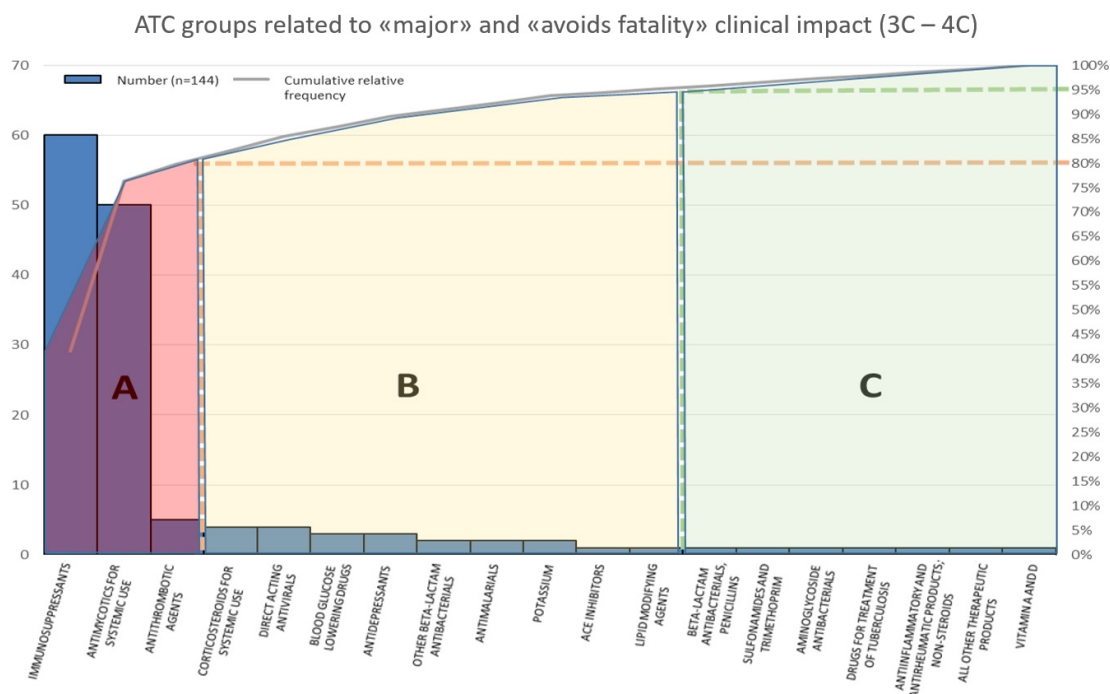
Figure 4 Pareto chart of 'major' and 'avoids fatality' clinical impact of accepted pharmacists' interventions (PIs) according to ATC groups (n=103), related to 144 drugs (group A: 80% of PIs; group B: 15% of PIs; group C: 5% of PIs). ATC, Anatomical Therapeutic Chemical .

PIs were mostly related to 'untreated indication' (n=42) and 'subtherapeutic dosage' (n=38) but the reason of non-acceptance was not explained in Act-IP database. However, we can hypothesise that the reasons of non-acceptance may be related to stable patient condition without any adverse event or pharmacist's lack of information at the time of analysis.

Our study highlights the added value of clinical pharmacist in lung transplantation as clinical impact of accepted PIs was positive in 98.9% of cases and none had negative clinical impact. PIs allowed stopping major or lethal clinical outcomes in 7.1% of cases. DRPs to be detected as a priority were wrong dosage and untreated indication problems, associated with a moderate clinical impact in almost 70% of cases. The clinical impact was more important for subtherapeutic dosage problem than for supratherapeutic dosage problem, according to the risk of graft rejection. Clinical pharmacists should be aware of drug–drug interactions as they were related to moderate or major clinical impact in more than 80% of cases. The Pareto chart revealed that immunosuppressants, antimycotics for systemic use and antithrombotic agents were the most implied drug classes in PIs with major or lethal clinical impact which require pharmacists' attention: clinical pharmacists took proactive steps with the transplant team to resolve these problems and developed or optimised protocols such as azole initiation monitoring recommendations.

One of the major strengths of this retrospective study relied on assessing clinical pharmacist's recommendations over a long period in a lung transplantation centre with a full time pharmacist involvement, contrary to previous studies.[7 15 27 28 31] A double quality control process was performed to guarantee data reliability. PIs' impact was assessed by consensus of a multidisciplinary expert committee, including a pulmonologist. Only accepted PIs were evaluated because they represented the real impact of the pharmacist in LT outpatients' management. We used a new validated tool to assess the clinical impact of PIs.[19] The CLEO tool has been recently created according to different scales available in the literature[24] and provided suitable inter-rater and intrarater reliabilities. This CLEO tool was used to assess clinical impact of PIs on injectable antineoplastic prescriptions in a French Hospital Chemotherapy Preparation Unit[33] and was translated and validated in a German version.[34] We acknowledge that the use of a new tool adapted to clinical practice for assessing clinical impact of PIs does not allow any comparison with previous studies in several solid organ transplantation,[7 15 27 28 31] which mainly used Overhage and Lukes and Hatoum *et al* scales.[35 36] However, we provided a new insight to assess the clinical impact of PIs by using the Pareto chart, a quality control tool which highlights drug groups that should be targeted in priority when pharmacists' time is lacking.

Some limitations have to be underlined. All the DRPs may be not detected by clinical pharmacists, because of pharmacist residents' lack of experience or pharmacist's lack of time. Indeed, each pharmacist resident is trained by a senior pharmacist at the beginning of his internship but without reaching senior's experience level, that is why the pharmacist controlled all recommendations to make sure they were optimised. In addition, not all identified DRPs may be recorded on the Act-IP database although it was mandatory, which may lead to an underestimate of DRPs prevalence. This possible under-reporting could not be excluded, particularly for non-accepted PIs. Our data could not be presented in terms of patient proportion as all the PIs were recorded anonymously in the Act-IP database. We acknowledge that there was no control group in this study. However, with a high acceptance rate and high significance of PIs, conducting randomised controlled trial may provoke ethical issues.

LT recipients require more and more organised multidisciplinary care to improve effective and safe drug use. In our collaborative model, clinical pharmacist plays an important role as an expert in drug therapy to detect and resolve DRPs for each outpatient's clinic visit and provides relevant PIs to physicians. This study demonstrates the added value of clinical pharmacists in collaborative practice model in lung transplantation care and also provides information to target PIs in the future.

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