ERS International Congress 2023: highlights from the Thoracic Surgery and Lung Transplantation Assembly

Andrea Zajacova[1], Marco Umberto Scaramozzino[2,3], Alice Bellini[4,5], Pallavi Purwar[6], Sara Ricciardi[7,8], Marcello Migliore[9,10], Federica Meloni[11] and Dorina Esendagli[12]

[1]Prague Lung Transplant Program, Department of Pneumology, Second Faculty of Medicine, Charles University, University Hospital Motol, Prague, Czech Republic. [2]Pulmonology "La Madonnina" Reggio Calabria, Reggio Calabria, Italy. [3]Villa aurora Hospital Reggio Calabria, Reggio Calabria, Italy. [4]Division of Thoracic Surgery, Department of Medical and Surgical Sciences (DIMEC) of the Alma Mater Studiorum, University of Bologna, Bologna, Italy. [5]Giovanni Battista Morgagni-Luigi Pierantoni Hospital, Forlì, Italy. [6]Sir Ganga Ram Hospital, New Delhi, India. [7]Unit of Thoracic Surgery, San Camillo Forlanini Hospital, Rome, Italy. [8]Alma Mater Studiorum, University of Bologna, Bologna, Italy. [9]Program of Minimally Invasive Thoracic Surgery and New Technologies, Policlinic Hospital, Department of Surgery and Medical Specialties, University of Catania, Catania, Italy. [10]Thoracic Surgery and Lung Transplantation, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. [11]Transplant Center, IRCCS Policlinico San Matteo Foundation, Pavia, Italy. [12]Baskent University, Faculty of Medicine, Chest Diseases Department, Ankara, Turkey.

Corresponding author: Dorina Esendagli (dr.dorina.de@gmail.com)

Shareable abstract (@ERSpublications)
Assembly 8 presents highlights of #ERSCongress 2023: management of spontaneous pneumothorax, malignant pleural effusion, results of the ScanCLAD study, infectious and immune-mediated complications and debate on age limit in lung transplantation https://bit.ly/3sm7NzC

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Abstract

Five sessions presented at the European Respiratory Society Congress 2023 were selected by Assembly 8, consisting of thoracic surgeons and lung transplant professionals. Highlights covering management of adult spontaneous pneumothorax, malignant pleural effusion, infectious and immune-mediated complications after lung transplantation, as well as the pro and con debate on age limit in lung transplantation and results of the ScanCLAD study were summarised by early career members, supervised by the assembly faculty.

Introduction

Assembly 8 of the European Respiratory Society (ERS) consists of 499 members, focused on state-of-the-art knowledge and both basic and translational research, encouraging interdisciplinary and multicentric interactions, as well as interconnection with the other scientific assemblies. Group 8.01 is formed by surgeons specialised in prevention, diagnostic and surgical interventions of a wide range of thoracic pathologies, such as trauma, infections and malignancies. Group 8.02 consists of physicians involved in lung transplantation (LuTx), focusing on risk prevention, diagnostics and therapy of a spectrum of immune- and non-immune-modulated pathologies affecting morbidity and mortality. The highlights of both groups presented during the 2023 ERS Congress are summarised in this article (figure 1).

Management of adult spontaneous pneumothorax

Medical management of spontaneous pneumothorax

Steven Walker (Bristol, UK) presented the first European guidelines on the management of spontaneous pneumothorax (SP). A literature review was conducted, followed by a meta-analysis with evaluation based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system, followed by an "Evidence to decision framework" process.

SP (therapeutic possibilities listed based on the level of their invasiveness):

- Conservative management: the literature review identified one large randomised controlled trial (RCT) favouring the observational approach compared to chest drain. This RCT demonstrated shorter duration of stay (median 4.5 days; min. 3.18; max. 5.82), lower recurrence rate (median 81 fewer per 1000

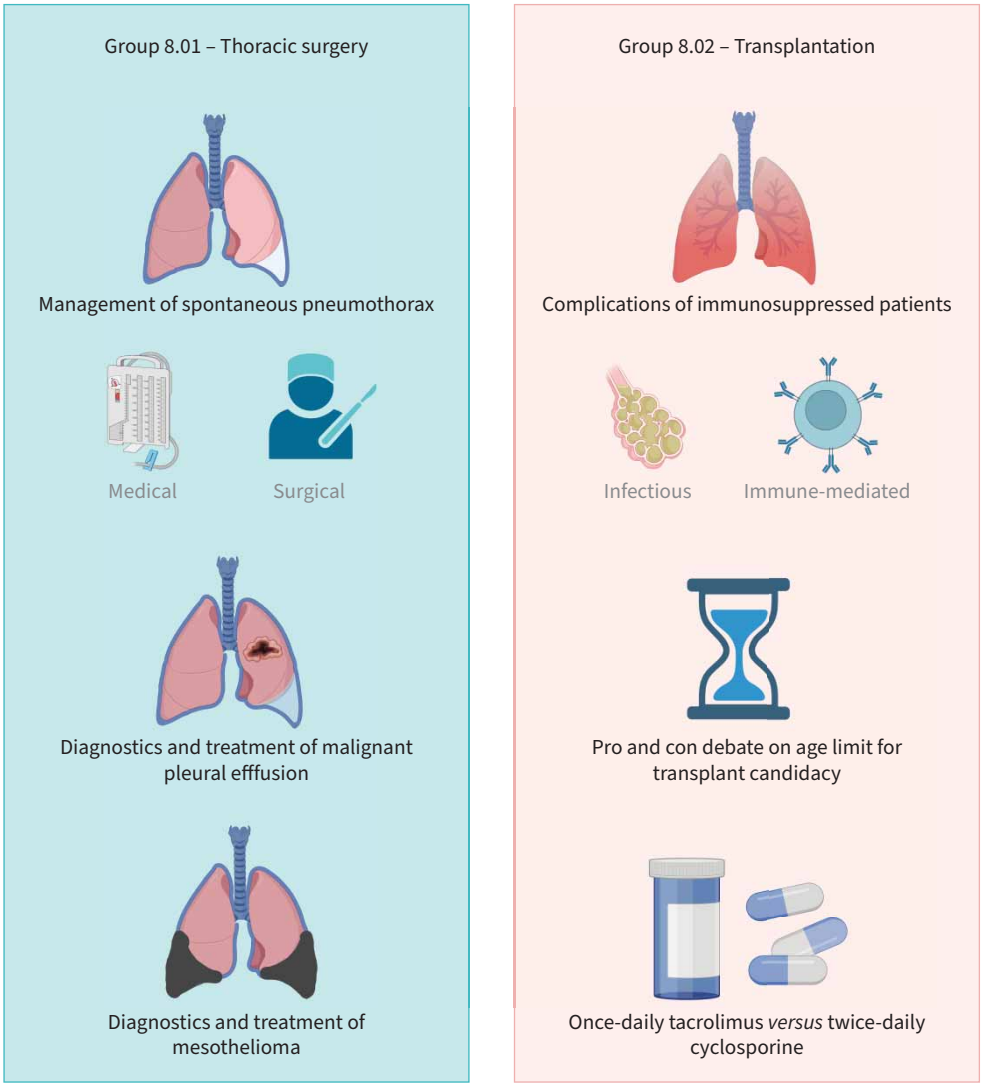

FIGURE 1 Highlights from the Thoracic Surgery and Lung Transplantation Assembly from the European Respiratory Society Congress 2023. Figure created using BioRender.

cases; min. 5; max. 121), and fewer overall repeated pleural procedures (median 152 fewer per 1000 cases; min. 94; max. 182). Based on this evidence, the panel suggested the conservative management of SP in selected cases (minimally breathless, clinically and radiologically stable patients), regardless of size of pneumothorax (conditional recommendation, very low certainty of evidence).

- Needle aspiration (NA): six RCTs showed that the NA was associated with lower length of stay (2.2 days lower, range 2.92 lower to 1.49 lower), lower symptom scores compared to chest drain management (1.21 lower, range 1.68 lower to 0.74 lower) and fewer overall repeated procedures (40 fewer per 1000 cases, range from 198 fewer to 59 more). Based on these findings the panel recommends NA over the chest tube drain for the initial treatment of SP (strong recommendation, low certainty of evidence).
- Ambulatory devices by using a Heimlich device: one RCT reviewed this topic. Ambulatory care compared to chest drain was associated with lower length of stay (3 days lower), fewer overall recurrences (39 fewer per 1000, from 122 fewer to 92 more) and fewer overall pleural procedures (148 fewer per 1000, from five fewer to 220 fewer). The panel suggested ambulatory management for the initial treatment of SP in centres with appropriate expertise and pathways to manage patients with ambulatory devices as outpatients (conditional recommendation, low certainty of evidence).
- Chest drain: the current standard of care in the majority of the centres (as confirmed by a voting during the presentation over a case report).
- Early surgical management: in the literature review, there were two studies that looked at the role of first-line approach of surgery for SP. They demonstrated tendency for a lower rate of recurrence

TABLE 1 Summary table comparing different clinical approaches in the management of spontaneous pneumothorax (SP)

Treatment option	Conservative	Needle aspiration	Ambulatory care	Chest drain	Surgery
Mean initial hospital stay, days	1.0	2.6	0	4.8	4.0
Chance of SP recurrence within 1 year	9%	25%	24%	21%	6%
Required further pleural procedure	15%	22%	21%	25%	3%

(271 fewer per 1000, from 339 fewer to 46 more) and fewer overall complications (95 fewer per 1000, from 119 fewer to 13 fewer) with early surgery compared to usual care (previous guidelines reserves surgery to more than once recurring pneumothorax). The panel suggested consideration of early surgical intervention for the initial treatment of SP in patients who prioritise recurrence prevention (conditional recommendation, lower certainty of care).

The recommendations for management of SP are summarised in table 1.

Persistent air leak (compared to the standard of care (chest tube)):

- Autologous blood patch (ABP): one RCT in the literature review demonstrated shorter length of stay (2.37 days fewer, range 3.09 fewer to 1.65 fewer) and quicker resolution of the pneumothorax (222 more per 1000, from 30 more to 462 more). Based on these findings, the panel suggests that ABP could be considered in patients with persistent air leak who are not fit for surgery (conditional recommendation, very low quality of evidence).
- Bronchial valves: one RCT in this topic demonstrated lower air leak duration (3.18 days fewer, range 3.93 fewer to 2.43 fewer) and quicker resolution of the pneumothorax (240 more per 1000, from 48 more to 486 more). However, the guideline stated no recommendation regarding bronchial valves in patients with secondary SP who are not fit for surgery due to lack of conclusive evidence (no recommendation, very low quality of evidence).
- Suction to chest drain: one RCT did not show any significant difference in any of the outcomes, looked at in terms of duration of air leak. The guideline gave no recommendation due to lack of conclusive evidence (no recommendation, very low quality of evidence).

Surgical management of spontaneous pneumothorax

Marcello Migliore (Catania, Italy) deliberated upon the existing literature, guidelines, as well as gaps in the current knowledge with regards to the surgical management of SP. According to British Thoracic Society (BTS) guidelines [1], surgical evaluation is indicated only for patients with recurrent or bilateral pneumothorax, hydropneumothorax or clinically unstable patients. In the ERS statement [2], no recommendations concerning surgical management were given for primary SP or persistent/recurrent pneumothorax due to the lack of randomised evidence. The ERS committee left a few open questions for further research, *e.g.* regarding 1) the relative benefits of talc *versus* talc and bullectomy in recurrence prevention, and 2) the role of lung parenchyma resection in recurrence prevention.

Meta-analysis by Vuong *et al.* [3] including 4262 patients of 29 RCTs concluded that in patients with first episode of pneumothorax, video-assisted thoracoscopic surgery (VATS) ranked the highest in preventing recurrence (p-score=0.95), followed by pleurodesis (p-score=0.69), aspiration (p-score=0.27) and tube drainage (p-score=0.08). The recurrence incidences of VATS, pleurodesis, tube drainage, and aspiration were 0, 8, 13 and 30 per 100 person-years, respectively. Brown *et al.* [4] evaluated 316 patients (154 patients in intervention group, 162 in conservative management group) in an open-label, multicentre, non-inferiority trial, assessing whether conservative management is an acceptable alternative to interventional management for uncomplicated, moderate-to-large primary SP. There was no difference in lung re-expansion (risk difference −3.8%; 95% CI −8.3 to 0.7) or time to resolution (15.5 *versus* 14 days in the intervention and conservative management group, respectively; hazard ratio (HR) 1.11; 95% CI 0.88–1.40). The conservative management arm had fewer invasive procedures, shorter hospital stays, faster return to work, less recurrence, and fewer adverse events.

A randomised study by Marx *et al.* [5] included 200 patients with NA and 202 with chest tube drainage from 31 French hospitals. Treatment failure was observed in 29% patients with NA and in 18% with chest tube drainage. Failures of NA were treated with chest drain insertion. The authors concluded that NA was better tolerated with fewer adverse events, leading to higher failure rates.

The discussion then moved on to the first European guidelines on adults with SP. Of the 12 clinical questions, the two questions of surgical relevance were as follows. 1) Should treatment with pulmonary intervention (VATS) be used for recurrence prevention in SP (compared with VATS plus pleurodesis)? 2) Should surgical pleurectomy be used for recurrence prevention in SP (compared to chemical pleurodesis delivered surgically or medically)? However, no recommendations could be made for either of these questions given the lack of available evidence.

The presentation proceeded with two clinical cases. The first case described a patient with persistent pneumothorax with a large bulla in the apex, resected with a base of normal lung tissue. The further management (no pleurodesis, pleurectomy, pleural abrasion, talc pleurodesis) is eminence-based, due to the lack of the evidence. The second case presented a patient with stage 1 pneumothorax, without any bulla/bleb: representing nearly 20% cases in experienced centres, with no current guidelines regarding further management (apical wedge resection, pleurodesis). M. Migliore shared his preference on performing a wedge resection, which may not have any implication in terms of recurrence prevention, but could aid in obtaining a definitive diagnosis of the cause of pneumothorax [6].

The current limitations on surgical management of pneumothorax are: no consensus on the size cut-off for small *versus* large pneumothorax, insufficient evidence for management of persistent air leak, surgical approach (uniportal/multiportal), method of pleurodesis and strategies for stage 1 pneumothorax. M. Migliore highlighted the unmet need of generating good quality evidence.

Optimising diagnostic tools and treatment for malignant pleural effusion and mesothelioma

Matthew Tate (Glasgow, UK) presented "The Scottish Mesothelioma Network: impact of a national multidisciplinary team (MDT) on overall survival in pleural mesothelioma". A dedicated Scottish MDT was established in 2019, collecting mesothelioma data pre- (April 2017–March 2019) and post-network (April 2019–April 2022) to set-up cohorts: 273 (41.4%) and 386 (58.6%) cases, respectively. Multivariable restricted mean survival time analysis proved better overall survival for post-network non-epithelioid cases in comparison to pre-network ones (+4.6 months; p=0.004), and no difference was observed for epithelioid cases between the groups. In patients receiving systemic anti-cancer therapy, overall survival in the post-network group was significantly increased in non-epithelioid cases (median 16.6 compared to 10.7 months in pre-network group; p<0.0001). The possible explanations are the use of immunotherapy as a standard of care in non-epithelioid malignant pleural mesothelioma (in 15.3% post-network patients), better histological classification, lower attrition on diagnostic pathways and better symptom management.

Dinesh Addala (Oxford, UK) presented "Qualitative study of patient priorities in the malignant pleural effusion (MPE) pathway". In the mixed methods study, 56 patients with MPE were included. Median time from first contact to diagnosis was 46 days (range 28–54) and to definitive treatment 70 days (range 45–84). The delays resulted in prolonged breathlessness (more than 1 month in 60% of patients), a higher number of required procedures (⩾3 in more than 70% of patients) and emergency procedures (60% of patients). In the survey, up to 70% of patients would be willing to consider an earlier indwelling pleural catheter (IPC). D. Addala summarised his talk addressing breathlessness and time to diagnosis being the key areas of concern, highlighting the urge to accelerate both diagnosis and treatment, suggesting earlier biopsy and IPC insertion.

Richa Gupta (Vellore, India) presented a study analysing the efficacy of the time-dependent (12 h) *versus* volume-dependent (<150 $mL \cdot day^{-1}$) chest tube removal for talc pleurodesis in patients with MPE. The results of this prospective RCT including 100 patients showed no differences in complications, mortality and pleurodesis success at day 7, 30 and 90 between time- and volume-dependent groups. Average time from pleurodesis to chest tube removal was 12±0.52 h for time- and 44±56 h for volume-dependent groups (p<0.001). R. Gupta concluded that comparable outcomes were achieved by both methods, with patients in the time arm having shorter hospital stays.

Hugh Welch (Bristol, UK) presented "Does a novel IPC drainage system improve patient experience?" IPCs are increasingly used to manage recurrent pleural effusions. Most systems involve vacuum bottle drainage, applying variable vacuum pressures, leading to drainage-related pain. The electronic pump system Geyser was designed to minimise the drainage pain by a ramped drainage profile consisting of 4-min cycles of maximum in-line pressure 50 cmH_2O, with maximum 250 mL of fluid removal. 15 patients were included in this single-centre prospective study. Geyser and standard of care IPC systems drained similar volumes of pleural fluid, with the Geyser group describing lower post-drainage pain scores. Further studies should be performed in order to avoid limitation by small-sized cohort and pro-innovation bias.

Maria Giovanna Mastromarino (Pisa, Italy) presented "Pressurised intrathoracic aerosol chemotherapy (PITAC): preliminary results in MPE". MPEs affect up to one third of oncological patients, lowering the quality of life and overall survival. PITAC is a novel therapy combining the advantages of surgery and loco-regional chemotherapy. Patients were divided into two groups: PITAC with tailored dose of cisplatin (10.5 $mg \cdot m^{-2}$) plus doxorubicin (2.1 $mg \cdot m^{-2}$), selected for their cytostatic and sclerosing effect, *versus* talc poudrage (current standard of therapy). Cytostatics were inserted into the chest cavity *via* a nebuliser and left in steady state for 30 min, with intrathoracic pressure 12 mmHg CO_2 to increase the drug penetration. Both groups developed effective pleurodesis at day 30 and month 5 follow-up, with no significant difference observed in pleural effusion recurrence survival (p=0.16). The study proved the comparability of the PITAC approach to talc pleurodesis in management of pleural effusion; however, its oncological role requires a further investigation.

Infectious and non-infectious complications of immunosuppressed patients

Mariagrazia Di Luca (Pisa, Italy) presented a pre-recorded session "Multidrug-resistant bacterial pulmonary infections: challenges of phage therapy". Phages are viruses with the ability to selectively and exclusively attach to harmful bacteria at the strain level, leading to their rapid lysis. Moreover, they are active as well against biofilm-embedded bacteria and might be used as adjuvant therapy to antibiotics, creating synergism, with some *in vitro* studies proving possible restoration of the sensitivity to antibiotics [7]. Currently, there are two ways of obtaining the phage therapy products: a personalised approach, using selected phages from the phage bank; or a standard formulation, a phage cocktail from a pharmaceutical company. M. Di Luca presented a published case report: a patient with a chronic infection caused by *Pseudomonas aeruginosa* treated by a combination of meropenem and personalised phage therapy. Over a 2-year follow-up, no severe adverse events or clinical signs of infection relapse were observed [8].

Robin Vos (Leuven, Belgium) followed with the presentation "Chronic lung allograft dysfunction (CLAD) and pulmonary chronic graft *versus* host disease (PcGvHD): common pathogenic mechanisms and clinical features". His talk covered the late-onset non-infectious pulmonary complications after transplantation, clinically manifesting as CLAD in LuTx and PcGvHD in haematopoietic stem cell transplantation (HSCT) recipients. Immunological pathways of CLAD are a consequence of allo-reactive lymphocytes of the recipient, while PcGvHD is caused by the graft-originated ones. Both CLAD and PcGvHD are driven by numerous risk factors, such as immune activation caused by human leukocyte antigen (HLA) and non-HLA mismatch, respiratory infections, systemic inflammation, gastro-oesophageal reflux, exposure to toxins or ex-smoking. CLAD and PcGvHD are very similar on the cellular level, with two common end-points: airway-centred fibrosis (bronchiolitis obliterans/constrictive bronchiolitis) and interstitium-affecting alveolar fibroelastosis (AFE) or fibrosis [9]. On a molecular level, study by Vanstapel *et al.* [10] showed increased expression of connective tissue growth factor in end-stage CLAD and PcGvHD, suggesting its potential role in CLAD, especially restrictive allograft syndrome (RAS), and PcGVHD. Jonigk *et al.* [11] proved that as well molecular characteristics in bronchiolitis obliterans and AFE are alike in CLAD and PcGvHD. Current definition of CLAD is based on the 2019 International Society for Heart and Lung Transplantation (ISHLT) consensus, identifying four different phenotypes: bronchiolitis obliterans syndrome (BOS), RAS, mixed and undefined [12]. However, current National Institutes of Health (NIH) PcGvHD consensus criteria account only for BOS [13]. A recent study by Pang *et al.* [14] divided PcGvHD patients based on CLAD 2019 ISHLT consensus definition, with less than a half of the patients meeting the NIH criteria for BOS, demonstrating the potential of adapting CLAD criteria in the PcGvHD population. The similarities and differences between obstructive and restrictive phenotypes of CLAD and PcGvHD are summarised in table 2. The NIH chronic graft *versus* host disease (cGvHD) working report 2020 recommended full pulmonary function tests (lung volumes and diffusing capacity of the lung for carbon monoxide included) prior to HSCT, at day 100 and year 1, followed by annual examination even in asymptomatic patients with spirometry on month 6 and 9, and in patients with cGvHD every 3 months. The threshold for referral to a specialised transplant team should be forced expiratory volume in 1 s (FEV_1) decline of $\geqslant$10% of the patient's pre-HSCT baseline or a day 100 assessment, followed by short interval repeat testing (within 2–4 weeks) [16]. R. Vos ended his presentation highlighting the necessity of earlier detection of both CLAD and PcGvHD, with randomised clinical trials being an unmet need in order to further improve outcomes after LuTx and HSCT.

Daniel Wolff (Regensburg, Germany) followed with the presentation "CLAD and PcGvHD: old and new therapeutic approaches". This presentation followed the path of analogies between PcGVHD and CLAD and analysed therapeutic strategies in order to highlight common therapeutic targets. Williams *et al.* [17] proved that the combination of inhaled fluticasone, azithromycin, and montelukast (FAM) with a brief steroid pulse may halt pulmonary decline in new-onset BOS in HSCT recipients: only 6% of the patients experienced treatment failure at month 3 (compared to 40% in historical controls). A study by Vos *et al.* [18]

TABLE 2 The clinical similarities and differences between obstructive and restrictive phenotypes of chronic lung allograft dysfunction (CLAD) and pulmonary chronic graft *versus* host disease (PcGvHD)

	BOS after LuTx	BOS after HSCT	RAS after LuTx	Restrictive PcGvHD after HSCT
Prevalence	Approx. 50%	Approx. 5–15%	⩽30%	Not accurately known, about 12–60% of LONIPC
Symptoms	Asymptomatic, cough, exertional dyspnoea, dyspnoea at rest, inability to perform activities of daily living			
Diagnosis	FEV_1 <80% of baseline and absence of CT opacities and exclusion of the other causes	FEV_1 <75% of predicted and >10% decline over <2 years and FEV_1/FVC <0.7 and signs of air-trapping (PFT/CT) or other organ cGvHD in absence of respiratory infection	FEV_1 <80% of baseline and TLC ⩽90% of baseline and persistent CT opacities and exclusion of the other causes	No definition yet
Grading	CLAD staging: Grade 1: FEV_1 >65–80% baseline Grade 2: FEV_1 >50–65% baseline Grade 3: FEV_1 >35–50% baseline Grade 4: ⩽35% baseline	NIH lung cGvHD grading: Grade 1: mild; FEV_1 60–79% predicted Grade 2: moderate; FEV_1 40–59% predicted Grade 3: severe; FEV_1 ⩽39% predicted	CLAD staging: Grade 1: FEV_1 >65–80% baseline Grade 2: FEV_1 >50–65% baseline Grade 3: FEV_1 >35–50% baseline Grade 4: ⩽35% baseline	NIH PcGvHD grading: Grade 1: mild; FEV_1 60–79% predicted Grade 2: moderate; FEV_1 40–59% predicted Grade 3: severe; FEV_1 ⩽39% predicted
CT findings	Air-trapping, bronchiolitis (tree-in-bud), bronchiectasis		Ground-glass opacities, consolidations, pleural or septal thickening, bronchiectasis, volume loss	Ground-glass opacities, consolidations and less often pleural or septal thickening, bronchiectasis, volume loss
Histology	Chronic bronchitis, bronchiolitis obliterans		Most common: DAD, AFE, PPFE, and concurrent OB/CB Other: NSIP, AFOP, (C)OP	More heterogeneous: NSIP, LIP, DAD, AFE, PPFE, and concurrent OB/CB Less frequent: OP, AFOP, (C)OP
Prognosis	Median survival 3–5 years	Median 5-year survival 60%	Median survival 1–2 years	Median 2-year survival 61% (less data)

BOS: bronchiolitis obliterans syndrome; LuTx: lung transplantation; HSCT: haematopoietic stem cell transplantation; RAS: restrictive allograft syndrome; CT: computed tomography; LONIPC: late-onset non-infectious pulmonary complications; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PFT: pulmonary function test; cGvHD: chronic graft *versus* host disease; TLC: total lung capacity; NIH: National Institutes of Health; DAD: diffuse alveolar damage; AFE: alveolar fibroelastosis; PPFE: pleuroparenchymal fibroelastosis; OB/CB: obliterative bronchiolitis/constrictive bronchiolitis; NSIP: nonspecific interstitial pneumonia; AFOP: acute fibrinous and organising pneumonia; (C)OP: (cryptogenic) organising pneumonia; LIP: lymphoid interstitial pneumonia. Reproduced and modified from [15] with permission.

included patients with different grades of CLAD (BOS 76.2%; RAS 24.8%) that started montelukast therapy. Montelukast was associated with attenuation of FEV_1 decline at month 3 and 6 ($p<0.0001$ for both), as well as significantly better progression-free ($p<0.0001$) and overall survival ($p=0.0002$) in the patients with improvement or stabilisation at month 3 of therapy. Li *et al.* [19] proved that azithromycin prophylaxis was associated with improved survival ($p=0.002$), but no significant reduction in CLAD onset ($p=0.0697$) was observed. Still considering azithromycin effect, the study by Bergeron *et al.* [20] in PcGvHD had to be pre-emptively stopped because the group with azithromycin prophylaxis had significantly higher cumulative incidence of haematological relapse within a 2-year follow-up period (33.5% *versus* 22.3% on placebo, $p=0.002$). Based on given data, D. Wolff summarised that in HSCT recipients, azithromycin prophylaxis and prolonged application should be avoided, with FAM being standard of care in manifest BOS or drop of FEV_1 without formal diagnosis of BOS. Special attention should be paid to patients with otherwise increased risk for secondary malignancies. A randomised trial by Zeiser *et al.* [21] in PcGvHD patients presented significantly better response to ruxolitinib in comparison to control group (49.7% *versus* 25.6%, respectively; $p<0.001$) at week 24, as well as longer median failure-free survival (>18.6 *versus* 5.7 months, respectively; $p<0.001$) and higher symptom response (24.2% *versus* 11.0%, respectively; $p=0.001$). A study by Hefazi *et al.* [22] showed results of retrospective analysis on the effect of extracorporeal-photopheresis (ECP) in BOS of HSCT recipients, where ECP was associated with a better overall survival ($p=0.001$). ECP is applied by 72% of German-speaking centres, with half of the centres using ECP either upfront or as the second line [23]. DeFilipp *et al.* [24] analysed HSCT patients with BOS, treated by belumosudil, showing higher response rates in less advanced disease; however, no significant correlation was observed in predominantly mild or moderate disease. Several trials still in the setting of PcGvHD were assessing the role of abatacept in BOS, demonstrating its effectiveness with an overall response rate of 57%, but subjective improvement appeared to be more sensitive compared to FEV_1 [25, 26]. Currently, there are no organ-specific trials available for treatment of BOS (except FAM);

TABLE 3 Recommendations on antifungal prophylaxis in lung transplantation (LuTx)

Prophylaxis or pre-emptive therapy can be employed as a strategy to prevent fungal infections, depending on the availability of the diagnostic tests (strong; moderate)
In cases where a pre-emptive treatment strategy is employed, both bronchoalveolar lavage culture and galactomannan should be incorporated into the protocol (strong; low)
It is recommended to initiate targeted antifungal prophylaxis if any of the risk factors is present (pre-LuTx or within first year after LuTx *Aspergillus* colonisation, single LuTx or positive *Aspergillus* perioperative culture in cystic fibrosis patient) (strong; moderate)
Duration 4–6 months in universal and targeted prophylaxis and 3–4 months in pre-emptive strategy (strong; moderate)
Caution with voriconazole in patients with history of squamous cell carcinoma, residing in geographic areas with higher incidence of cutaneous malignancy and photo-protective measurements and enhanced skin surveillance to be put in place (strong; high)
Alternatives to voriconazole may include posaconazole or isavuconazole (weak; low)

however, some agents have supportive data of use in this clinical setting. D. Wolff concluded his presentation by highlighting the need for early intervention in patients affected by CLAD or PcGvHD.

Shahid Husain (Toronto, ON, Canada) talked about preventive and treatment strategies around fungal infections in solid organ and bone marrow transplant recipients. A study by Kontoyiannis *et al*. [27] showed that the cumulative overall incidence of invasive fungal infection (IFI) within the first year in HSCT recipients was 3.4%. In comparison, cumulative incidence of IFI for solid organ transplant recipients (SOTRs) was 3.1%: 11.6% for small bowel, 8.6% for lung and heart-lung, 4.7% for liver, 4.0% pancreas and kidney-pancreas, 3.4% for heart and 1.3% for kidney transplant recipients [28]. In SOTRs, candidiasis was the most common IFI within 12 months (71.4%), except for LuTx recipients (23.9%), where the most common was aspergillosis (24.8% compared to 12.6% in other SOTRs) [29]. Moreover, cumulative probability of IFI rose consistently over the first 5 years following LuTx, reaching 20.1% [30]. Different prophylactic strategies are used across the centres; however, three meta-analyses did not prove any advantage of universal prophylaxis on the incidence of invasive aspergillosis (IA) compared to none [31–33]. Meta-analysis by Phoompoung *et al*. [34] showed that risk factors for IFI in LuTx include previous fungal colonisation (OR 2.44; 95% CI 0.08–0.47), cytomegalovirus infection (OR 1.96; 95% CI 1.08–3.56), and single LuTx (OR 1.77; 95% CI 1.08–2.91), with pre-emptive antifungal therapy being a protective factor for IA (OR 0.2; 95% CI 0.08–0.47). As well, statins were proved to be associated with a lower risk of IA (subdistribution HR 0.30; 95% CI 0.14–0.64; p=0.002) [34]. In terms of *Aspergillus* colonisation, meta-analysis by Bhaskaran *et al*. [32] did not prove any significant difference between groups with and without voriconazole prophylaxis (21% and 28%, respectively; p=0.48). S. Husain presented data of his own study from 2018 regarding pre-emptive treatment based on bronchoalveolar lavage galactomannan and cultures: pre-emptive therapy was associated with significantly lower rates of IA at 1 year post-LuTx compared to no pre-emptive therapy (HR 0.23, 95% CI 0.09–0.58) [35]. In a multicentre RCT, no difference in 6-month fungal-free survival was proved between patients treated with fluconazole or voriconazole, despite trends to fewer IFIs favouring voriconazole (7.3% *versus* 11.2% in fluconazole group, p=0.12) [36]. A study by Wang *et al*. [37] found posaconazole to be as effective as fluconazole in preventing IFI (OR 0.56, 95% CI 0.30–1.07; p=0.07) and superior in prevention of proven or probable IA (OR 0.31, 95% CI 0.13–0.75; p=0.006). In the posaconazole group, fewer breakthrough IFIs (2.4% *versus* 7.6%; p=0.004%) and particularly IA (1.0 *versus* 5.9%; p=0.001) were observed. A study by Bose *et al*. [38] regarding isavuconazole prophylaxis demonstrated probable and proven IFI in 6% and 12% patients, respectively, with excellent tolerability. Meta-analysis including 69 RCT patients concluded that posaconazole was associated with the best probability of success against IFI and IA and voriconazole was associated with significant reduction in invasive candidiasis compared to placebo [37]. A study by Marty *et al*. [39] regarding mucormycosis management demonstrated that day 42 all-cause mortality of 33% in primary-treatment isavuconazole cases was similar to 39% in amphotericin B-treated matched controls (p=0.595). Novel promising antifungals such as fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin are not ready to be used in clinical settings yet. Recommendations on prophylaxis are summarised in table 3.

The pro and con debate on age limit for lung transplant candidacy

Pro: age of 65 years is no longer a barrier for lung transplant candidacy

Konrad Hoetzenecker (Vienna, Austria) highlighted the differences between chronological and actual biological age. According to the 2021 ISHLT consensus on the selection of LuTx candidates, age between

65 and 70 years is considered to be a risk factor while age >70 years is a relative contraindication [40]. Zhou *et al.* [41] observed a prominent increase in ⩾70-year-old LuTx recipients (from 2.2% in 2005 to 14.3% in 2020), with a 83% increase in the number of LuTx performed in patients aged ⩾70 years. Candidates ⩾70 years had favourable waitlist outcomes (LuTx within 1 year since listing) in comparison to those 60–69 years old (81.2% and 72.7%, respectively; p=0.001). The odds for death or deterioration within 1 year since listing were as well in favour of ⩾70-year-old candidates, when compared to those aged 60–69 years (9.1% and 10.1%, respectively; p<0.001). Moreover, older recipients had superior perioperative outcomes in terms of acute rejection incidence (6.7% in patients aged ⩾70 years, 7.4% in those aged 60–69 years and 9.2% in the group aged 18–59 years; p<0.001) and prolonged intubation (21.7% in ⩾70 years, 27.4% in 60–69 years and 34.5% in the group aged 18–59 years; p<0.001) [41]. The study by Singer *et al.* [42] demonstrated that age was not associated with meaningful differences in the health-related quality of life benefits of LuTx. However, frailty was a significant risk factor, leading to a 12.2% (95% CI 3.1–21%) increased risk of death within the first year after LuTx. Additionally, it was proved that frailty is reversible and possesses prognostic value in only ∼15% of LuTx recipients remaining frail at post-LuTx 6-month frailty assessment [43]. A novel approach combining standard frailty tests in combination with biomarkers such as interleukin-6 (IL-6), growth differentiation factor-15 (GDF-15) or apelin might allow us to improve the evaluation of these patients [44]. K. Hoetzenecker presented data from the Vienna LuTx Program. In 2022, 23% of their donors were aged 65–69 years and 15% >70 years, raising the question about why there is discrimination against the older generation if there is a significant organ donor pool created by the very same age groups: the aim could be not to discuss the acceptability of older LuTx candidates, but to foster the research improving their post-LuTx outcomes.

Con: age still matters in candidate selection for lung transplantation

Are Martin Holm (Oslo, Norway) stated that given the limited amount of donor organs available, three main questions should be asked by the clinicians. 1) Who is the most urgent? (Following the rule of rescue and saving lives.) 2) Who has the best prognosis? (Assessing priority by medical criteria.) 3) Who has the most to lose? (Addressing justice and equity.)

A.M. Holm presented data from the Oslo LuTx Center, comparing significantly differing survival of patients after LuTx (survival at year 5 ∼70%, year 10 ∼55%) to non-transplanted patients (50% deceased at year 2). Data from the Organ Procurement and Transplantation Network Registry 2021 demonstrated unfavourable survival outcomes in recipients aged >65 years [45]. The retrospective analysis by Iyanna *et al.* [46] demonstrated that the rate of LuTx in recipients aged ⩾70 years increased particularly in

TABLE 4 Summarised highlights of the European Respiratory Society Congress 2023 and take-home messages

Group 8.01 - Thoracic surgery
Management of adult spontaneous pneumothorax
• Patients with spontaneous pneumothorax may benefit from VATS as a modality for recurrence prevention. However, more research is needed.
• Currently there is variability in practice with regards to the method of pleurodesis and RCTs are needed to choose between nothing, pleurectomy, pleural abrasion and talc pleurodesis.
• In stage 1 pneumothorax when no bulla/bleb is noted, wedge resection may be useful for diagnosis of pneumothorax.
Optimising diagnostic tools and treatment for malignant pleural effusion and mesothelioma
• Patients with mesothelioma might benefit from a centralised, multidisciplinary network.
• Earlier insertion of indwelling pleural catheter should be offered to patients with malignant pleural effusion.
• Time-dependent (12 h) chest tube removal for talc pleurodesis in patients with malignant pleural effusion showed comparable results as volume-dependent (<150 mL·day^{-1}).
Group 8.02 - Lung transplantation
Infectious and non-infectious complications of immunosuppressed patients
• Earlier detection and better diagnostics of both CLAD and PcGvHD is necessary in order to improve survival.
• Multicentric RCT are necessary in development of novel, effective therapeutic options for both CLAD and PcGvHD.
• Prophylaxis or pre-emptive antifungal therapy can be employed as a strategy to prevent, depending on the availability of the diagnostic tests.
The pro and con debate on age limit for lung transplant candidacy
• LuTx for recipients >65 years of age leads to good short- and acceptable long-term survival with an excellent quality of life.
• Well selected patients >70 years with acceptable risk profile should not be excluded from LuTx candidacy.
• Among many valid criteria for rationing life years, such as sarcopenia, urgency, frailty or telomere lengths, the age is the only one absolutely certain and absolutely fair.
ScanCLAD: RCT on once-daily tacrolimus *versus* twice-daily cyclosporine
• Tacrolimus should be regarded as the first choice of calcineurin inhibitor after LuTx.

VATS: video-assisted thoracoscopic surgery; RCT: randomised controlled trial; CLAD: chronic lung allograft dysfunction; PcGvHD: pulmonary chronic graft *versus* host disease; LuTx: lung transplantation.

low-volume centres (LVCs), and currently high-volume centres (HVCs) and LVCs perform similar rates of LuTx for recipients aged ⩾70 years. Survival time was shorter for recipients aged ⩾70 years compared to recipients aged <70 years (HR 1.36, 95% CI 1.28–1.44; p<0.001). HVCs were associated with a survival advantage in recipients aged <70 years (HR 0.91, 95% CI 0.88–0.94; p<0.001); but for recipients aged ⩾70 years survival did not differ significantly between HVCs and LVCs (HR 1.11, 95% CI 0.99–1.25; p<0.08) [46]. A.M. Holm summarised that among many valid criteria for rationing life years, such as sarcopenia, urgency, frailty or telomere lengths, the age is the only one absolutely certain and absolutely fair.

ScanCLAD: RCT on once-daily tacrolimus *versus* twice-daily cyclosporine

Göran Dellgren (Gothenburg, Sweden) presented the results of the ScanCLAD study, a multi-national, multicentric, randomised, parallel group and open-label study evaluating if once-daily tacrolimus *versus* twice-daily cyclosporine reduces the 3-year incidence of CLAD [47]. There is low-level evidence regarding the impact of choice of calcineurin inhibitor on CLAD incidence [48, 49], and none is based on the current CLAD definition [12]. As all programmes in Scandinavia were using twice-daily cyclosporine (CyA group), 1:1 randomisation to once-daily tacrolimus (Tac group) was performed. Patients were enrolled over a period of 24 months and follow-up was for another 36 months. Repetitive spirometric measurements were performed in all of the included patients and evaluation was performed based on current CLAD definition [12]. Of 249 patients included in the final analysis, 125 were in the CyA group (50.2%) and 124 in the Tac group (49.8%). Six and nine patients were not evaluated due to early death in the CyA and Tac groups, respectively (4.8% and 7.3%). Results showed significantly higher incidence of acute rejection (p=0.011) in the CyA (56.8%) than in the Tac group (40.3%). Significant difference (p=0.002) was described also in acute rejection episodes in the affected patients with 118 and 71 episodes described in the CyA and Tac group, respectively (average 1.67 and 1.42 episodes per patient, respectively). Cumulative incidence of CLAD was 38.4% in the CyA group and 12.9% in the Tac group with death/re-LuTx as competing events (p<0.001). Composite event-free survival was significantly inferior for the CyA group (p=0.0024). No statistically significant difference was observed in overall and graft survival between the groups (p=0.25 and p=0.058, respectively). In patients affected by CLAD, graft survival was statistically higher in the Tac group (p=0.021). No significant difference in serious adverse effects was observed. G. Dellgren concluded that tacrolimus should be regarded as the first choice of calcineurin inhibitor after LuTx.

Conclusion

We have aimed to summarise the diverse, inspiring presentations, covering a wide range of challenging topics in both thoracic surgery and LuTx, presented at the ERS Congress 2023 (table 4). We look forward to the next ERS Congress, in Vienna, Austria, 7–11 September 2024!

Provenance: Commissioned article, peer reviewed.

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References

1 MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. *Thorax* 2010; 65: Suppl. 2, ii18–ii31.
2 Tschopp JM, Bintcliffe O, Astoul P, *et al.* ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. *Eur Respir J* 2015; 46: 321–335.
3 Vuong NL, Elshafay A, Thao LP, *et al.* Efficacy of treatments in primary spontaneous pneumothorax: a systematic review and network meta-analysis of randomized clinical trials. *Respir Med* 2018; 137: 152–166.
4 Brown SGA, Ball EL, Perrin K, *et al.* Conservative versus interventional treatment for spontaneous pneumothorax. *N Engl J Med* 2020; 382: 405–415.
5 Marx T, Joly LM, Parmentier AL, *et al.* Simple aspiration versus drainage for complete pneumothorax: a randomized noninferiority trial. *Am J Respir Crit Care Med* 2023; 207: 1475–1485.
6 Migliore M, Di Maria G, Criscione A, *et al.* Clinico-pathological findings in stage-I primary spontaneous pneumothorax: analysis of 19 cases and literature review. *Eur Surg* 2013; 45: 83–86.
7 Gordillo Altamirano FL, Barr JJ. Phage therapy in the postantibiotic era. *Clin Microbiol Rev* 2019; 32: e00066-18.
8 Cesta N, Pini M, Mulas T, *et al.* Application of phage therapy in a case of a chronic hip-prosthetic joint infection due to *Pseudomonas aeruginosa*: an Italian real-life experience and in vitro analysis. *Open Forum Infect Dis* 2023; 10: ofad051.

9 Verleden SE, Von der Thüsen J, Roux A, *et al.* When tissue is the issue: a histological review of chronic lung allograft dysfunction. *Am J Transplant* 2020; 20: 2644–2651.
10 Vanstapel A, Goldschmeding R, Broekhuizen R, *et al.* Connective tissue growth factor is overexpressed in explant lung tissue and broncho-alveolar lavage in transplant-related pulmonary fibrosis. *Front Immunol* 2021; 12: 661761.
11 Jonigk D, Rath B, Borchert P, *et al.* Comparative analysis of morphological and molecular motifs in bronchiolitis obliterans and alveolar fibroelastosis after lung and stem cell transplantation. *J Pathol Clin Res* 2017; 3: 17–28.
12 Verleden GM, Glanville AR, Lease ED, *et al.* Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment – a consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant* 2019; 38: 493–503.
13 Jagasia MH, Greinix HT, Arora M, *et al.* National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 2015; 21: 389–401.
14 Pang Y, Charya AV, Keller MB, *et al.* The ISHLT chronic lung allograft dysfunction consensus criteria are applicable to pulmonary chronic graft-versus-host disease. *Blood Adv* 2022; 6: 4196–4207.
15 Bos S, Beeckmans H, Vanstapel A, *et al.* Pulmonary graft-versus-host disease and chronic lung allograft dysfunction: two sides of the same coin? *Lancet Respir Med* 2022; 10: 796–810.
16 Kitko CL, Pidala J, Schoemans HM, *et al.* National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: IIa. The 2020 Clinical Implementation and Early Diagnosis Working Group report. *Transplant Cell Ther* 2021; 27: 545–557.
17 Williams KM, Cheng GS, Pusic I, *et al.* Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2016; 22: 710–716.
18 Vos R, Vanden ER, Ruttens D, *et al.* Montelukast in chronic lung allograft dysfunction after lung transplantation. *J Heart Lung Transplant* 2019; 38: 516–527.
19 Li D, Duan Q, Weinkauf J, *et al.* Azithromycin prophylaxis after lung transplantation is associated with improved overall survival. *J Heart Lung Transplant* 2020; 39: 1426–1434.
20 Bergeron A, Chevret S, Granata A, *et al.* Effect of azithromycin on airflow decline-free survival after allogeneic hematopoietic stem cell transplant: the ALLOZITHRO randomized clinical trial. *JAMA* 2017; 318: 557–566.
21 Zeiser R, Polverelli N, Ram R, *et al.* Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med* 2021; 385: 228–238.
22 Hefazi M, Langer KJ, Khera N, *et al.* Extracorporeal photopheresis improves survival in hematopoietic cell transplant patients with bronchiolitis obliterans syndrome without significantly impacting measured pulmonary functions. *Biol Blood Marrow Transplant* 2018; 24: 1906–1913.
23 Wolff D, Hilgendorf I, Wagner-Drouet E, *et al.* Changes in immunosuppressive treatment of chronic graft-versus-host disease: comparison of 2 surveys within allogeneic hematopoietic stem cell transplant centres in Germany, Austria, and Switzerland. *Biol Blood Marrow Transplant* 2019; 25: 1450–1455.
24 DeFilipp Z, Kim HT, Yang Z, *et al.* Clinical response to belumosudil in bronchiolitis obliterans syndrome: a combined analysis from 2 prospective trials. *Blood Adv* 2022; 6: 6263–6270.
25 Wertheimer T, Dohse M, Afram G, *et al.* Abatacept as salvage therapy in chronic graft-versus-host disease – a retrospective analysis. *Ann Hematol* 2021; 100: 779–787.
26 Koshy AG, Kim HT, Liegel J, *et al.* Phase 2 clinical trial evaluating abatacept in patients with steroid-refractory chronic graft-versus-host disease. *Blood* 2023; 141: 2932–2943.
27 Kontoyiannis DP, Marr KA, Park BJ, *et al.* Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) database. *Clin Infect Dis* 2010; 50: 1091–1100.
28 Pappas PG, Alexander BD, Andes DR, *et al.* Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis* 2010; 50: 1101–1111.
29 Neofytos D, Fishman JA, Horn D, *et al.* Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis* 2010; 12: 220–229.
30 Hosseini-Moghaddam SM, Ouédraogo A, Naylor KL, *et al.* Incidence and outcomes of invasive fungal infection among solid organ transplant recipients: a population-based cohort study. *Transpl Infect Dis* 2020; 22: e13250.
31 Pennington KM, Baqir M, Erwin PJ, *et al.* Antifungal prophylaxis in lung transplant recipients: a systematic review and meta-analysis. *Transpl Infect Dis* 2020; 22: e13333.
32 Bhaskaran A, Mumtaz K, Husain S. Anti-*Aspergillus* prophylaxis in lung transplantation: a systematic review and meta-analysis. *Curr Infect Dis Rep* 2013; 15: 514–525.
33 Pilarczyk K, Haake N, Heckmann J, *et al.* Is universal antifungal prophylaxis mandatory in adults after lung transplantation? A review and meta-analysis of observational studies. *Clin Transplant* 2016; 30: 1522–1531.

34 Phoompoung P, Villalobos APC, Jain S, *et al.* Risk factors of invasive fungal infections in lung transplant recipients: a systematic review and meta-analysis. *J Heart Lung Transplant* 2022; 41: 255–262.

35 Husain S, Bhaskaran A, Rotstein C, *et al.* A strategy for prevention of fungal infections in lung transplantation: role of bronchoalveolar lavage fluid galactomannan and fungal culture. *J Heart Lung Transplant* 2018; 37: 886–894.

36 Wingard JR, Carter SL, Walsh TJ, *et al.* Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood* 2010; 116: 5111–5118.

37 Wang J, Zhou M, Xu JY, *et al.* Comparison of antifungal prophylaxis drugs in patients with hematological disease or undergoing hematopoietic stem cell transplantation: a systematic review and network meta-analysis. *JAMA Netw Open* 2020; 3: e2017652.

38 Bose P, McCue D, Wurster S, *et al.* Isavuconazole as primary antifungal prophylaxis in patients with acute myeloid leukemia or myelodysplastic syndrome: an open-label, prospective, phase 2 study. *Clin Infect Dis* 2021; 72: 1755–1763.

39 Marty FM, Ostrosky-Zeichner L, Cornely OA, *et al.* Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis* 2016; 16: 828–837.

40 Leard LE, Holm AM, Valapour M, *et al.* Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2021; 40: 1349–1379.

41 Zhou AL, Karius AK, Ruck JM, *et al.* Outcomes of lung transplant candidates aged ⩾70 years during the lung allocation score era. *Ann Thorac Surg* 2023; in press [https://doi.org/10.1016/j.athoracsur.2023.04.046].

42 Singer LG, Chowdhury NA, Faughnan ME, *et al.* Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. *Am J Respir Crit Care Med* 2015; 192: 965–973.

43 Venado A, McCulloch C, Greenland JR, *et al.* Frailty trajectories in adult lung transplantation: a cohort study. *J Heart Lung Transplant* 2019; 38: 699–707.

44 Singer JP, Christie JD, Diamond JM, *et al.* Development of the Lung Transplant Frailty Scale (LT-FS). *J Heart Lung Transplant* 2023; 42: 892–904.

45 Lehr CJ, Schold JD, Arrigain S, *et al.* New OPTN/UNOS data demonstrates higher than previously reported waitlist mortality for lung transplant candidates supported with ECMO. *J Heart Lung Transplant* 2023; 42: 1399–1407.

46 Iyanna N, Chan EG, Ryan JP, *et al.* Lung transplantation outcomes in recipients aged 70 years or older and the impact of center volume. *J Clin Med* 2023; 12: 5372.

47 Dellgren G, Lund TK, Raivio P, *et al.* Effect of once-per-day tacrolimus versus twice-per-day ciclosporin on 3-year incidence of chronic lung allograft dysfunction after lung transplantation in Scandinavia (ScanCLAD): a multicentre randomised controlled trial. *Lancet Respir Med* 2024; 12: 34–44.

48 Hachem RR, Yusen RD, Chakinala MM, *et al.* A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. *J Heart Lung Transplant* 2007; 26: 1012–1018.

49 Treede H, Glanville AR, Klepetko W, *et al.* Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. *J Heart Lung Transplant* 2012; 31: 797–804.