Optimizing management of bronchiolitis obliterans syndrome: Current strategies, future directions

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Pathogenesis and burden of bronchiolitis obliterans syndrome on post-lung transplant recipients

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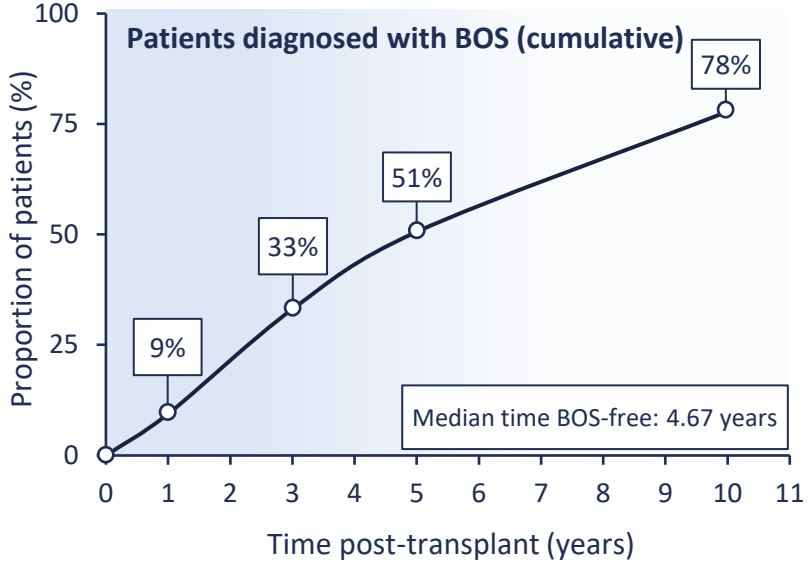
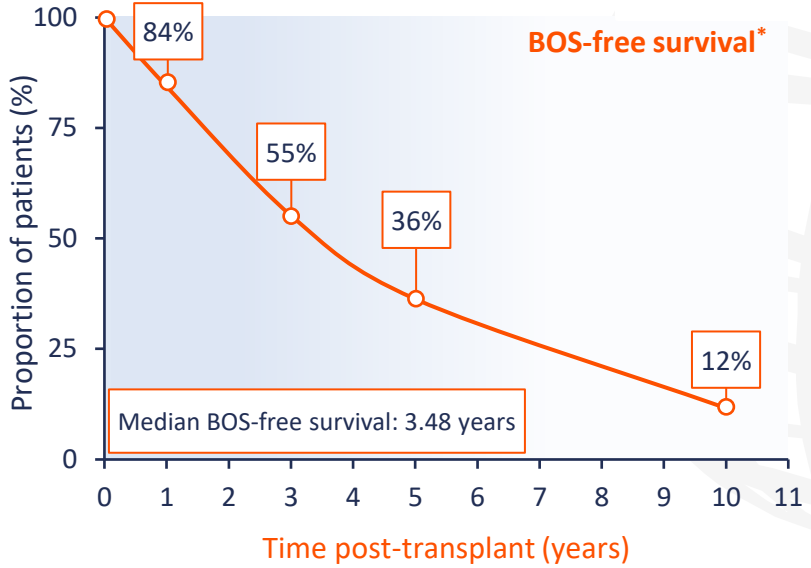
What is the incidence of BOS following lung transplantation?

Incidence of BOS post-lung transplantation

ISHLT Thoracic Transplant Registry (1994–2011)
(N=15,268; single LTx: 43%; bilateral LTx: 57%)





*BOS-free survival: A composite endpoint that includes patients without BOS and patients who have died.
BOS, bronchiolitis obliterans syndrome; ISHLT, International Society for Heart and Lung Transplantation; LTx, lung transplantation.
Kulkarni HS, et al. *J Heart Lung Transplant*. 2019;38:5–16.

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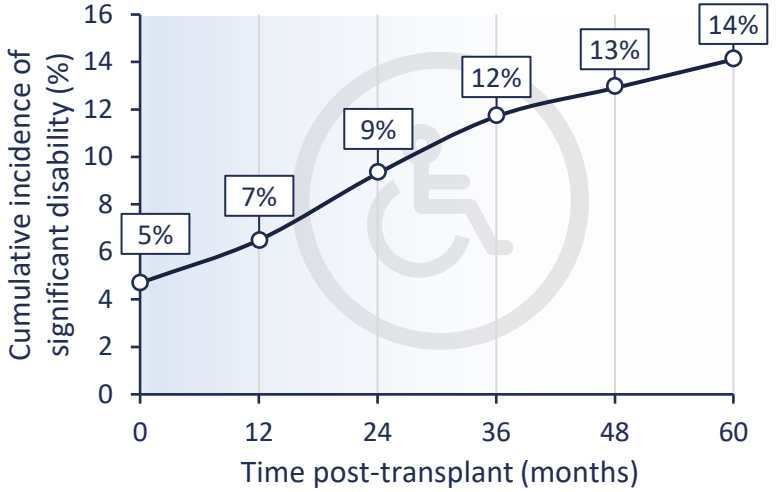
What is the disease burden associated with BOS?

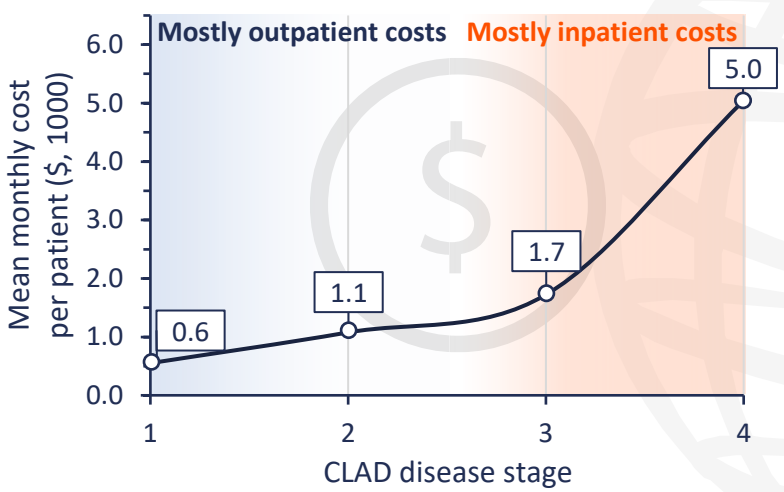
The disease burden associated with BOS

Disability: Prospective single-centre cohort study (Germany, 2010–2020; N=1,025)[1]



Patients with CLAD lost 1.3 life years and lived for 0.8 years with their disability; this added up to 2.1 DALYs/patient[1]

Economic impact: Retrospective analysis, claims database (2006–2018; N=134)[2]



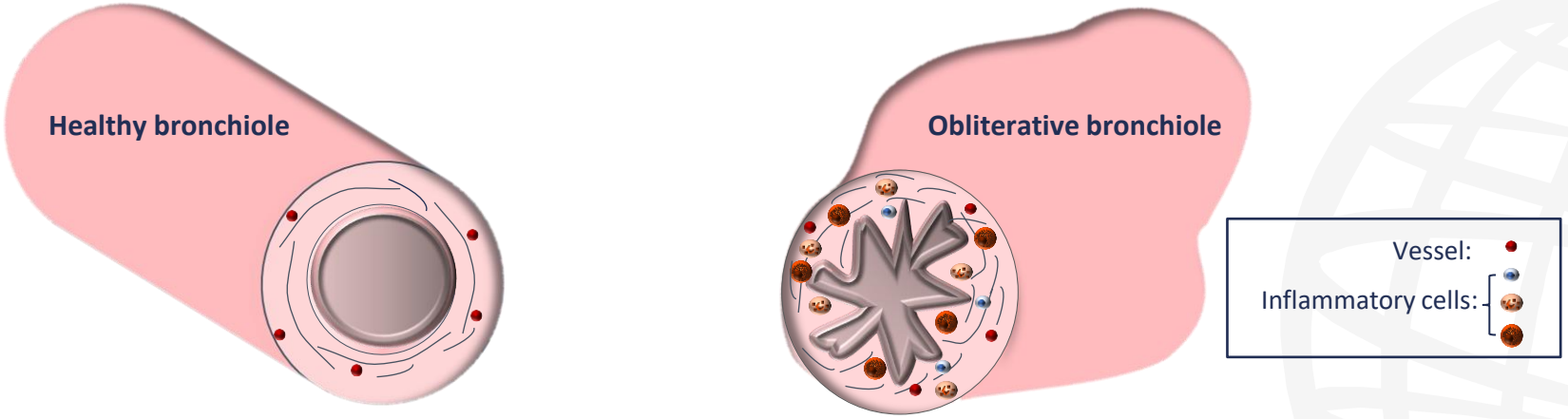
BOS post-LTx imposes a large economic burden on patients and healthcare systems, particularly in later stages of disease[2]

BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; DALY, disability-adjusted life years; LTx, lung transplantation.

1. Diel R, et al. *Adv Respir Med*. 2023;91:432–44; 2. Sheshadri A, et al. *J Heart Lung Transplant*. 2021;40(Suppl. 4):S70.

What is the pathogenesis of BOS in lung transplant recipients?

The pathogenesis of BOS[1–3]



Endogenous and exogenous risk factors → Primary damage to airway epithelium → Injury through innate/adaptive/ autoimmune responses ↔ Fibroblast proliferation and ECM deposition

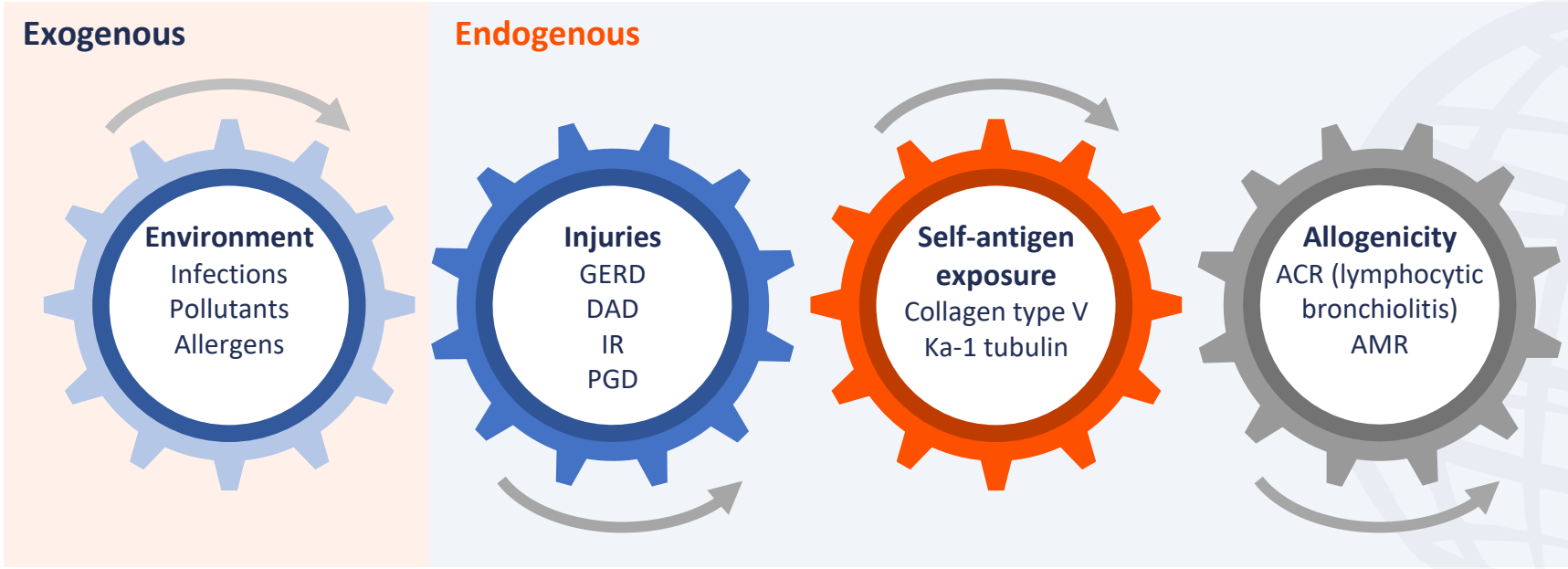
The predominant pathologic mechanism underlying BOS is obliteration of the small airways with advancing atherosclerotic changes in the pulmonary vasculature

BOS, bronchiolitis obliterans syndrome; ECM, extracellular matrix.

1. Arjuna A, et al. *Expert Rev Respir Med*. 2021;15:339–50; 2. Royer P-J, et al. *Transplantation*. 2016;100:1803–14; 3. Cleveland Clinic: Popcorn lung (bronchiolitis obliterans). Available at: https://bit.ly/3VH5pzm (accessed 24 April 2024).

What are the primary triggers for BOS following lung transplantation?

Risk factors and triggers for BOS[1–3]



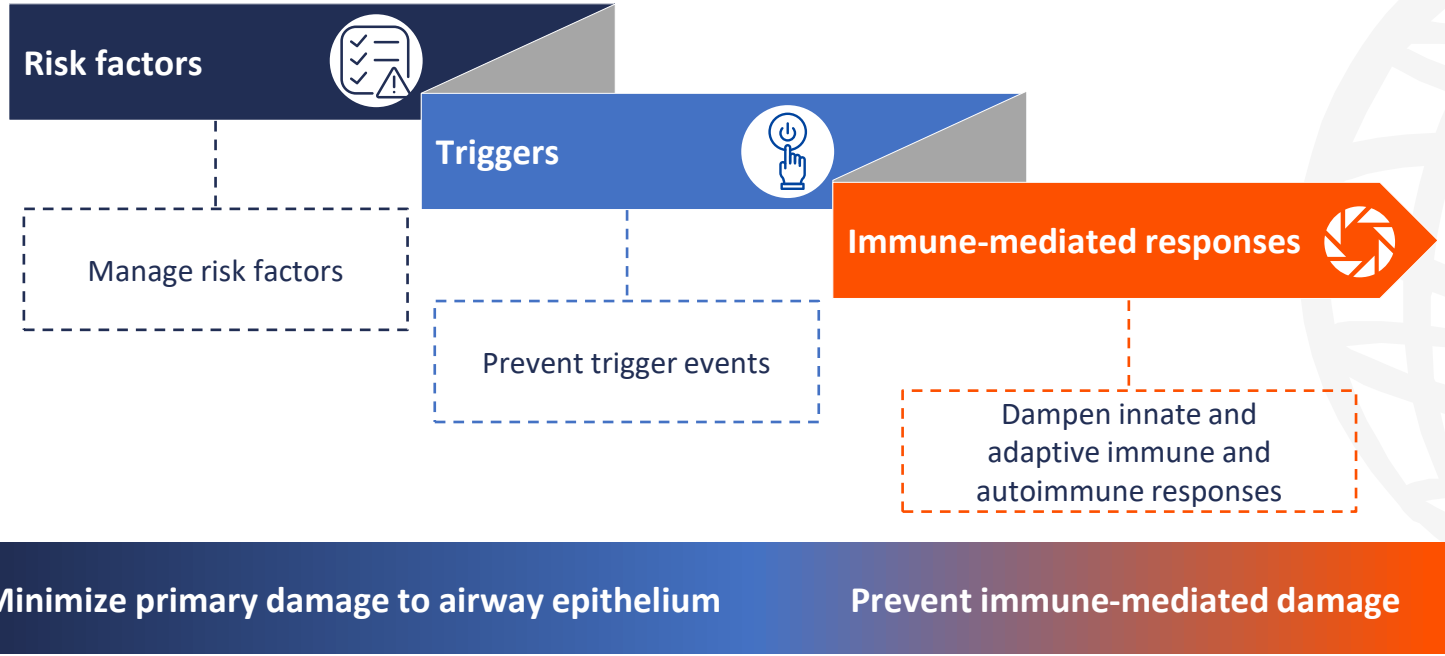
Immune- or non-immune-related factors can increase the risk of, or directly cause, excessive scarring and aberrant healing of the lung allograft leading to BOS and/or RAS

ACR, acute cellular rejection; AMR, antibody-mediated rejection; BOS, bronchiolitis obliterans syndrome; DAD, diffuse alveolar damage; GERD, gastroesophageal reflux disease; IR, ischaemia reperfusion; PGD, primary graft dysfunction; RAS, restrictive allograft syndrome.

1. Royer P-J, et al. *Transplantation*. 2016;100:1803–14; 2. Sato M. *Ann Transl Med*. 2020;8:418; 3. Santos J, et al. *Front Immunol*. 2022;13:908693.

How does current understanding of the pathogenesis of BOS impact management practices?

A rational approach to the management of BOS[1–3]



BOS, bronchiolitis obliterans syndrome.

1. Arjuna A, et al. *Expert Rev Respir Med*. 2021;15:339–50; 2. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022; 3. Royer P-J, et al. *Transplantation*. 2016;100:1803–14.

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Applying practice guidelines to establish a diagnosis of bronchiolitis obliterans syndrome

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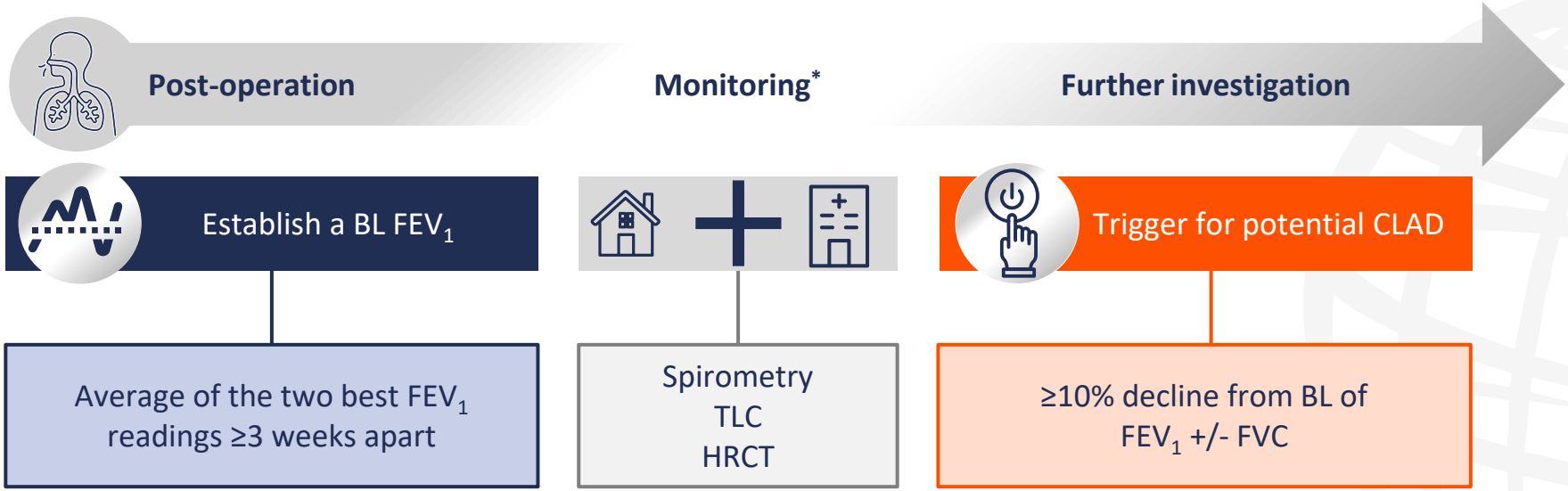
When, and how, should a lung recipient be monitored for changes in lung function?

Monitoring for signs of allograft dysfunction[1,2]



CLAD: An umbrella term for the clinical manifestations of pathologic processes in the airway and parenchymal compartments of the lung allograft that occur >3 months after LTx and lead to a significant and persistent deterioration in lung function (with or without chest radiologic changes)[2]

*Generally sustained beyond 6–12 months post-transplantation.

BL, baseline; CLAD, chronic allograft dysfunction; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HRCT, high-resolution computerized tomography; LTx, lung transplantation; TLC, total lung capacity.

1. Meyer KC, et al. *Eur Respir J*. 2014;44:1479–503; 2. Verleden GM, et al. *J Heart Lung Transplant*. 2019;38:493–503.

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What causes of FEV_1 reduction should be excluded prior to diagnosing CLAD?

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Non-CLAD-related reductions in FEV_1[1,2]

Factors leading to a reduction in FEV_1*

- Reduced lung function due to **normal ageing**
- **Surgical**, e.g. transplant lung resection, chest-wall surgery, phrenic nerve damage
- **Mechanical**, e.g. airway stenosis, weight gain, persistent pleural effusion
- **Localized infection with chronic scarring,** e.g. abscess, empyema or mycetoma

Resetting BL FEV_1 may be valid

- Any factor from **column 1 with instability for ≥6 months**
- Acute/subacute: **Generalized infection**, **CR** or **AMR**, or effects of **aspiration**
- Infiltration with **tumour** or infiltration of the **allograft with proven recurrent disease**
- **Pulmonary toxicity** (drug-induced or other)
- **Pulmonary arterial strictures** or **emboli**

Resetting BL FEV_1 is never valid

*Patients may also fail to reach a normal predicted lung function due to an age difference between the donor and the recipient, or intra-operative allograft reduction surgery/lobectomy.

AMR, antibody-mediated rejection; BL, baseline; CLAD, chronic allograft dysfunction; CR, cellular rejection; FEV_1, forced expiratory volume in one second.

1. Meyer KC, et al. *Eur Respir J.* 2014;44:1479–503; 2. Verleden GM, et al. *J Heart Lung Transplant*. 2019;38:493–503.

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What role do biopsies and bronchoalveolar lavage play in diagnosing CLAD?

Role of biopsies and BAL in diagnosing of BOS

Transbronchial biopsy[1,2]

- The gold standard diagnostic modality to rule out other causes of FEV_1 decline, such as ACR
- Cannot reliably identify BOS

Bronchoalveolar lavage[1,3]

- Provides information about immunologic, inflammatory and infectious markers
  - BAL neutrophilia has been associated with the development of CLAD
- Should be assessed for signs of aspiration

Transbronchial biopsy and BAL have a major role in identifying treatable causes of reductions in lung function, prior to the diagnosis of definite CLAD

ACR, acute cellular rejection; BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; FEV_1, forced expiratory volume in one second.

1. Verleden GM, et al. J *Heart Lung Transplant*. 2019;38:493–503; 2. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022;
3. Verleden SE, et al. *Transplantation*. 2023;107:341–50.

What role do pulmonary function tests and CT scans play in diagnosing BOS?

Establishing the CLAD phenotype[1,2]

Definite CLAD

≥20% decline in FEV_1 ± FVC for >3 months after the first value is taken

PFTs

- FEV_1:FVC <0.7, declining
- TLC stable/increasing

- FEV_1:FVC >0.7
- TLC decreasing

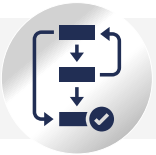
- Obstruction ± restriction

CT scans

- No evidence of pulmonary or pleural fibrosis

- Multi-lobar persistent parenchymal and/or pleural opacities

- CT opacities present or absent



BOS (~65–70%) → **Mixed** (~5%) ← **RAS*** (10–35%)

Undefined (~10%)

Restrictive, obstructive, mixed or undefined clinical phenotypes of CLAD are defined based on the predominant ventilatory pattern, TLC and presence/absence of opacities on chest CT scans

*Proportion of patients vary with different studies, and whether the mixed phenotype is recognized as a separate entity.

BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CT, computerized tomography; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PFT, pulmonary function tests; RAS, restrictive allograft syndrome; TLC, total lung capacity.

1. Verleden GM, et al. *J Heart Lung Transplant*. 2019;38:493–503; 2. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022.

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Overview of the current treatment landscape for bronchiolitis obliterans syndrome

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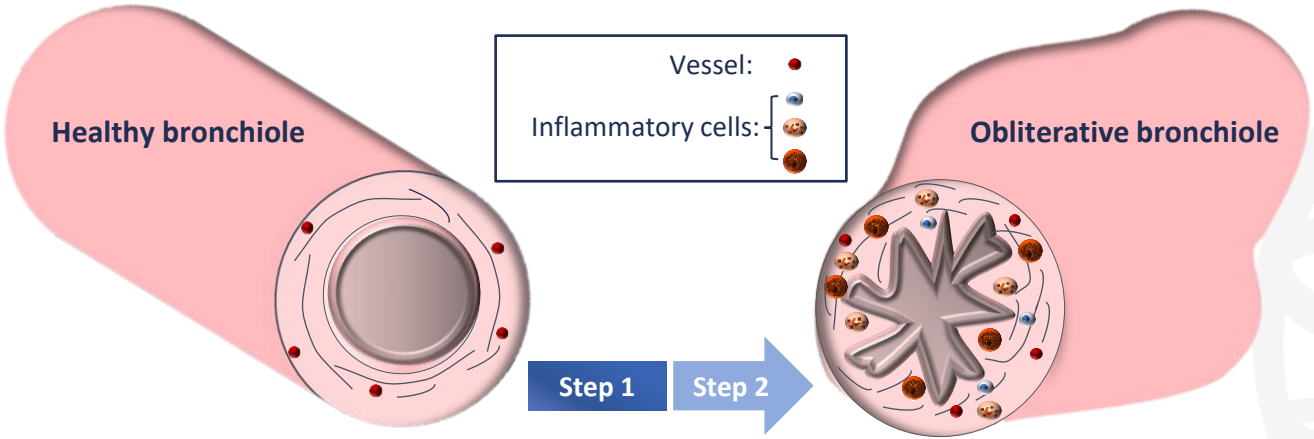
What is the main treatment goal for patients with BOS and why is it challenging to achieve?

Treatment goals for BOS[1–3]



Step 1: Mitigate risk factors and prevent triggers

Step 2: Identify a treatment strategy

The primary goal of treatment is to delay the irreversible, fibrotic airway changes and progressive loss of lung function[1]

BOS, bronchiolitis obliterans syndrome.

1. Arjuna A, et al. *Expert Rev Respir Med*. 2021;15:339–50; 2. Cleveland Clinic: Popcorn lung (bronchiolitis obliterans). Available at: https://bit.ly/3VH5pzm (accessed 24 April 2024); 3. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022.

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What are the current approaches for managing BOS in the first line?

Strategies for managing BOS in the first line

CNI switch (cyclosporin to tacrolimus)[1,2]	Azithromycin[1]	Montelukast[1]
• May stabilize/slow FEV_1 decline	• May increase FEV_1 • Airway neutrophilia and early treatment initiation predict response • Recommended to initiate treatment as early as possible, even prior to definite BOS diagnosis	• Some evidence for slowed FEV_1 decline • May be effective in azithromycin-refractory patients with late-onset stage 1 BOS[4] • No serious adverse effects
• Potential adverse effects of nephrotoxicity and hyperglycaemia • Risk of serious infections[3]	• No improvement in ≥50% of patients • Most common adverse effects are gastrointestinal disorders	• Mixed results

BOS, bronchiolitis obliterans syndrome; CNI, calcineurin inhibitor; FEV_1, forced expiratory volume in one second.

1. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022; 2. Meyer KC, et al. *Eur Respir J.* 2014;44:1479–503;
3. FDA. Tacrolimus prescribing information. Available at: https://bit.ly/3UygaTC (accessed 24 April 2024); 4. Ruttens D, et al. *PLoS ONE*. 2018;13:e0193564.

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What are the current approaches for managing BOS in the second line?

Strategies for managing BOS in the second line

ATG[1]	ECP[2]	TLI[2,3]
• Appears to be effective in stabilizing or attenuating FEV_1 decline* • May be more effective in early stages of disease	• Slows rate of FEV_1 decline	• Slows rate of FEV_1 decline, including in azithromycin non-responders
• Better efficacy and safety profile with rabbit vs equine ATG • Common adverse events include infusion-related reactions, CRS, leukopenia, thrombocytopenia and infections	• Expensive, not universally available and burdensome for some patients • Well-tolerated	• Treatment discontinuation due to bone marrow suppression and infections

*In a subgroup of patients with CLAD, including RAS.

ATG, anti-thymocyte globulin; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CRS, cytokine release syndrome; ECP, extracorporeal photopheresis; FEV_1, forced expiratory volume in one second; RAS, restrictive allograft syndrome; TLI, total lymphoid irradiation.

1. Bos S, et al. *Pharmacol Rev*. 2023;75:1200–17; 2. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022; 3. Arjuna A, et al. *Expert Rev Respir Med*. 2021;15: 339–50.

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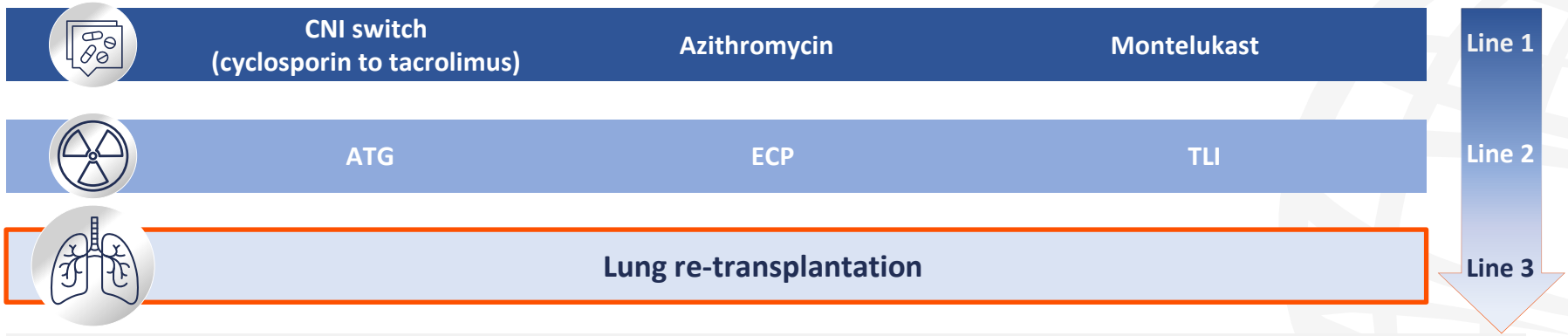
When should patients be referred for re-transplantation?

Treatment options for BOS in the third line



- For carefully selected patients who are treatment-refractory[1,2]
- One- and five-year survival comparable to primary lung transplantation[2,3]

- Shortage of donor lungs[2,3]
- Higher rates of cardiopulmonary bypass, re-exploration for bleeding and post-retransplant extra-corporeal membrane oxygenation support for primary graft dysfunction than primary transplant recepients[2,3]

ATG, anti-thymocyte globulin; BOS, bronchiolitis obliterans syndrome; CNI, calcineurin inhibitors; ECP, extracorporeal photopheresis; TLI, total lymphoid irradiation.

1. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022; 2. Arjuna A, et al. *Expert Rev Respir Med*. 2021;15:339–50; 3. Roy SB, et al. *Ann Thorac Surg*. 2018;105:221–7.

Expanding the armamentarium: Future directions for bronchiolitis obliterans syndrome

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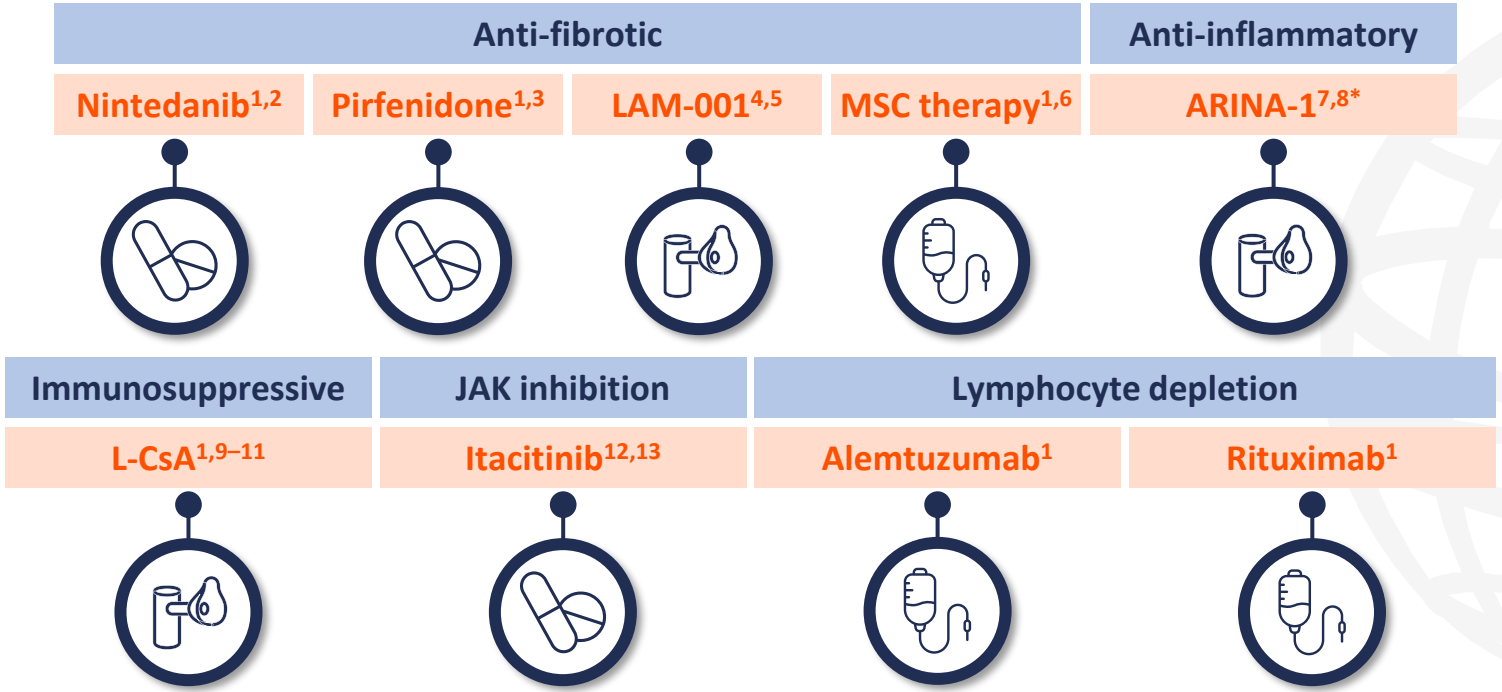
What are some of the key agents under investigation for managing BOS post-lung transplantation?

Investigational agents for BOS post-lung transplant



*Ascorbic acid and glutathione.[7]

BOS, bronchiolitis obliterans syndrome; JAK, Janus kinase; L-CsA, liposomal cyclosporine A; MSC, mesenchymal stem cell.

1. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022; 2. ClinicalTrials.gov. NCT03283007; 3. ClinicalTrials.gov. NCT02262299; 4. ClinicalTrials.gov. NCT06018766; 5. Arjuna A, et al. *Expert Rev Respir Med*. 2021;15:339–50; 6. ClinicalTrials.gov. NCT02181712; 7. ClinicalTrials.gov. NCT05654922; 8. Clinical Trials Arena. Available at: https://bit.ly/3Q3yBxb (accessed 24 April 2024); 9. ClinicalTrials.gov. NCT03657342; 10. ClinicalTrials.gov. NCT03656926; 11. ClinicalTrials.gov. NCT04039347; 12. ClinicalTrials.gov. NCT04640025; 13. ClinicalTrials.gov. NCT03978637. Clinical trials are available at: https://ClinicalTrials.gov using the study identifier (accessed 24 April 2024).

What role could lymphocyte depletion play in managing BOS in lung transplant recipients?

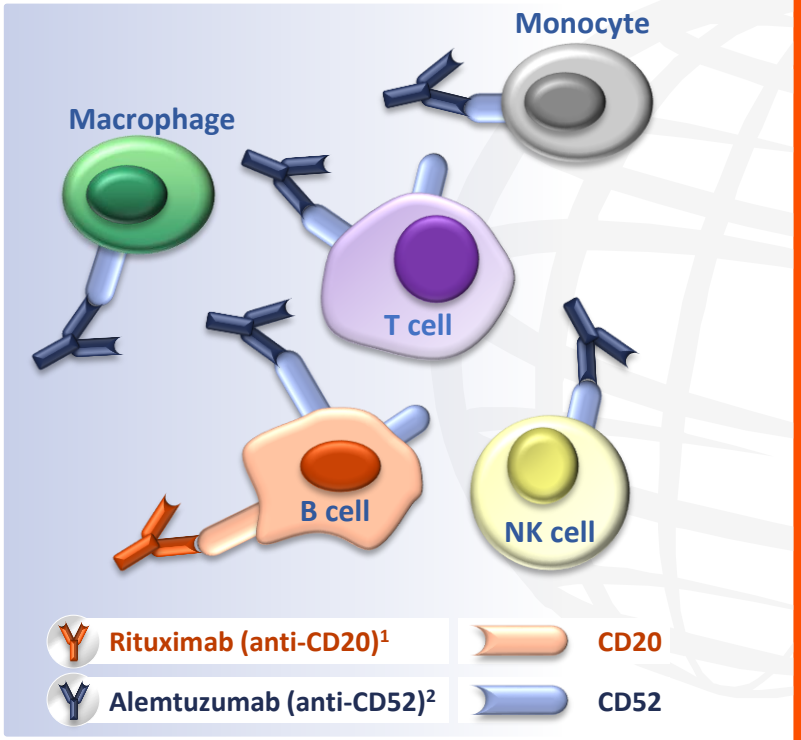
Role of lymphocyte depleting agents in managing BOS

Rituximab

- **CTOTC-08 trial; paediatric patients post-LTx (N=27):** Rituximab induction + SoC* significantly reduced incidence of DSA development vs placebo + SoC (p=0.017)[1]
- **Retrospective chart review (2008–2018, N=8):** Rituximab may prevent progression of AMR in selected patients[2]

Alemtuzumab

- **The United Network for Organ Sharing database; adult double LTx recipients, 2006–2013 (N=6117):** Lower incidence of BOS at 5 years with alemtuzumab induction vs basiliximab or no induction (p<0.001)[3]
- **LTx recipients treated with rescue alemtuzumab (N=51):** Freedom from BOS progression was 53% at 180 days[4]
- **Retrospective studies and a case series** report attenuation of lung function decline, particularly for early vs late-stage BOS;[3–5] it is unclear if this is a direct effect of treatment[6]
- Associated with a high risk of infectious complications[6]



*SoC includes RATG and tacrolimus, mycophenolate mofetil, and corticosteroid maintenance immunosuppression.[1]
AMR, antibody-mediated rejection; BOS, bronchiolitis obliterans syndrome; CD, cluster of differentiation; DSA, donor specific antibody; LTx, lung transplant; NK, natural killer; RATG, rabbit anti-thymocyte globulin; SoC, standard of care.

1. Sweet SC, et al. *Am J Transplant*. 2022;22:230–44; 2. Yamanashi K, et al. *Gen Thorac Cardiovasc Surg.* 2020;68:142–9; 3. Furuya Y, et al. *Am J Transplant.* 2016;16:2334–41; 4. Ensor CR, et al. *Clin Transplant*. 2017;31:e.12899; 5. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022; 6. Bos S, et al. *Pharmacol Rev*. 2023;75:1200–17.

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What role could antifibrotic agents play in treating patients who develop BOS post-transplantation?

Clinical trials of anti-fibrotic agents for managing BOS

Agent	Nintedanib[1]	Pirfenidone[2,3]	LAM-001[4]	MSC therapy[5,6]
Study	**INFINITx-BOS, phase III** NCT03283007	**EPOS, phase II/III** NCT02262299	**INSPO-BOS, phase II** NCT06018766	**Phase I** NCT02181712
Regimen	150 mg BID vs placebo over 6 months	Titrated to 2,403 mg/day vs placebo over 6 months	QD vs placebo over 48 weeks	0.5 or 1.0 million cells/kg
Patients	• N=80 • BOS (Grade 0p–2) post-single/double LTx • Azithromycin ≥4 weeks prior to the end of the screening period	• N=90 • BOS (Grade 1–3) post-double LTx • Azithromycin ≥4 weeks prior to the study start	• N=30 • BOS post-double LTx • No oral sirolimus or everolimus ≥4 weeks prior to screening	• N=13 • Moderate-to-severe BOS (Grade 3) post-single/ double LTx • Treatment refractory
Primary Endpoint	Reduction in rate of decline of FEV_1 over 6 months	Change in FEV_1 over 6 months	PFS and change in FEV_1 over 48 weeks; safety and tolerability	Safety and change in PFTs over 2 weeks
Completion	**Estimated completion** June 2024	**Completed December 2019** • Negative results[7]	**Estimated completion** December 2025	**Completed August 2021** • Well tolerated, with evidence of stabilized FEV_1

BID, twice daily; BOS, bronchiolitis obliterans syndrome; FEV_1, forced expiratory volume in one second; LTx, lung transplant; MSC, mesenchymal stem cell; PFS, progression-free survival; PFT, pulmonary function test; QD, every day.

1. ClinicalTrials.gov. NCT03283007; 2. ClinicalTrials.gov. NCT02262299; 3. Perch M, et al. *J Heart Lung Transplant.* 2020;39:S12; 4. ClinicalTrials.gov. NCT06018766; 5. ClinicalTrials.gov. NCT02181712; 6. Erasmus DB, et al. *Stem Cells Transl Med*. 2022;11:891–9; 7. Glanville AR, et al. *ERJ Open Res*. 2022;8:00185-2022.

Clinical trials are available at: https://ClinicalTrials.gov using the study identifier (accessed 24 April 2024).

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What role could aerosolized liposomal cyclosporine play in managing BOS post-lung transplantation?

Clinical trials of L-CsA for managing BOS

Agent	L-CsA			
Study	**BOSTON-1, phase III**[1] NCT03657342	**BOSTON-2, phase III**[2] NCT03656926	**BOSTON-3, phase III OLE**[3] NCT04039347	**Phase IIb**[4,5] NCT01650545
Regimen	5 mg BID + SoC vs SoC alone for 48 weeks	10 mg BID + SoC vs SoC alone for 48 weeks	5 mg BID + SoC or 10 mg BID + SoC for 24 weeks	5 mg or 10 mg BID* + SoC vs SoC alone for 48 weeks†
Patients	• N=220 • BOS post-single LTx • Tacrolimus-based SoC	• N=220 • BOS post-double LTx • Tacrolimus-based SoC	• N=262 • Completed participation in BOSTON-1 or BOSTON-2	• N=21 • BOS (Grade 1 or 2) post-single/double LTx • Tacrolimus-based SoC
Primary Endpoint	Mean change in FEV_1 from BL to Week 48	Mean change in FEV_1 from BL to Week 48	Mean change in FEV_1 from BL to Week 24	PFS‡ and BOS progression by grade change over 48 weeks
Completion	**Estimated completion** November 2024	**Estimated completion** October 2024	**Estimated completion** September 2024	**Completed November 2019** • Stabilized FEV_1 without systemic toxicity

*5 mg L-CsA for single LTx and 10 mg for double LTx. †Patients in the L-CsA arm received L-CsA for 24 weeks followed by SoC for 24 weeks.
‡Absence of ≥20% decline in FEV_1, re-transplantation or death.
BID, twice daily; BL, baseline; BOS, bronchiolitis obliterans syndrome; FEV_1, forced expiratory volume in one second; L-CsA, liposomal cyclosporine A; LTx, lung transplant; OLE, open label extension; PFS, progression-free survival; SoC, standard of care.

1. ClinicalTrials.gov. NCT03657342; 2. ClinicalTrials.gov. NCT03656926; 3. ClinicalTrials.gov. NCT04039347; 4. Iacono A, et al. *ERJ Open Res*. 2019;5:00167-2019; 5. ClinicalTrials.gov. NCT01650545. Clinical trials are available at: https://ClinicalTrials.gov using the study identifier (accessed 24 April 2024).

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How do you think the clinical management of patients with BOS post-transplantation may change in the future?