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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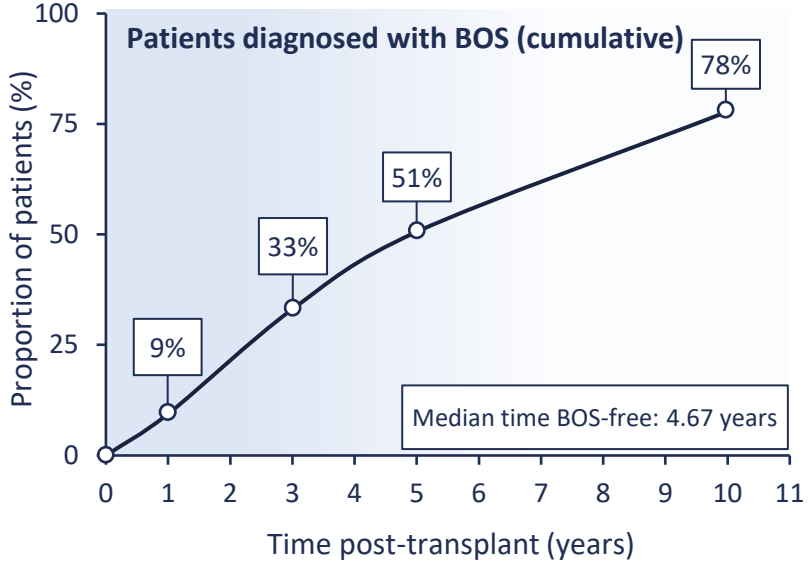
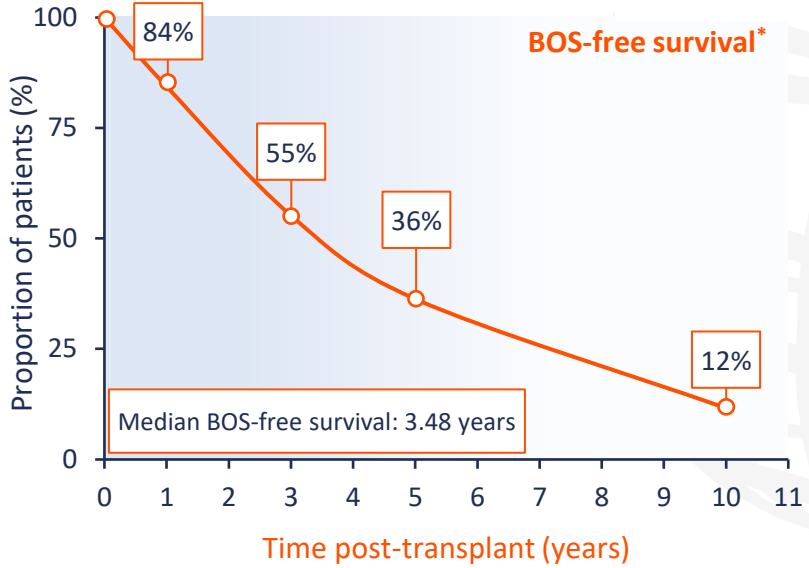
What is the incidence of BOS following lung transplantation?

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?

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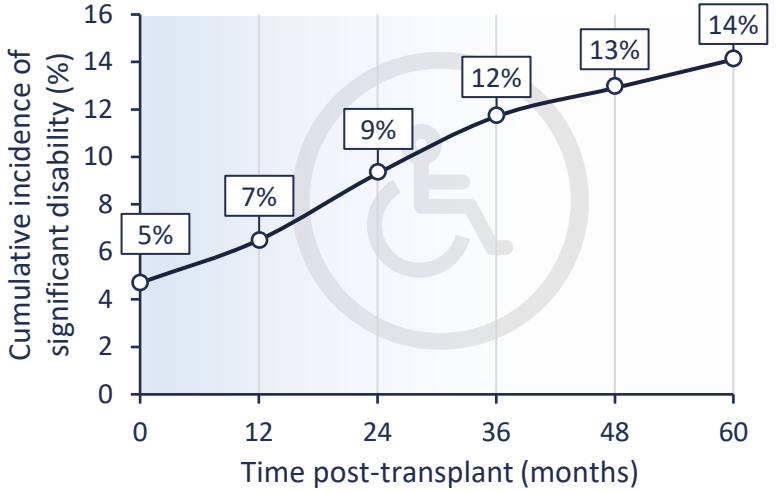
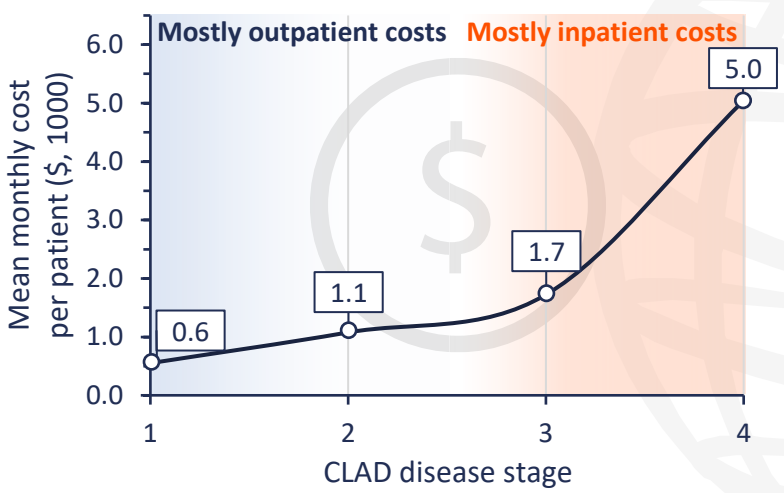
The disease burden associated with BOS

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.

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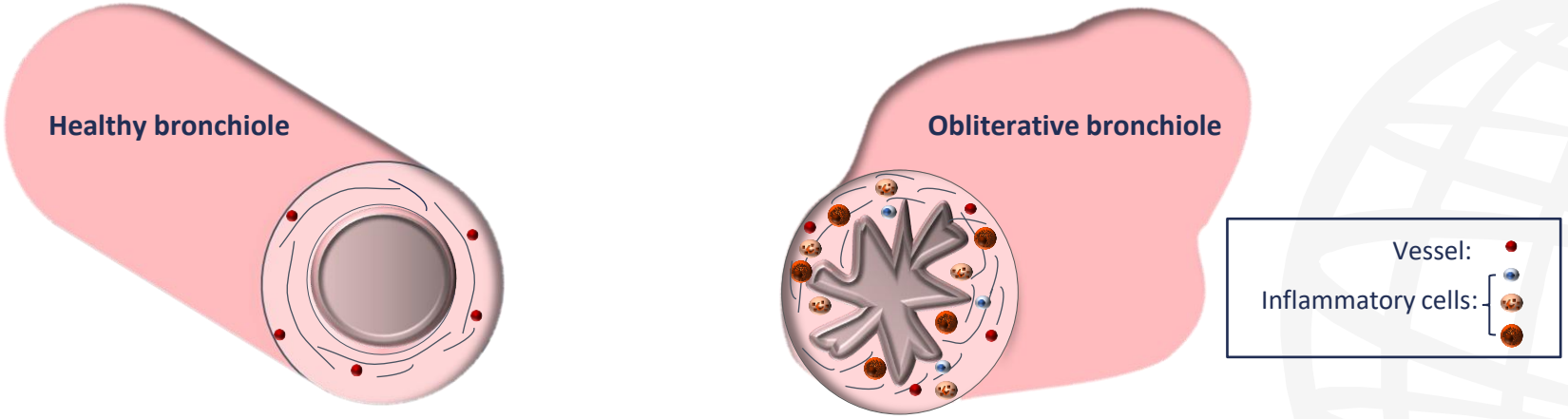
What is the pathogenesis of BOS in lung transplant recipients?

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).

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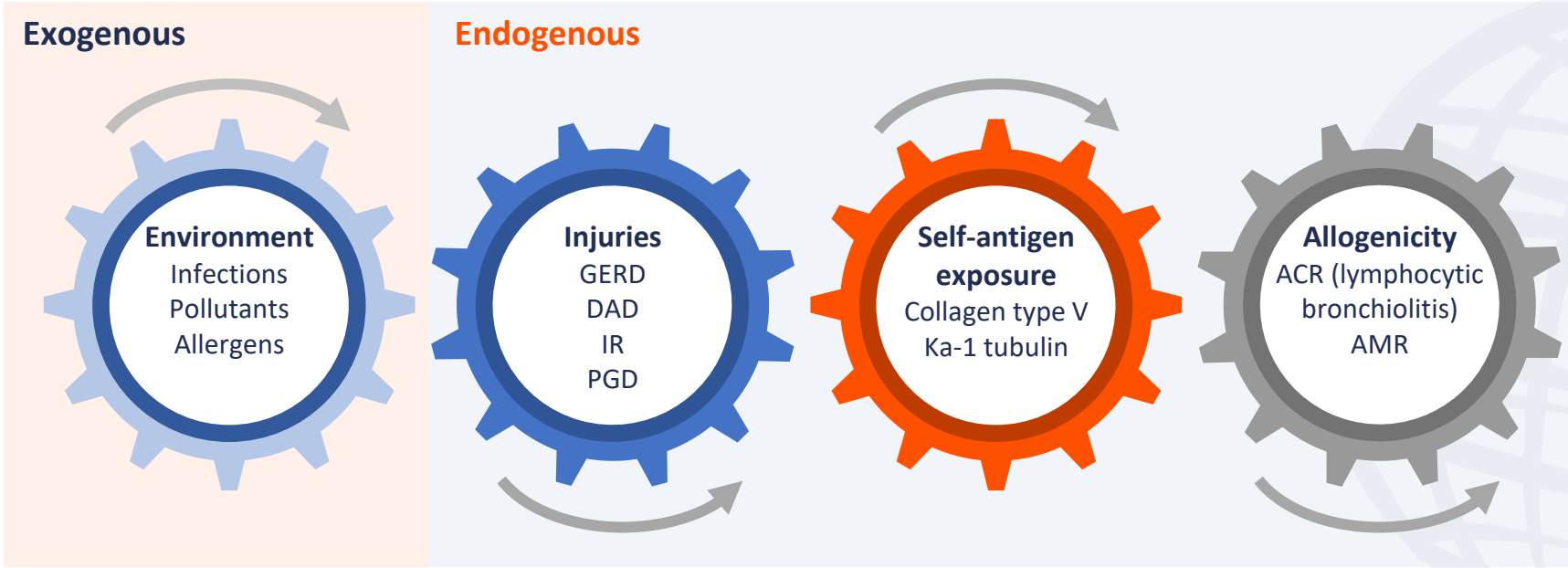
What are the primary triggers for BOS following lung transplantation?

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.

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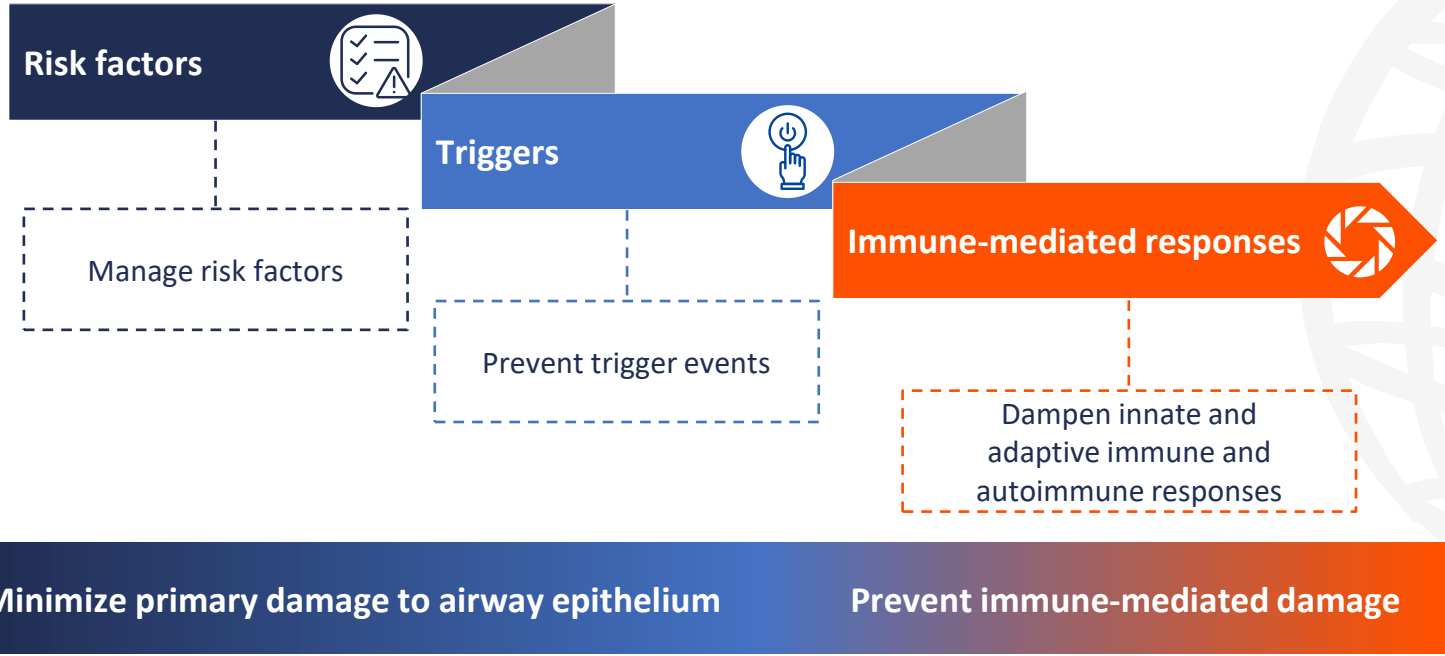
How does current understanding of the pathogenesis of BOS impact management practices?

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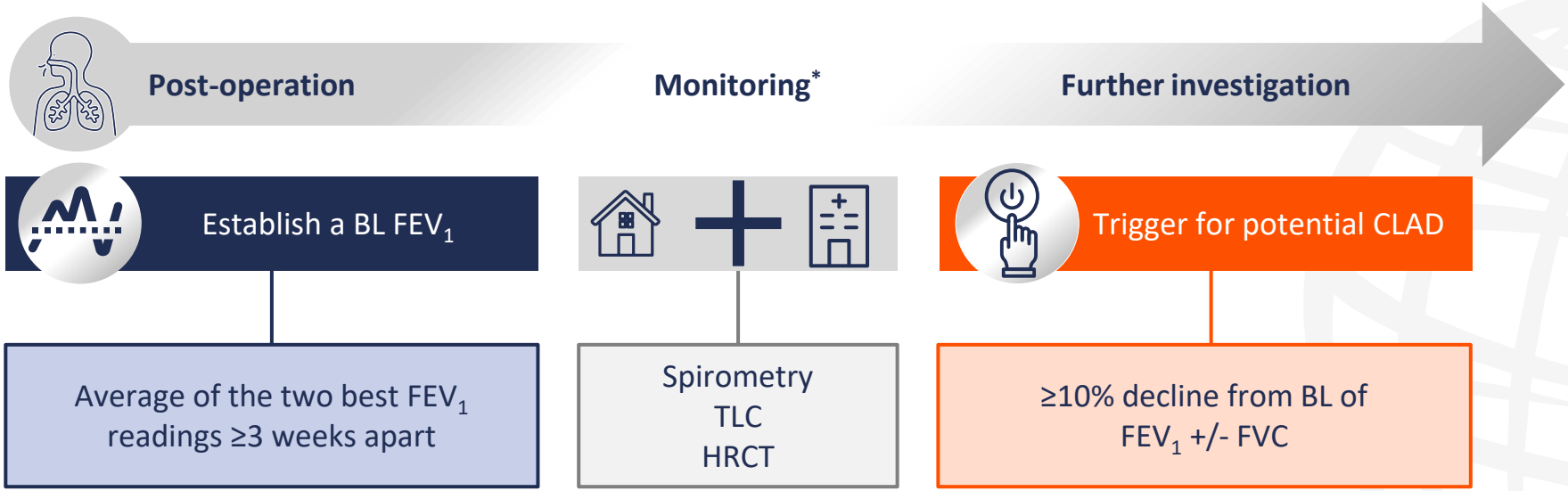
When, and how, should a lung recipient be monitored for changes in lung function?

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?

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.

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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

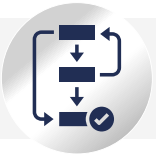
- Obstruction ± restriction

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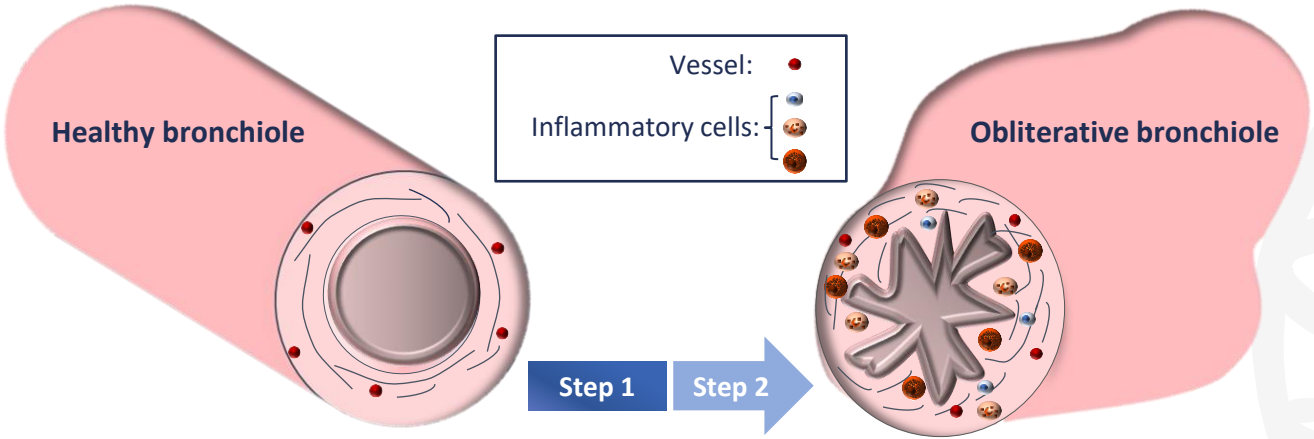
What is the main treatment goal for patients with BOS and why is it challenging to achieve?

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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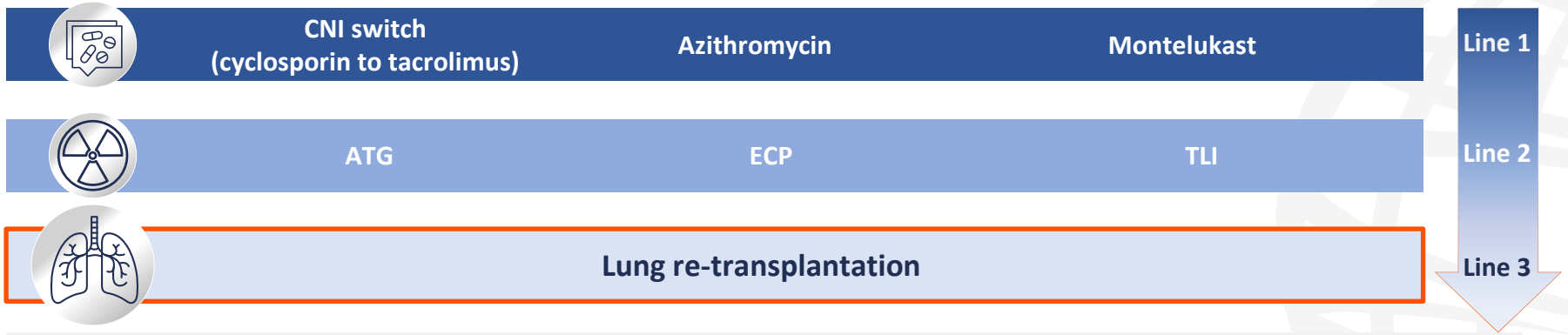
When should patients be referred for re-transplantation?

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.

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Expanding the armamentarium: Future directions for bronchiolitis obliterans syndrome

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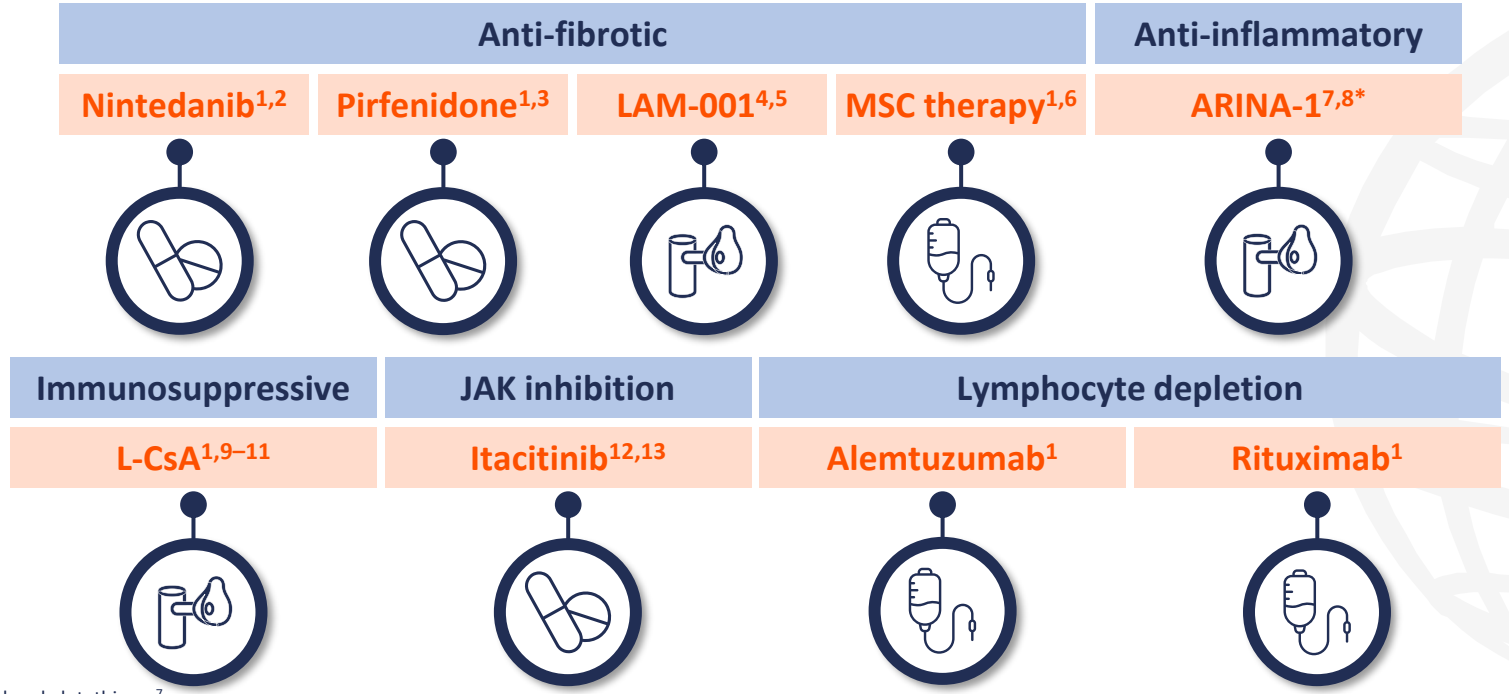
What are some of the key agents under investigation for managing BOS post-lung transplantation?

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).

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

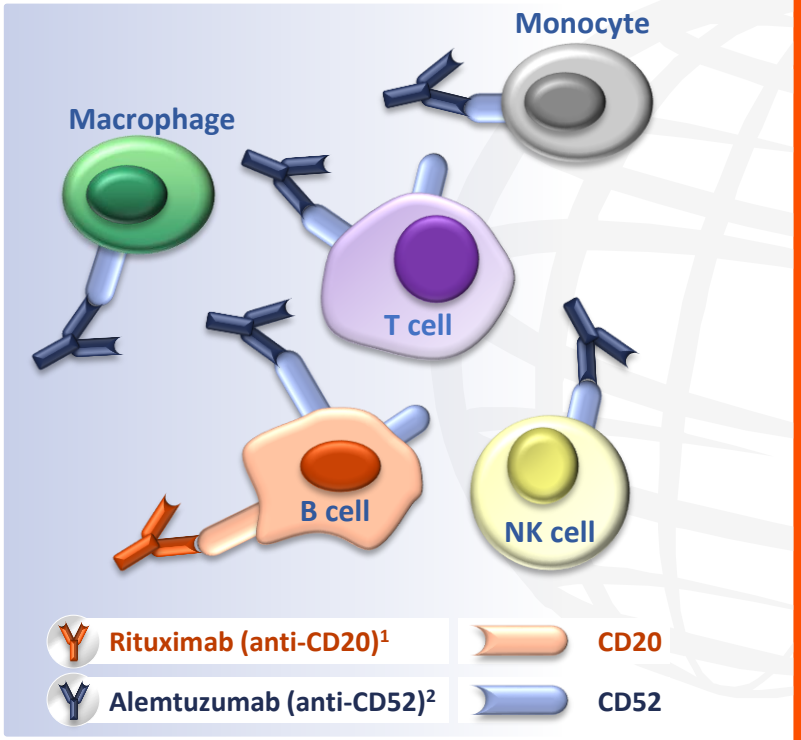
Role of lymphocyte depleting agents in managing BOS

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?