Chronic Lung Allograft Dysfunction

More than just Bronchiolitis Obliterans Syndrome

Partha Hota DO, Chandra Dass MD, Scott Simpson DO

Department of Radiology
Temple University Hospital
Philadelphia, PA USA
Disclosures

No relevant disclosures
Learning Objectives

- Illustrate the proposed pathophysiology of Chronic Lung Allograft Dysfunction (CLAD) subtypes including:
  - Bronchiolitis Obliterans Syndrome (BOS)
    - Neutrophilic Reversible Allograft Dysfunction (NRAD)
  - Restrictive Allograft Syndrome (RAS)
    - Acute Fibrinoid Organizing Pneumonia (AFOP)

- Describe the unique characteristics of CLAD phenotypes on CT imaging with practical tips for aiding in diagnosis as well as describing current diagnostic challenges

- Provide correlation with pulmonary function tests and pathology
Introduction

Long-term survival and function following lung transplantation is significantly shorter than other organ transplants with an estimated survival rate of 50% approximately 5 years post-transplantation.

This discordance is felt to be secondary to the development of Chronic Lung Allograft Dysfunction.

With continual yearly growth in the number of lung transplantations understanding the unique features of CLAD subtypes is increasingly important.

Chronic Lung Allograft Dysfunction

- Chronic Lung Allograft Dysfunction is defined as a persistent decline in FEV$_1$ < 80% of baseline
- Classically favored to be synonymous with bronchiolitis obliterans syndrome
- It is now recognized that CLAD is a heterogeneous group of disorders with unique imaging and clinical manifestations that may co-exist:
  - Bronchiolitis Obliterans Syndrome (BOS)
    - Neutrophilic Reversible Allograft Dysfunction (NRAD)
  - Restrictive Allograft Syndrome (RAS)
    - Acute Fibrinoid Organizing Pneumonia (AFOP)
Chronic Lung Allograft Dysfunction

**BOS**
- Irreversible small airway obliteration and fibrosis
- FEV$_1$ decline ≥ 20% + obstructive physiology
- CT features:
  - Air trapping
  - Bronchiectasis
  - Bronchial wall thickening

**RAS**
- Irreversible pleural and parenchymal fibrosis
- TLC ≤ 90% baseline + restrictive physiology
- CT features:
  - Upper lung zone reticulation/fibrosis
  - Peripheral consolidation
  - GGO in acute exacerbation

**NRAD**
- Reversible small airway obstruction
- Initial FEV$_1$ decline with an increase ≥ 10% after azithromycin treatment
- BAL neutrophil% ≥ 15%
- CT features:
  - Reversible findings
  - Centrilobular / TiB nodules
  - Bronchial wall thickening
  - Air trapping
Bronchiolitis Obliterans Syndrome

**Irreversible** small airway obliteration

Most common form of CLAD accounting for 74% of all cases\(^1\) with ~48% of all transplant patients affected within the first 5 years\(^2\)

**Risk Factors:** acute rejection, primary graft dysfunction, HLA mis-matching, CMV pneumonitis, bacterial pneumonia, aspiration, medication non-compliance, single lung transplant

**Initial symptoms:** asymptomatic or dyspnea on exertion

**Advanced symptoms:** dyspnea at rest, hypoxia, productive cough, fever

**Post-transplant pulmonary function tests** will demonstrate:

1. Decline in FEV\(_1\) per ISHLT criteria
2. Irreversible obstructive physiology

With abnormal spirometry, a diagnosis of BOS **does not** require tissue pathology

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2. The National Lung Transplant Foundation 2013
Bronchiolitis Obliterans Syndrome

Multifactorial Pathophysiology

Direct Allorecognition:
- Donor antigen presenting cells (APCs) migrate to recipient lymphoid tissue
- Activate immune response initiating lymphocytic infiltration with resultant bronchiolar epithelial injury, followed by release of cytokines (ex: TGF-β)
- Production of intraluminal obstructing fibroproliferative granulation tissue

Indirect Allorecognition:
- Recipient APCs migrate to lung allograft secondary to either normal surveillance or an early inciting event (ex: acute rejection, PGD, infection, aspiration)
- Activate immune response → lymphocytic infiltration → bronchial epithelial injury → production of intraluminal obstructing fibroproliferative granulation tissue

Autoimmunity: Unmasked epitopes of allograft type V collagen activate Th17 immunity
Bronchiolitis Obliterans Syndrome

Histopathology

Complete or partially obstructed bronchiole lumen by a combination of dense infiltration consisting of smooth muscle cells, myofibroblasts, and mature collagen

Tissue diagnosis from transbronchial biopsy may be limited by a false negative biopsy secondary to the patchy geographic distribution

Fig A: Dense myofibroblast and smooth muscle cell infiltrate within the bronchiole lumen

Fig B: Extensive collagen deposition within the bronchiole lumen

Hematoxylin Eosinophilin

Masson’s Trichrome

**Bronchiolitis Obliterans Syndrome**

**Geographic areas of air trapping**
Most reliable finding if > 32% total volume\(^1\)
Sensitivity: 83 - 100% Specificity: 71- 89%
PPV: 64% NPV: 100%\(^2\)
Best appreciated on expiratory phase imaging

**Bronchiectasis**
Secondary to obstruction from distal airway obstruction

**Bronchial wall thickening**
CT manifestation of lymphocytic infiltration / inflammation

**Centrilobular micronodules**
CT manifestation of distal airway impaction secondary to mucus and fibroproliferative changes

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Bronchiolitis Obliterans Syndrome

Mosaic perfusion pattern with sharply demarcated areas of air trapping demonstrated on expiratory images

Bronchiectasis

Bronchial wall thickening

Centrilobular micronodules

FEV₁ (%baseline): 18%
FEV₁/FVC (%baseline): 30%

23 year-old female with bilateral lung transplant for cystic fibrosis 9 years post-transplant
Bronchiolitis Obliterans Syndrome

75 year-old female 5 years following bilateral lung transplant with non-contrast CT images demonstrating a pattern of *mosaic perfusion* with large geographic areas of *air trapping* on expiratory phase imaging.

There is **lower lung zone predominant bronchiectasis** (solid arrows) and **bronchial wall thickening** (dashed arrows).
Bronchiolitis Obliterans Syndrome

Scoring Systems

Multiple scoring systems have been proposed utilizing both air trapping parameters as well as secondary HRCT features of BOS; however, there is currently no consensus scoring system.

Limitations of HRCT

HRCT findings have been found to be limited in the diagnosis of BOS prior to the clinical manifestations.

<table>
<thead>
<tr>
<th>HRCT Finding</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Mosaic perfusion</td>
<td>4%</td>
<td>100%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>25%</td>
<td>80%</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>4%</td>
<td>96%</td>
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</table>


Neutrophilic Reversible Allograft Dysfunction

Reversible form of CLAD characterized by excessive neutrophil activation

Reversible decline in lung function after neomacrolide therapy (ex: azithromycin)

Proposed spirometric criteria:
1. Initial FEV₁ decline (<80% baseline)
2. FEV₁ improvement (≥ 10%) 3 – 6 months after azithromycin therapy

If BOS and NRAD co-exist, patients may not demonstrate complete FEV₁ resolution

Bronchoalveolar lavage ≥ 15% neutrophils may predict response to treatment

Approximately 40% of patients with previously suspected BOS may respond to neomacrolide therapy

Some advocate a 3 month course of neomacrolide therapy before a diagnosis of BOS or RAS is made

Unclear if NRAD is a risk factor for BOS but it has been shown to be a risk factor for long term graft survival

Neutrophilic Reversible Allograft Dysfunction

Pathophysiology

Characterized by BAL neutrophilia and resultant cellular bronchiolitis

While not entirely understood, several studies have implicated IL-8 in the development of NRAD

IL-8 recruits neutrophils with resultant bronchiole epithelial injury, followed by release of cytokines (ex: MMPs and TGF-β) and subsequent cellular bronchiolitis with eventual BOS fibrosis in absence of treatment

Factors that elevate IL-8 include bile acids from GERD, environmental particles, infection, and IL-17

Role of azithromycin

Combination of anti-inflammatory and antimicrobial properties with safest profile

Compared to BOS, it has been shown that certain proteins such as MCP-1, RANTES, IL-1β, IL-8, IL-17, TIMP-1, MMP-8, MMP-9, HGF, MPO are up-regulated in NRAD

Following azithromycin therapy, studies have shown that levels of MMP-9 gelatinase were significantly decreased in humans as was IL-17 (a stimulator of IL-8) in similar small animal trials

Some hypothesize lymphocytic bronchiolitis and NRAD are on a similar spectrum with overlapping features including azithromycin responsiveness and BAL neutrophilia

Neutrophilic Reversible Allograft Dysfunction

Histopathology

Cell type depends on the compartment of lung sampled

**Lung biopsy:** Small airway infiltration by lymphocytes and macrophages similar to findings early in BOS, however reversible with macrolide treatment

**BAL:** Will demonstrate neutrophils with ≥ 15% neutrophils predicting response to treatment in the absence of infection

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**Fig A**
Open biopsy sample demonstrates both lymphocytes and macrophages

**Fig B**
Concurrent BAL demonstrates numerous neutrophils

Neutrophilic Reversible Allograft Dysfunction

**Centrilobular Micronodules**
Best feature to differentiate from BOS
CT manifestation of distal airway bronchiolitis
May present with *tree in bud* micronodules
Resolves with treatment

**Air Trapping**
Present in 82% of patients in initial stage
*Resolves with treatment*
Persistent air trapping following treatment is suggestive of BOS

**Bronchial Wall Thickening**
CT manifestation of inflammation
Non-specific, may be seen in BOS/RAS
*Resolves with treatment*

**Bronchiectasis**
Secondary to air trapping
*Resolves with treatment*
Persistent bronchiectasis following treatment is suggestive of BOS

**Common HRCT features**
Resolution after treatment is the NRAD hallmark

**Additional HRCT features**

- **Ground Glass Opacification / Consolidation**
  Should resolve following treatment with macrolide

- **Large Airway Mucus**
  Reported but not specific

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Neutrophilic Reversible Allograft Dysfunction

Figure A: 15 year-old male 3.2 years following heart-lung transplant with **centrilobular** and **tree-in-bud micronodules** (closed arrows) with mild bronchiectasis and moderate bronchial wall thickening (dashed arrow) with concurrent decline in FEV$_1$

Figure B: Following 6 months of azithromycin therapy, there has been **near complete resolution** of the prior CT findings with FEV$_1$ nearly returned to baseline

Neutrophilic Reversible Allograft Dysfunction

Figure A: 52 year-old male 4.2 years following double lung transplant with centrilobular and tree-in-bud micronodules (arrows) at the right lung apex and base with concurrent decline in FEV\textsubscript{1} and 89.6% neutrophils on BAL

Figure B: Following 6 months of azithromycin therapy, there is complete resolution of the prior CT findings with > 10% FEV\textsubscript{1} improvement on spirometry

Restrictive Allograft Syndrome

Restrictive form of CLAD characterized by irreversible pleuroparenchymal fibrosis secondary to diffuse alveolar damage.

Prevalence between 25 – 35% with median survival after onset worse with RAS vs BOS (541 days vs 1421 days) 1

Risk factors: similar to BOS including acute rejection, bronchiolitis, infection.

Symptoms: dyspnea at rest, hypoxia, productive cough, fever.

Two main patterns of disease:
1. Sporadic acute exacerbations followed by stepwise decline in function.
2. Stable disease followed by sudden decompensation.

No defined spirometric criteria.

Post-transplant pulmonary function tests:
1. Irreversible FEV$_1$ decline (<80% baseline)
   -AND-
2. Irreversible TLC decline (<90% baseline)

Decreased FEV$_1$ and TLC following episodes of acute exacerbation.

Restrictive Allograft Syndrome

Pathophysiology

While there is significant overlap between the immunologic mechanisms of RAS and BOS, key differentiating features include RAS specific risk factors, the timeline of diffuse alveolar damage, disease specific cytokines, as well as the overall pattern and distribution of fibrosis.

<table>
<thead>
<tr>
<th>Multifactorial</th>
<th>RAS</th>
<th>BOS</th>
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<tbody>
<tr>
<td></td>
<td>Direct allorejection, Indirect allorejection, Autoimmunity</td>
<td>Direct allorejection, Indirect allorejection, Autoimmunity</td>
</tr>
<tr>
<td>Diffuse Alveolar Damage Timeline</td>
<td>Late onset diffuse alveolar damage,</td>
<td>Early onset diffuse alveolar damage</td>
</tr>
<tr>
<td>Specific Risk Factors</td>
<td>Alarmins (S100, HMGB1) Immunosuppression</td>
<td></td>
</tr>
<tr>
<td>Cytokines and Growth Factors</td>
<td>Specific IL-6, CXCL10, and CXCL11 cytokines found on BAL of RAS patients suggests a stronger role of B lymphocytes and NK cells</td>
<td>TGF-β, PDGF and IGF-1</td>
</tr>
<tr>
<td>Fibrosis Pattern</td>
<td>Involves visceral pleura, alveolar interstitium, and interlobular septa</td>
<td>Involves bronchiole lumen</td>
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</tbody>
</table>

Restrictive Allograft Syndrome

**Histopathology**

Characterized by *fibroelastosis* with dense fibrous infiltration consisting of smooth muscle cells, myofibroblasts, and mature collagen within the visceral pleura, alveolar interstitium, and interlobular septa.

Areas of concurrent bronchiolitis obliterans lesions have been reported.

Fig A
Diffuse alveolar damage characterized by alveolar hyaline membrane material

Fig B
Organizing phase with intralveolar fibroelastic plugs

Restrictive Allograft Syndrome

**Ground Glass Opacification**
- Seen during acute exacerbation
- CT manifestation of diffuse alveolar damage
- May see interlobular septal thickening
- Can also progress to consolidation

**Subpleural Reticulation**
- Upper lung zone predominant subpleural reticulation earlier in the disease process

**Pleural/Subpleural Fibrosis**
- Fibroelastosis in later stages with affected and unaffected lung sharply demarcated in addition to volume loss.

**Traction Bronchiectasis**
- Irreversible bronchiectasis secondary to underlying fibrosis

**Common HRCT features**

**Uncommon HRCT features**

- **Honeycombing**
  - Reported in a minority of patients

- **Non-subpleural distribution**
  - Minority in a centrilobular, paraseptal, random, or mid/lower lung distribution

Coronal non-contrast CT images demonstrate upper lung zone predominant bilateral subapical reticulation (Fig A) with mild progression 3 years later (Fig B).

7 months later (Fig C), there is sudden marked progressive fibrosis and volume loss.

Concurrent spirometry demonstrates decreased FEV₁ with restrictive physiology.
Restrictive Allograft Syndrome

Axial non-contrast CT images demonstrate subapical reticulation and progressive pleural/subpleural fibrosis in a stair-step progression following episodes of acute exacerbation manifested by CT findings of diffuse alveolar damage including ground glass opacification and septal thickening.

Corresponding PFTs demonstrate irreversible decline in FEV₁ and TLC

Restrictive Allograft Syndrome

Co-existent BOS

Identification of RAS may be limited secondary to co-existent BOS early in the disease process with overlapping imaging and histologic features.

In a cohort of 16 RAS patients, 14 demonstrated histologic findings of concurrent obliterative bronchiolitis in regions of fibroelastosis.

Grading Systems

Grading systems have been proposed utilizing both the degree of fibrosis, distribution, and character of bronchiectasis, however, there is currently no consensus scoring system.

| Histologic features of pleuroparenchymal fibroelastosis in restrictive allograft syndrome patients |
|---------------------------------------------------|-------------------------------------------------|
| Pleural fibrosis                                  | 16/16 (100%)                                    |
| Obliterative bronchiolitis                        |                                                |
| Within areas of fibroelastosis                    | 14/16 (87.5%)                                   |
| Outside areas of fibroelastosis                   | 9/16 (56.3%)                                    |
|                                                   | 12/16 (75%)                                     |


Grading Systems

Grade 1: cylindrical bronchiectasis, pleuroparenchymal and blotchy opacities distributed in the upper zones, sparing the middle and lower zones, without consistent volume reduction and with blotchy ground glass areas possibly present.

Grade 2: cylindrical bronchiectasis, pleuroparenchymal and blotchy opacities distributed in the upper and middle zones, sparing the lower zones, without consistent volume reduction and with blotchy ground glass areas possibly present.

Grade 3: cystic bronchiectasis, pleuroparenchymal and blotchy opacities distributed in the upper or in both the upper and middle zones, sparing the lower zones, with consistent volume reduction because of the upper lobe collapse and with blotchy ground glass areas possibly present.

Grade 4: cystic bronchiectasis, pleuroparenchymal and blotchy opacities involving the entire lung, including the lower zones, with the collapse of the entire lung and without blotchy ground glass areas.

Acute Fibrinoid Organizing Pneumonia

Restrictive form of CLAD characterized by peribronchial fibrin deposition

Currently unclear if AFOP is pathologically linked to RAS but it has been suggested both diseases may share at least some overlap

<table>
<thead>
<tr>
<th>Patterns of Disease Progression</th>
<th>AFOP</th>
<th>RAS</th>
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<tbody>
<tr>
<td>Conflicting views:</td>
<td></td>
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<tr>
<td>Some believe in a single pattern characterized by sudden decline in transplant function</td>
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<tr>
<td>A subacute form following recovery with steroids has also been proposed⁹</td>
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<tr>
<td>High mortality compared to BOS</td>
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<td>Two accepted patterns:</td>
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<tr>
<th>PFTs</th>
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<th>RAS</th>
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<tr>
<td>Role of Diffuse Alveolar Damage</td>
<td></td>
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<tr>
<td>DAD is not favored to have a role</td>
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<tr>
<td>Transbronchial biopsy and post-mortem studies on a single cohort demonstrated no DAD⁹</td>
<td></td>
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</tr>
<tr>
<td>Fibrosis Pattern</td>
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<td></td>
</tr>
<tr>
<td>Peribronchial deposition with normal interlobular septa ± intraalveolar organizing response</td>
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Acute Fibrinoid Organizing Pneumonia

Common HRCT features\textsuperscript{1,2}

- **Consolidation**
  - Most widely accepted finding
  - May present as patchy or lobar

- **Ground Glass Opacification**
  - Will also see interlobular septal thickening in association

- **Bilateral Disease**
  - Seen in up to 75\% patients on a single cohort

Less common HRCT features\textsuperscript{2}

- **Pleural effusion**
- **Reverse Halo Sign**
- **Band-like consolidation**
- **Bronchovascular distribution**

\textsuperscript{1} Paraskeva M, et al. Am J Respir Crit Care Med. 2013 187(12):1360-8
Acute Fibrinoid Organizing Pneumonia

62 year-old male 7 months post left lung transplant with non-contrast CT images demonstrating consolidation (asterisk) in the left lung allograft and ground glass opacification (arrows) in the native right lung.

Concurrent transbronchial biopsy demonstrated intra-alveolar fibrin deposition.

Following pulsed steroid treatment, 6 days later there was marked improvement, suggestive of the subacute form of AFOP.
Coronal non-contrast CT images demonstrate **subpleural consolidation** (asterisk), **patchy nodular consolidation** (dashed arrows), **traction bronchiectasis** (solid arrow), and **ground glass opacification** (open arrow) throughout the left lung allograft.

Findings are new from the CT dated one year prior (Fig A) and markedly progressed from the more recent CT dated 2 months prior (Fig B).

Transbronchial biopsy demonstrated **intra-alveolar fibrin deposition**.
Summary

- It is important to understand that CLAD is **not** synonymous with bronchiolitis obliterans syndrome.
- CLAD is not a diagnosis but rather a composite of unique subtypes of chronic allograft dysfunction.
  - **Bronchiolitis Obliterans Syndrome (BOS)**
    - Neutrophilic Reversible Allograft Dysfunction (NRAD)
  - **Restrictive Allograft Syndrome (RAS)**
    - Acute Fibrinoid Organizing Pneumonia (AFOP)
- Each phenotype has distinctive imaging features, clinical findings, and pathologic manifestations that are able to aid in diagnosis.
- With continual yearly growth in number of lung transplantations, it is essential for radiologists to be familiar with each of the CLAD subtypes.
References


8. Royer, Pierre-Joseph; Olivera-Botello, Gustavo; Koutskoka, Angela; Aubert, John-David; Bernasconi, Eric; Tissot, Adrien; Pison, Christophe; Nicod, Laurent; Boissel, Jean-Pierre; Magnan, Antoine. Chronic Lung Allograft Dysfunction: A Systematic Review of Mechanisms. Transplantation 2016;100: 1803-1814


Contact Information

Partha Hota DO
partha.hota@tuhs.temple.edu
Department of Radiology
Temple University
3401 N. Broad St
Philadelphia, PA 19140