

# Noninfectious Pulmonary Complications

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## 52.1 Introduction

Lung injury occurs frequently following HSCT and significantly contributes to morbidity and mortality in the immediate post transplant period and in the months and years that follow. It can be observed in 25–55% of recipients (Cooke and Yanik 2016).

Historically, approximately half of all pulmonary complications seen after HSCT were secondary to infection, but the judicious use of broad-spectrum antimicrobial agents has tipped the balance toward noninfectious causes.

Noninfectious lung injury following HSCT may be mediated by either immune or nonimmune mechanisms and could represent up to the 50% of noninfectious mortality after allo-HSCT.

These complications have been classified by the American Thoracic Society according to the

tissue primarily injured and its etiology (Panoskaltzis-Mortari et al. 2011) (Table 52.1).

**Table 52.1** Noninfectious pulmonary complications after HSCT<sup>a</sup>

Localization	Entity
Pulmonary parenchyma	<ul style="list-style-type: none"> <li>– Acute interstitial pneumonitis<sup>b</sup></li> <li>– Acute respiratory distress syndrome (ARDS)<sup>b</sup></li> <li>– BCNU pneumonitis</li> <li>– Radiation pneumonitis</li> <li>– Delayed pulmonary toxicity syndrome<sup>b</sup></li> <li>– Post-HSCT lymphoproliferative disease (see Chap. 45)</li> <li>– Eosinophilic pneumonia</li> <li>– Pulmonary alveolar proteinosis</li> </ul>
Vascular endothelium	<ul style="list-style-type: none"> <li>– Peri-engraftment respiratory distress syndrome (PERDS)<sup>b</sup></li> <li>– Capillary leak syndrome (CLS)<sup>b</sup> (see Chap. 42)</li> <li>– Diffuse alveolar hemorrhage (DAH)<sup>b</sup></li> <li>– Pulmonary VOD</li> <li>– Transfusion-assoc. acute lung injury</li> <li>– Pulmonary cytolytic syndrome</li> <li>– Pulmonary arterial hypertension</li> <li>– Pulmonary thromboembolism</li> </ul>
Airway epithelium	<ul style="list-style-type: none"> <li>– Cryptogenetic organizing pneumonia (COP)<sup>b,c</sup></li> <li>– Bronchiolitis obliterans syndrome (BOS)<sup>b</sup></li> </ul>

<sup>a</sup>Importantly, this classification does not include the most frequent lung complication after HSCT, i.e., pulmonary edema secondary to fluid overload

<sup>b</sup>All these complications are categorized as IPS

<sup>c</sup>Formerly called bronchiolitis obliterans organizing pneumonia (BOOP)

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## 52.2 Diagnostic Methodology of Pulmonary Complications

Ideally, any respiratory/pulmonary complication observed after HSCT must be evaluated following a predetermined institutional protocol (Lucena et al. 2014), which should include:

1. Noninvasive tests: Blood samples for culture and antigen determination, sputum culture, nasopharyngeal swabs testing CMV, respiratory syncytial virus (RSV), *Legionella*, *Pneumocystis jirovecii* (PJ), parainfluenza virus (PIV), adenovirus (ADV), as well as urinary antigen tests and chest x-ray.
2. If negative → empirical treatment (variable behavior; some centers start empirical treatment before the BAL, but many others start the treatment after BAL).
3. If no response in a maximum of 2–3 days (or if galactomannan (GM) +) →
  - (a) High-resolution chest-computed tomography (HRCT).
  - (b) Fiber-optic bronchoscopy (FOB) including bronchial aspiration and BAL to analyze: PCR for *Legionella*, *Mycoplasma*, *Chlamydia*, herpesvirus (all), polyomavirus, ADV, parvovirus, enterovirus, and respiratory virus (RSV; influenza a, B, and C; PIV types 1–4; rhinovirus; bocavirus; metapneumovirus; and others) and GM.
4. In some selected cases, a transbronchial biopsy could be considered.

### 52.2.1 Results Reported Using this Methodology (Seo et al. 2015; Lucena et al. 2014; Shannon et al. 2010)

Diagnostic yield could be as high as 80%.

Sixty percent of diagnosis is achieved with noninvasive techniques.

FOB/BAL permits an etiological diagnosis in up to 78% of cases.

In suspected IPS, a BAL study may detect a pathogen in ~50% of cases.

For pathogen detection, early FOB (<5 days) offer better yield than late FOB.

The risk of complications with FOB is <5%.

## 52.3 Pulmonary Edema Due to Fluid Overload

Despite not being included in most classifications of pulmonary complications after HSCT, pulmonary edema (PE) as a consequence of a fluid overload (FO) is extremely frequent (Rondón et al. 2017).

Incidence	FO may be observed in up to 60% of patients in the first days after HSCT. The exact incidence of PE is not established although it could be higher than 20%
Symptoms and signs	<ul style="list-style-type: none"> <li>– Weight gain, moderate breathlessness, nonproductive cough, moderate hypoxemia</li> <li>– Crackles and rales in both lung bases</li> <li>– Chest radiology with diffuse alveolar/interstitial infiltrates</li> </ul>
Diagnosis	PE should be suspected in the context of weight gain, an increased cardiothoracic index, and crackles/rales. Though rarely necessary, the diagnosis can be confirmed by pulmonary pressure measurements
Differential diagnosis	<ul style="list-style-type: none"> <li>– Heart failure (prior anthracycline toxicity or conditioning with CY)</li> <li>– Endothelial syndromes: SOS, CLS, ES (see Chaps. 42 and 49)</li> <li>– Respiratory tract infections</li> <li>– Post transfusion reactions</li> </ul>
Treatment	Hydro-saline restriction, diuretics

## 52.4 Idiopathic Pneumonia Syndrome

### 52.4.1 Definition

Widespread alveolar injury in absence of active lower respiratory tract infection, cardiac or renal dysfunction, and iatrogenic fluid overload (Clark et al. 1993; Panoskaltis-Mortari et al. 2011)

### 52.4.2 Clinical Manifestations

Characterized by development around day +20 after HSCT of fever and nonproductive cough, dyspnea, tachypnea, hypoxemia, rales, and diffuse alveolar or interstitial infiltrates on x-rays or CT scans.

### 52.4.3 Diagnosis

All of the following must be present for accepting the IPS diagnosis:

#### 1. Evidence of widespread alveolar injury

- (a) Multilobar infiltrates on chest radiographs or CT
- (b) Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, crackles/rales)
- (c) Evidence of abnormal pulmonary physiology
  - Increased alveolar to arterial oxygen difference; need for supplemental O<sub>2</sub> therapy
  - New or increased restrictive PFTs abnormality

#### 2. Absence of active lower respiratory tract infection based upon

- (a) BAL negative for significant bacterial pathogens including acid-fast bacilli, *Nocardia*, and *Legionella* species
- (b) BAL negative for pathogenic nonbacterial microorganisms (*Note of the authors*: Most of the following diagnostic methods despite included in the initial diagnostic methodology have nowadays largely been replaced by PCR techniques)
  - Routine culture for viruses and fungi
  - Shell vial culture for CMV and respiratory RSV
  - Cytology for CMV inclusions, fungi, and *Pneumocystis jirovecii*
  - Direct fluorescence staining with antibodies against CMV, RSV, HSV, VZV, influenza virus, parainfluenza virus, adenovirus, and other organisms
- (c) Other organisms/tests to also consider:
  - PCR for human metapneumovirus, rhinovirus, coronavirus, and HHV6
  - PCR for *Chlamydia*, *Mycoplasma*, and *Aspergillus* spp.
  - Serum and BAL fluid GM for *Aspergillus* species
- (d) Transbronchial biopsy if condition of the patient permits

#### 3. Absence of

Cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

### 52.4.4 Pathogenesis, Incidence, Presentation, and Risk Factors

Pathogenesis	The pathophysiology of IPS is complex. Data generated using experimental models support that IPS is a process in which the lung is susceptible to two distinct but interrelated pathways of immune-mediated injury: a T-cell axis and an inflammatory cytokine axis. These distinct but related pathways of inflammation culminate in the recruitment of immune cells to the lung leading to tissue damage and dysfunction (Cooke and Yanik 2016)
Incidence	<ul style="list-style-type: none"> <li>– The strict methodology required to establish IPS diagnosis and the increased use of RIC have reduced its incidence of 20% to 25% observed 20 years ago (at that time IPS was called idiopathic pneumonia)</li> <li>– This reduction runs in parallel of the improvement in the diagnostic methodologies to detect infectious pathogens. However, the frequent absence of response to the specific treatment against a detected pathogen suggests that the true incidence of IPS may be underestimated</li> <li>– Nowadays: &lt;10% of allo-HSCT (8% after MAC; 2% after RIC)</li> </ul>
Timing	<ul style="list-style-type: none"> <li>– Within first 120 days after BMT, usually observed between days +18 and +21 (20 years ago: around days +40 to +50)</li> <li>– Late IPS can be observed but they are exceptional (Thompson et al. 2017)</li> </ul>
Risk factors (from Cooke and Yanik 2016)	Older age / Karnofsky index <90 / higher interval diagnosis-HSCT MAC or TBI (≥12 Gy) / HLA disparity / GVHD prophylaxis with MTX Acute GVHD/previous viral infection / other malignancies than leukemia

### 52.4.5 Treatment and Prognosis

Supportive measures	<ul style="list-style-type: none"> <li>– Supplemental O<sub>2</sub> therapy</li> <li>– Mechanical ventilation (invasive or not [high-flow nasal O<sub>2</sub>, CPAP])</li> <li>– Empiric broad-spectrum antimicrobials</li> <li>– Strict control of fluids balance/hemofiltration</li> </ul>
Specific treatment	<p>As mentioned, lung injury in IPS can occur through two pathways, the TNF-<math>\alpha</math>/LPS dependent and IL6/IL17 dependent (Cooke and Yanik 2016); consequently, treatment options are focused in these directions</p> <ul style="list-style-type: none"> <li>• <i>Methyl-PDN</i> <math>\leq 2</math> mg/kg/d; if not clear response, consider as soon as possible:</li> <li>• Anti-TNF<math>\alpha</math>: <i>Etanercept</i> 0.4 mg/kg twice weekly (maximum of 8 doses) + systemic steroids (2 mg/kg/d). The randomized study of etanercept + steroids vs. steroids + placebo was terminated prematurely due to slow accrual. In the limited number of patients examined, there were no differences in response rates (<math>\approx 60\%</math>) at day +28. These results do not necessarily imply that this agent is not effective (lack of evidence does not imply lack of effectiveness) (Yanik et al. 2014). In a phase II trial in children, the CR rate was 71% and 1 y survival was 63% (Yanik et al. 2015). This combination has also been shown to be effective in exceptional cases of late IPS with a 42% of CR and a 2 y survival of 62% among responders (Thompson et al. 2017)</li> <li>• Other <i>investigational agents</i> such as <ul style="list-style-type: none"> <li>– MoAb anti-IL6: Tocilizumab (experimental IPS; Varelias et al. 2015)</li> <li>– MoAb anti-IL17: Brodalumab (experimental IPS; Varelias et al. 2015)</li> </ul> </li> </ul>
Evolution	Despite the diagnosis and therapeutic advances, the mortality from IPS remains high at 59–80% at $\approx 2$ weeks of evolution (95% if mechanical ventilation is required)

### 52.5 Diffuse Alveolar Hemorrhage (DAH)

Diffuse alveolar hemorrhage (DAH) is a relevant cause of acute respiratory failure that occurs in 2–14% of recipients, with similar incidence in both auto- and allo-HSCT recipients (Afessa et al. 2002a).

DAH is probably a consequence of damage to the alveolar capillary basement membrane (see Chap. 42). It is difficult to differentiate a true DAH from the alveolar hemorrhage associated with an infection (Majhail et al. 2006).

#### 52.5.1 Clinical Aspects of DAH

Clinical manifestations	Usually observed within the first month after HSCT (a median of 23 days), often during the pre-engraftment phase; however, later onset is encountered in up to 42% of cases The clinical manifestations are those of all IPS. Hemoptysis is exceptional
Diagnosis	Based on BAL: Same criteria as IPS plus a differential characteristic; the progressive bloodier return of BAL fluid aliquots, in at least three segmental bronchi, indicating the presence of blood in the alveoli (or 20% hemosiderin-laden macrophage, although their absence does not exclude the diagnosis as it can take 72 h to appear). <i>Note:</i> DAH can have infectious or noninfectious etiologies (Majhail et al. 2006)
Risk factors	<ul style="list-style-type: none"> <li>– Higher incidence after TBI and high-dose CY</li> <li>– Similar incidence among MAC and RIC</li> <li>– There is no correlation with the platelet counts</li> </ul>
Differential diagnosis with	<ul style="list-style-type: none"> <li>– Classic IPS: Very difficult, only by means of BAL. IPS usually appears after the engraftment, predominates in allo-HSCT, does not respond to steroids, and progresses to fibrosis in 85% of cases (only 15% on DAH). <i>Note:</i> Noninfectious DAH falls under the “diagnostic umbrella” of IPS (Panoskaltis-Mortari et al. 2011)</li> <li>– PERDS: Almost impossible except for LBA progressively bloodier</li> <li>– Pulmonary hemorrhage: By FOB, no blood is seen in DAH</li> <li>– DAH associated with infection: Impossible without detection of the pathogen (Majhail et al. 2006)</li> </ul>

### 52.5.2 Treatment and Prognosis of DAH

Treatment	<ul style="list-style-type: none"> <li>– Although systematically treated with high doses of methyl-PDN (250–500 mg q6h × 5 days, followed by tapered dosage over 2–4 weeks) and aminocaproic acid (ACA), the overall response to this treatment is disappointing (Rathi et al. 2015)</li> <li>– A recent study seems to show that the best treatment is to use low steroid doses (<math>\leq 250</math> mg/d) ± ACA (Rathi et al. 2015)</li> <li>– Factor VIIa addition does not appear to improve the results obtained with PDN (Elinoff et al. 2014)</li> <li>– Try to avoid mechanical ventilation by means of CPAP</li> </ul>
Prognosis	<ul style="list-style-type: none"> <li>– Poor: Overall mortality as high as 85% by day 100 (Rathi et al. 2015)</li> <li>– Less than 15% of patients die as a direct consequence of DAH, but the frequent evolution to MOF increases mortality to &gt;60% (30% in auto and 70% in allo-HSCT) (Afessa et al. 2002b)</li> <li>– DAH that appear early after allo-HSCT (32% early vs. 70% late) or after auto-HSCT have a better prognosis (Afessa et al. 2002b; Majhail et al. 2006)</li> </ul>

## 52.6 Late-Onset Noninfectious Pulmonary Complications (LONIPC)

In addition to late-onset IPS mentioned before and some other exceptional complications (thromboembolisms, pneumomediastinum), there are two forms of chronic pulmonary dysfunction commonly observed in patients surviving more than 100 days after allo-HSCT. One is an obstructive lung disease (bronchiolitis obliterans syndrome, BOS) and the other a restrictive lung disease (cryptogenetic organizing pneumonia, COP).

A recent prospective study showed that among 198 patients included after day +100, the cumulative incidence of LONIPC is 20%, and that of BOS is 11% at 3 years among allo-HSCT recipients (Bergeron et al. 2018). Another study shows the impact of these complications on 5-year survival (28% with vs. 87% w/o LONIPC) (Nishio et al. 2009).

### 52.6.1 Bronchiolitis Obliterans Syndrome (BOS)

Pathogenesis, timing, incidence, clinical manifestations, diagnosis, and radiology of BOS are shown in Table 52.2.

Treatment and prognosis of BOS are included in Table 52.3.

### 52.6.2 Cryptogenetic Organizing Pneumonia (COP)

Formerly called BOOP (bronchiolitis obliterans with organizational pneumonia). COP is a LONIPC of that is associated with restrictive pulmonary dysfunction. Reportedly, the incidence of COP among HSCT recipients is increasing due to the use of transbronchial biopsies as diagnostic tool. The greatest diagnostic challenge is the differentiation of COP from BOS (see Table 52.4) (Yoshihara et al. 2007; Cooke et al. 2017).

**Table 52.2** Main clinical characteristics of BOS

Pathogenesis	The same as cGVHD but specifically involving the lung (Cooke et al. 2017). Its course may be aggravated by respiratory infections, viral infections, and gastroesophageal reflux
Timing and incidence	<ul style="list-style-type: none"> <li>– Average starting period: 12 (3–24) months</li> <li>– Incidence: 3% at 2 years in the longest series (Arora et al. 2016); 11% in a prospective study (Bergeron et al. 2018)</li> </ul>
Clinical manifestations	<ul style="list-style-type: none"> <li>– Variable clinical course, usually insidious onset with progressive deterioration. Sometimes can present as an acute, fulminating course</li> <li>– Progressive breathlessness, nonproductive cough, and wheezing, although some asymptomatic cases are only detected by PFTs.</li> <li>– It is necessary to carry out PFT every 3 m in the first year after HSCT for an early detection<sup>a</sup></li> <li>– In &gt;75% of the BOS, there are chronic GVHD in other locations</li> </ul>

(continued)

**Table 52.2** (continued)

Diagnosis	<ul style="list-style-type: none"> <li>• <i>Suspicion</i>: The so-called <i>BOS stage Op</i>. More than 85% of cases can be diagnosed early by observing a 10–19% drop in the FEV1 or a reduction in FEF25–75 &gt; 25% (Abedin et al. 2015)</li> <li>• <i>Clinical</i> (NIH consensus) (Chien et al. 2010; Uhlving et al. 2012) <ul style="list-style-type: none"> <li>– Clinical manifestation (may be asymptomatic and only detected on PFT) +</li> <li>– Absence of active infection (demonstrated by BAL) +</li> <li>– Chronic GVHD in other locations<sup>b</sup> +</li> <li>– Obstructive alteration with air entrapment (FEV1 &lt; 75% NV or &gt; 10% decrease; ratio FEV1/FVC ratio &lt; 0.7; residual volume &gt; 120%) with nonsignificant bronchodilator test and a decreased DLCO +</li> <li>– Compatible radiology (see below)</li> </ul> </li> <li>• <i>Definitive</i>: Histologic confirmation by thoracotomy, VATS, or transbronchial biopsy<sup>c</sup></li> </ul>
Radiology	<ul style="list-style-type: none"> <li>– Chest x-ray: Normal or with signs of hyperinflation</li> <li>– CT scan: Radiological pattern of constrictive bronchiolitis with arial entrapment, attenuation in mosaic, bronchiectasis and bronchial wall thickening, characteristic air trapping at exhalation</li> </ul>

DLCO transfer capacity of CO, FEV1 maximum expiratory volume in the first second, FVC forced vital capacity, VATS video-assisted thoracoscopic surgery

<sup>a</sup>Some experts consider that a 10% decrease in the FEV1 basal after HSCT should make you suspect in BOS diagnosis

<sup>b</sup>If the lung is the only organ with cGVHD, a biopsy is needed to confirm the diagnosis (NIH criteria)

<sup>c</sup>Rarely transbronchial biopsy is used (low sensitivity and low predictive value) to establish a diagnosis that is eminently clinical. If histology is available, the term bronchiolitis obliterans can be used; if not available, the process is referred to as BOS

**Table 52.3** Treatment and prognosis of BOS

Treatment	<p><i>Supportive measures:</i></p> <ul style="list-style-type: none"> <li>Anti-infectious prophylaxis</li> <li>If hypogammaglobulinemia: IVIg</li> <li>Treatment of gastroesophageal reflux</li> <li>Respiratory physiotherapy</li> </ul> <p><i>Specific treatment</i></p> <ul style="list-style-type: none"> <li>• <i>Prednisone</i>: 1–1.5 mg/kg/day, transient and unsatisfactory response in most cases. The addition of CSA, azathioprine, ATG, or photopheresis has few advantages</li> <li>• <i>Budesonide/inhaled formoterol</i> has been shown to be transiently effective in 60% of the patients (Bergeron et al. 2015)</li> <li>• <i>Etanercept/infliximab</i>: Effective in some cases (Yanik et al. 2012)</li> <li>• <i>FAM combination</i> therapy: Effective in disease stabilization<sup>a</sup>: <ul style="list-style-type: none"> <li>– Fluticasone inhaled 440 mcg c/12 h (adult), 220 mcg in children +</li> <li>– Azithromycin 250 mg/d (adults), 5 mg/kg/d (children)<sup>b</sup> +</li> <li>– Montelukast 10 mg orally at night (adults), 5 mg (children)</li> </ul> </li> </ul> <p>Two weeks before FAM increase (or start) PDN to 1 mg/kg/d, then decrease 0.25 mg/kg/d × week (Williams et al. 2015)</p> <ul style="list-style-type: none"> <li>• In BOS controlled but with a severe residual respiratory insufficiency, lung transplantation may be considered after a few years (Cheng et al. 2014)</li> </ul>
Prognosis	<ul style="list-style-type: none"> <li>– TRM is very high; 32% (18–57%) at 2 years of HSCT almost always get associated with progressive respiratory failure and opportunistic infections</li> <li>– SRV around 65% (4%–80%) at 2 years</li> </ul>

<sup>a</sup>Fluticasone theoretically decreases the inflammatory pulmonary component; azithromycin reduces IL-8 levels and neutrophilia; and montelukast is an antagonist of the leukotriene receptors (bronchodilator)

<sup>b</sup>However, the ALLOZITHRO randomized trial has shown that early administration of azithromycin resulted in worse airflow decline-free survival than did placebo; the value of these findings is limited by early termination of the trial (Bergeron et al. 2017)

**Table 52.4** Differential diagnosis between BOS and COP

First symptoms	BOS: >day +100 HSCT COP: Mostly in the first 100 days <sup>a</sup>
Incidence	BOS: 3–11% allo-HSCT (35% if cGVHD) COP: Up to 10% in URD HSCT
Clinical context	BOS: Allo-HSCT with cGVHD COP: Auto- or allo-HSCT. Almost always previous respiratory infection
Symptoms, signs	BOS: Asymptomatic, or progressive breathlessness, dry cough, wheezing. No fever, normal blood test COP: Fever, dry cough. Leukocytosis, increased CRP
Etiology	BOS: cGVHD COP: Idiopathic? Triggered by infection <sup>b</sup> or drugs <sup>c</sup> ?
Pulmonary auscultation	BOS: Wheezing, hypoventilation COP: Crackles/rales
RFT	BOS: Obstructive pattern: FEV1/FVC <70%, FEV1 <75%, DLCO reduced COP: Restrictive pattern: FEV1/FVC >80%, TLC <80%, DLCO reduced
Chest radiology	BOS: Normal or airtrapping COP: Alveolar or interstitial pattern
Thoracic CT scan	BOS: Thickening of bronchial walls, bronchiectasis, air trapping on expiratory views COP: Uni- or bilateral patched bindings, glass images dull, or nodular infiltrators
BAL	BOS: Neutrophilia COP: Lymphocytosis, decreased CD4/CD8 ratio
Diagnosis	BOS: Clinical manifestations + PFTs + radiology COP: Requires lung biopsy
Response to steroids	BOS: Limited COP: Response in >80%
Prognosis	BOS: SRV <20% at 5 years if no response to steroids COP: Potentially reversible

CRP C-reactive protein

<sup>a</sup>If patients are adequately controlled, it is common to detect restrictive alterations before the day +100 although clinical manifestations may appear later

<sup>b</sup>*Mycoplasma*, *Coxiella*, *Nocardia*, and various viruses

<sup>c</sup>Amiodarone, bleomycin, busulfan, and cephalosporins

### Key Points

- Lung injury occurs frequently following HSCT and significantly contributes to morbidity and mortality in the immediate post transplant period and in the months and years that follow. It can be observed in 25–55% of recipients.
- Noninfectious lung injury following HSCT may be mediated by either immune or non-immune mechanisms and could represent up to the 50% of noninfectious mortality after allo-HSCT.
- Most relevant noninfectious early pulmonary complications are pulmonary edema by fluid overflow, idiopathic pneumonia syndrome, and diffuse alveolar hemorrhage, a vascular endothelial syndrome.
- The most relevant late-onset noninfectious pulmonary complications are bronchiolitis obliterans and cryptogenetic organizing pneumonia.
- All of them have specific diagnostic criteria, management, treatment, and prognosis.

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