# INITIAL MANAGEMENT OF PATIENTS WITH SUSPECTED PULMONARY CHRONIC GVHD

Chronic graft versus host disease (cGVHD) is the major cause of long term morbidity and mortality following allogeneic haematopoietic stem cell transplantation (HSCT). Lung cGVHD or bronchiolitis obliterans syndrome (BOS) manifests as a new onset obstructive lung defect and results from an alloimmune response in the small airways, leading to fibrotic occlusion and obliteration. BOS has a poor prognosis (OS at 2 years 44, at 5 years 13%). BOS typically develops within the the first 2 years post-transplant with a prevalance of 5.5% among all transplant recipients and 14% among patients with cGVHD. The clinical symptoms may include shortness of breath on exertion, nonproductive cough or wheezing. Recurrent infections might accompany the course.

Importantly, the onset of BOS is usually insidious and asymptomatic; by the time patients become symptomatic their pulmonary function has usually declined significantly, therefore screening by regular pulmonary function testing (PFT) is now recommended. In general in asymptomic patients screening should be carried out at 6, 9, 12, 18 and 24 months post-transplant. More frequent PFT monitoring is recommended in patients diagnosed with BOS, in those with significant decline in lung function but not yet meeting the criteria for BOS, and in those who show progression of cGVHD in other organs.

On the "**Referral for Pulmonary Function Tests**" form the following tests should be requested:

- Spirometry
- Gas Transfer
- Static lung volumes
- Bronchodilator reversibility studies

Handheld spirometry may replace PFT for some monitoring visits. Avoid performing pulmonary function tests and spirometry in patients with a pneumothorax, subcutaneous emphysema, or pneumomediastinum.

The diagnosis of BOS mainly relies on PFT and high resolution CT chest with expiratory views. In line with NIH consensus criteria (2014) BOS can be diagnosed when all of the following criteria are met:

1. **FEV1** (forced expiratory volume in 1s) **/FVC** (forced vital capacity or slow vital capacity VC, whichever is greater) ratio **< 0.7** or the fifth percentile of predicted.

2. **FEV1 < 75%** of predicted with ≥ 10% decline over less than 2 years. FEV1 should not correct to > 75% of predicted with salbutamol, and the absolute decline for the corrected values should still remain at ≥ 10% over 2 years.

3. **Absence of infection** in the respiratory tract (see below).

4. **Either**:
    A. Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high resolution chest CT, or
    B. Evidence of air trapping by PFTs: residual volume > 120% of predicted or residual volume/total lung capacity elevated outside the 90% confidence interval, or
    C. Pre-exisiting diagnosis of chronic GVHD in other organ system.

Note that lung biopsy carries significant morbidity and mortality in this patient group and is not routinely performed, hence the diagnosis is BO syndrome rather than biopsy-proven BO.

Patients fulfilling the above criteria should be **referred to the Respiratory Team** (see current list of link consultants). At the same time patients with PFTs suggestive of BOS should be started on the **following medications** (FAM regimen) in the BMT clinic until respiratory review can be arrenged:

1. Inhaled Corticosteroids/Bronchodilators: **Budesonide** 800 mcg plus **Formoterol** 24 mcg BD inh (Symbicort 400/12 Turbohaler two puffs BD inh), reduced to half dose after a month if improvement in PFTs noted. An alternative is **Fluticasone** 500 mcg plus **Salmeterol** 50 mcg BD inh (Seretide 250/25 Evohaler two puffs bd inh).

2. **Azithromycin** 250 mg 3 days per week (Monday/Wednesday/Friday) PO.

3. **Montelukast** 10 mg ON PO.

The above treatment does not replace systemic immunosuppression, which should be continued/adjusted on discreation of treating physician. The rationale behind early initation of FAM therapy is that this is relatively non-toxic and may halt or slow progression of BOS in some patients.

Steroid burst (prednisolone 1mg/kg) with rapid taper (0.25mg/kg per week) should be considered alongside FAM therapy for BOS patients with significant symptoms or marked lung function decline in whom infection has been excluded. Extended courses of oral steroids are no longer recommended for BOS therapy.

Further treatments that may be helpful in severe or progressive BOS include management of gastro-oesophageal disease, nutritional support, pulmonary rehabilitation, inhaled tiotropium, n-acetylcysteine, inhaled tobramycin (if chronic bacterial airways infection), extracorporeal photopheresis, and lung transplantation (consider in young patients with refractory severe BOS with no other active GVHD, on minimal or no immunosuppression, without other end organ damage, and >1 year post-HSCT without relapse).

**Precautions with Azithromycin use:**

**1. Cardiac issues:**
In patients with **QT interval prolongation** azithromycin should be avoided.
In situations that may lead to increased risk of ventricular arrhythmias azithromycin should be used with caution such as treatment with other active substances known to prolong QT interval: antiarrhythmics of class IA (quinidine and procainamide ) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as **citalopram**; and **fluoroquinolones** such as **moxifloxacin and levofloxacin**, electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia, clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

To minimise the risk of cardiac arrhythmia baseline **ECG** should be performed, followed by a repeat ECG at next visit within 3 months of treatment.

**2. Liver function:**
The liver is the principal route of elimination for azithromycin, therefore the use of azithromycin should be undertaken with caution in patients with significant hepatic disease.

- Do NOT initiate treatment if **ALT, AST or bilirubin value is more than 3 fold** upper limit of normal.

Stop treatment if derangement of LFTs at the above degree develops during treatment.

**3.** Azithromycin should be avoided in the setting of suscepted or confirmed infection with **non-tuberculous mycobacteria**, given the risk of inducing macrolide resistance.

**4. Relevant drug interactions:**
Azithromycin might result in elevated levels of **Ciclosporin and Tacrolimus** and dose reduction might be necessary. Close blood level monitoring is required. Remember to readjust Ciclosporin and Tacrolimus dose if/when the Azithromycin is stopped.

**5.** Increased **relapse risk** with prophylactic administration
A recent publication found higher relapse rate and worse survival with azithromycin use when azithromycin was given at a dose of 250 mg orally 3 times a week from start of conditioning for 2 years post-transplant compared with placebo. However, in the patient population with cGVHD relapse rate is low and considering that infections can trigger significant worsening of BOS, patients with proven BOS are expected to benefit from azithromycin administration.

**Pharmacokinetic interactions of Symbicort**

Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, **voriconazole, posaconazole, clarithromycin**, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide. If concomitant use is not avoidable, the time interval between administration of the inhibitor and budesonide should be as long as possible.

## Other causes of pulmonary disease post-HSCT

**Infection** should be considered in all patients with new chest symptoms and/or decline in PFTs. CXR often appears normal; suggest low threshold for CT chest and microbiologic cultures (consider upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage). Sputum culture is particularly helpful in patients with established bronchiectasis. If BAL is performed, samples should be sent for microscopy and culture, respiratory virus PCR, fungal microscopy and culture, mycobacterial microscopy and culture, Nocardia culture, cytological examination for Pneumocytis jirovecii and fungi, fungal PCR, and measurement of galactomannan and beta-D glucan. Lung biopsy may be required in select cases to exclude infection, depending upon imaging appearances.

**Restrictive** PFTs are not characteristic of BOS; possible causes include interstitial lung disease (including cryptogenic organising pneumonia), drug-induced or radiation pneumonitis, advanced sclerotic GVHD of the chest wall, GVHD myositis, steroid myopathy, or respiratory weakness secondary to polyneuritis.

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**Audit**

These processes are subject to the OxBMT/IEC audit programme

**Circulation**

NSSG Haematology Website

**Review**

| Name | Revision | Date | Version | Review date |
|---|---|---|---|---|
| James Davies | Minor revisions | Apr 2022 | 1.1 | Apr 2024 |