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### Bullous Lung Disease (BLD): A Narrative Literature Review

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#### ABSTRACT

Bullous lung disease (BLD) is often associated with spontaneous pneumothorax, but its role as a predisposing factor for recurrent pneumothorax is still not clearly revealed. Many factors are associated with lung BLD, but because BLD cases are still quite rare, efforts need to be made research further to find out more about the relationship between predisposing factors and BLD. Diagnosis of BLD by paying attention to the history, physical examination and appropriate radiological examination is necessary to determine whether surgery is necessary or not. Management of BLD has now developed with many different therapy options. The choice of invasive or non-invasive procedures is adjusted to clinical needs, equipment availability and medical personnel. Good treatment will of course provide satisfactory results, especially in terms of improving the patient's quality of life.

#### 1. Introduction

Bullous lung disease (BLD) is considered a variant of pulmonary emphysema characterized by damage, stretching, or merging of the alveoli to form cavities larger than 1 cm.<sup>1</sup> BLD based on the underlying cause is grouped into primary and secondary, resulting from chronic obstructive pulmonary disease (COPD) where BLD is formed as a result of pathological emphysematous changes and then gradually normal lung tissue is replaced by many bullae, which are visible on chest radiographs. BLD can also occur in the late stages of pulmonary fibrosis in sarcoidosis or complicated pneumoconiosis.<sup>2</sup> There is not much epidemiological data on BLD in the literature; in general, it is known that BLD occurs in more than 5% of the world's population, with a total prevalence of

around 12% in adults over 30 years. In the United States, BLD is in 3rd place among diseases that cause death and kills more than 120,000 people per year.<sup>3</sup> BLD is most often experienced by elderly patients (> 45 years) who show disturbances in ventilation, gas exchange, and lung expansion accompanied by decreased respiratory function.<sup>3</sup> Chest X-rays are often carried out for supporting examinations, where hyperradiolucent images are found due to excessive distension of the airspace (acinus and alveoli). When the bulla gets bigger (more than 50% of the hemithorax) in the lung lobe, it is usually called giant Bulla Emphysema or vanishing lung syndrome, especially if the bullae fill almost the entire hemithorax; there will be a compression effect on the lung tissue which will cause respiratory problems.<sup>4</sup>

Bullae, blebs, and cysts have many similarities.<sup>5,6</sup> The differences between these three diseases are based on pathomorphological structure. Bleb is an accumulation of air between the two layers of the visceral pleura - the outer and the inner elastic layer. Its origin is associated with the pathological penetration of air from the lung parenchyma into the visceral pleura.<sup>7</sup> A cyst is a cavity lined with a layer of epithelial cells. Chest X-ray images of lung cysts can be very similar to bullae.<sup>8</sup> Surgical therapy is chosen for the management of BLD because patients with BLD cannot be managed with medication. Surgical management of damaged lung areas using the LVRS method (lung volume reduction surgery) can improve the quality of life of patients, but in recent years, BLVR (Bronchoscopy lung volume reduction) has become an alternative and promising treatment in the management of BLD-type severe.<sup>9-11</sup>

**Etiology**

The cause of BLD is not fully understood, and it is thought that the cause can originate from a variety of clinical conditions with chronic cough, emphysema of the distal acinus, loss of lung elasticity, allergies, recurrent bronchial infections, and secondary changes in the chest wall. Chronic inflammation and destructive changes in the terminal respiratory bronchioles are present. resulting in distension of the

air space due to delayed emptying.<sup>11</sup> Environmental factors such as smoking and exposure to dust are additional risk factors and are associated with a rapid deterioration in the patient's condition. Patient factors such as genetics and age also influence the development of the disease, and a link has been found between smoking and  $\alpha$ 1-antitrypsin deficiency, resulting in the formation of BLD.<sup>12</sup> Lung BLD patients are divided into two general groups: first, COPD (chronic obstructive pulmonary disease) patients, and second, patients with relatively normal lung parenchyma among BLD without airflow obstruction. The second group usually has a family history (familial occurrence). (1) The incidence of pulmonary BLD is increased in patients with Marfan syndrome and Ehlers-Danlos syndrome, suggesting an association between connective tissue disorders and BLD disease.<sup>13-15</sup>

**Classification**

Classification of patients with BLD aims to facilitate the evaluation of patients who are surgical candidates and predict respiratory function after the procedure. The classification of bullous diseases by DeVries and Wolfe (1980) divides these disorders into categories, as shown in Table 2.<sup>16,18</sup>

Table 1. Classification of BLD based on etiology.

Primary	Vanishing lung syndrome Single giant BLD
Secondary	Emphysema Paraseptal Panacinar Centriacinar
Pulmonary fibrosis	COVID-19 Sarcoidosis Idiopathic pulmonary fibrosis Tuberculous fibrosis Other pulmonary fibrosis diseases
Hereditary factors	Alpha 1 antitrypsin deficiency Ehlers-Danlos syndrome Salla disease Marfan syndrome

Table 2. Classification of bullous DeVries and Wolfe.

Category	BLD	Underlying lung disease
I	Big, single	Normal
II	Multiple	Diffuse emphysema
III	Multiple	Diffuse emphysema
IV	Multiple	Other lung diseases (scleroderma, histoplasmosis, pulmonary fibrosis, granuloma eosinophilic, pneumoconiosis)

### Pathophysiology

The mechanism for the formation of BLD is currently not known with certainty. The theory regarding the pathophysiology of pulmonary BLD explains that there is a ball-valve mechanism between the BLD and the bronchus causing the BLD to enlarge progressively. Another explanation for the degradation of lung elastin fibers, which is triggered by an increase in the influx of neutrophils and macrophages, is related to smoking habits. Degradation of elastic fibers causes an imbalance in the protease-antiprotease and oxidant-antioxidant systems. After bullae form, obstruction of the small airways occurs caused by a prolonged inflammatory process resulting in increased alveolar pressure, which causes air to seep into the interstitial spaces of the lungs.<sup>1,13</sup> Another theory states that  $\alpha 1$ -antitrypsin deficiency is a risk factor for emphysema and airway obstruction. Antitrypsin inhibits neutrophil elastase and serine proteinase, which function in the major proteolytic cascade processes. Decreased proteinase inhibitor ( $\alpha 1$  antitrypsin) causes uncontrolled intrapulmonary elastase activity and neutrophil elastase (produced from inflammatory cells), which causes panacinar emphysema.<sup>19,20</sup>

Emphysema is characterized by damage to the alveolar walls distal to the terminal bronchioles. This process will continue to enlarge the distal air space accompanied by the formation of blebs, cysts, and BLD. The alveolar walls, which are rich in capillaries, are also damaged in areas of emphysema, causing the formation of physiological dead space. This increase in respiratory dead space will reduce breathing efficiency and cause an increase in the work of breathing and

impaired air exchange.<sup>13</sup> Enlarged BLD due to increased intra-BLD pressure will cause the surrounding lung tissue to collapse. Inflammation and partial occlusion of the small airways leads to destruction of the BLD with progressive enlargement and subsequent occlusion of the airways. Finally, BLD will generate space occupying lesion which is large with good ventilation but without good perfusion, resulting in resistance to movement of the diaphragm and chest wall, shifting of the mediastinum and pressure on the healthy side of the surrounding lung and on the contralateral lung.<sup>13</sup>

Damage to the alveolar walls causes a decrease in the lung's elastic recoil ability and decreases traction support from the lumen of the small airways, causing disruption of the exhalation process. Decreased elastic recoil ability accompanied by collapse of the expiratory airway results in hyperinflation and the presence of air-trapping in areas of emphysema. This hyperinflation can put pressure on the surrounding lung tissue so that the ventilation-perfusion ratio will decrease in the area of the lung that is experiencing pressure, which, over time, causes disruption of air exchange and hypoxemia.<sup>13</sup> Difficulty breathing in patients with BLD occurs due to maximal expansion of the chest wall, with the diaphragm "flattening" during maximal inspiration so that each inspiration produces only minimal air movement. Resection of the damaged part of the lung will allow the chest wall to return to its normal condition and restore the mobility of the diaphragm to its original state.<sup>13</sup>

## **Diagnosis**

Clinical diagnosis of pulmonary BLD is made based on history, physical examination, and supporting procedures. The symptom most often found in anamnesis is that patients complain of shortness of breath. Shortness of breath depends on the size, location, compressed tissue around the BLD, decreased vital lung capacity, and changes in intrathoracic pressure, as well as the formation of cysts and pneumothorax. Localized chest pain is found in fairly large BLDs. The risk factors for BLD that are most often found are a history of previous illnesses, such as asthma, congenital abnormalities, and COPD, and habitual factors, such as smoking.<sup>14</sup> Patients rarely experience clear complaints, especially if other parts of the lung do not experience abnormalities. Physical examination in patients with pulmonary BLD is difficult to assess when the BLD they suffer from is complicated by spontaneous pneumothorax. Shortness of breath that occurs in patients is difficult to differentiate, whether it is caused by pneumothorax or due to worsening lung function due to increasing BLD size. Lung BLD is often only discovered after supporting examinations.<sup>13</sup> Supporting examinations are usually radiological examinations used to identify the size, location, and spread of space-occupying lesions and assess the condition of the lung parenchyma around the BLD, which is useful for predicting increased lung function after surgery. Radiological examinations that can be carried out in the diagnosis of lung BLD include plain chest radiographs, bronchography, angiography, CT scans, and ventilation-perfusion scanning.

## **Thoracic photo**

The diagnosis of pulmonary BLD can be confirmed by a plain chest X-ray if a hyperlucent, avascular, well-defined area with thin walls is found. BLD walls show a typical hair-like appearance, but sometimes, only

part of the wall can be seen. The size of the BLD will be relatively larger during expiration because the BLD will trap air during expiration. Chest images during inspiration and expiration are often also needed to differentiate diffuse emphysema from more localized lung BLD. In diffuse emphysema, expiration does not increase the hemithorax volume significantly, whereas, in BLD, expiration dramatically increases the hemithorax volume as a result of deflation that occurs in the normal lung around the BLD.<sup>8</sup>

The diagnosis of pneumothorax on plain radiographs can be confirmed if a visceral pleural line is visible. If this image is difficult to find, additional procedures can be performed. In the first procedure, the patient is photographed in an upright position and maximally exhaled. Lung volume will decrease, but the volume of air in the pleural cavity remains so that the surface of the visceral pleura in contact with air is smaller. Another procedure is in the lateral decubitus position, and the beam direction is from the lateral. This procedure will cause it to be at the highest point of the hemithorax so that it can be seen at the top when viewed from the lateral side of the chest wall. In BLD, the location of the avascular hyperlucent area remains in any photo position and actually experiences relative enlargement during maximum expiration. These two procedures can differentiate between pneumothorax and BLD.<sup>8</sup> Plain radiographs can see compression of lung tissue by BLD accompanied by pressure on the diaphragm. Pressure on the diaphragm is localized, with the upper surface of the diaphragm being slightly concave downwards. The boundary line of the BLD wall can be seen on the lateral side of the diaphragm basin. BLD very rarely presses on the trachea and heart, although sometimes it can extend into the retrosternal space and form a depression in the contralateral lung.<sup>9</sup>

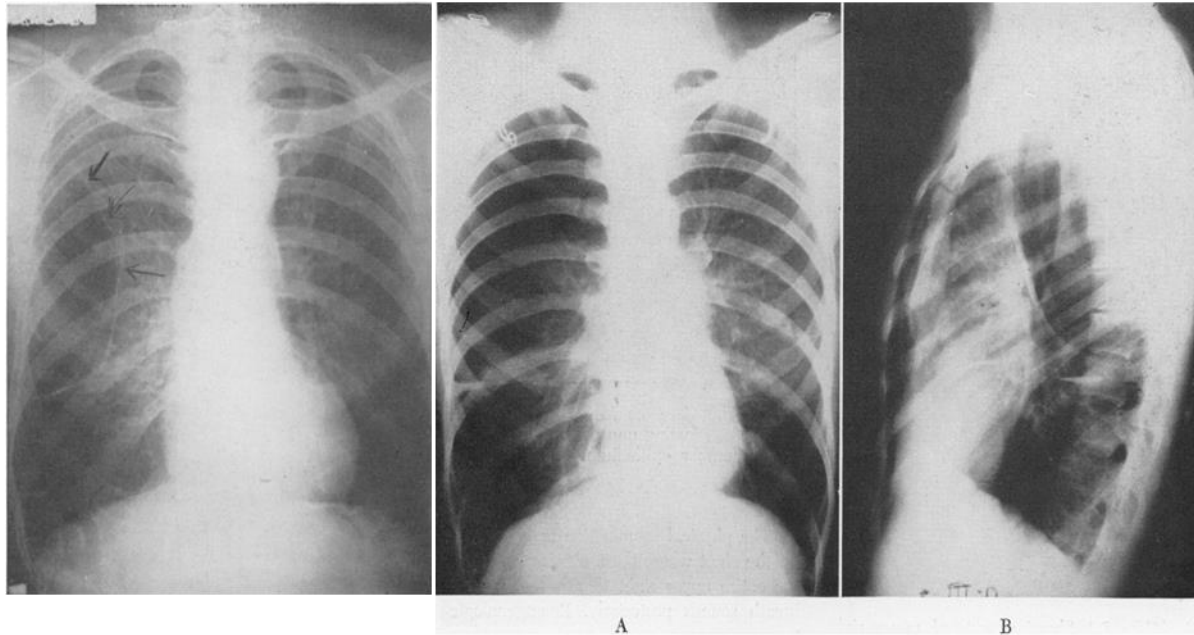


Figure 1. Bullous on the hemithorax.

**Thoracic CT scan**

CT scan is the examination gold standard diagnostic of BLD who experience acute shortness of breath because of its great benefits in diagnosing BLD and pneumothorax. Criteria for the radiological diagnosis of bullous emphysema include the discovery of a radiolucent area that usually does not contain blood vessels and is limited by a visible wall in one or both lobes of the lung. Stern et al. (1994) presented a typical CT scan picture of giant bullous emphysema,

which includes multiple large BLDs, between 1 - 20 cm in diameter, without the presence of one dominant BLD.<sup>13, 23</sup>

CT scans can be used to (1) differentiate pulmonary BLD from pneumothorax, (2) see the presence of lung BLD elsewhere, and (3) assess general lung conditions. The image obtained from a CT scan can show the size, location, and extent of BLD better than other types of examination.

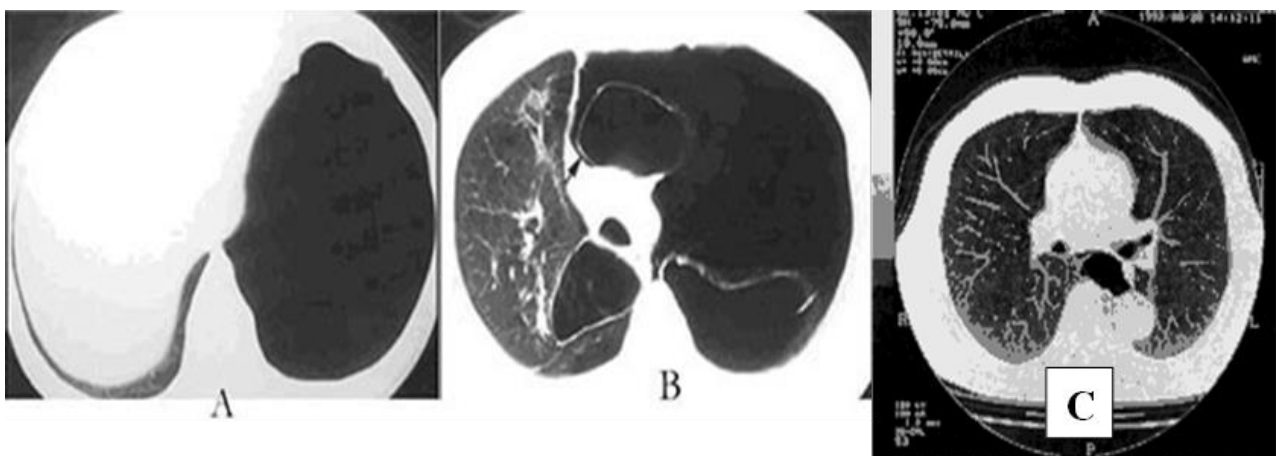


Figure 2. CT scan of the bullous.

Patients with giant bullous emphysema are susceptible to spontaneous pneumothorax. Specific signs found on CT scans are very helpful in distinguishing between these two disorders: compression and consolidation of the lung around the BLD, hyperlucency, and decrease or disappearance of symptoms immediately after the chest tube is installed. Another important sign is the "double wall sign" on the CT scan results, namely an image of air on both sides of the BLD wall, which is parallel to the chest wall. The discovery of this sign indicates the presence of a pneumothorax in a patient with BLD. It is important to differentiate BLD from pneumothorax

to prevent unnecessary chest tube placement. This double-wall sign may not be immediately found on a CT scan, especially if there is pressure on the bullae.

### Angiography

Another examination that is also useful is angiography. Angiography can identify lung tissue that is still functioning well. The presence of alveolar "blush" in the peripheral parts of the lungs is the main indicator that there is still capillary circulation in the lungs, which indicates that this part of the lungs is still functional.<sup>13</sup>



Figure 3. Angiographic picture of pulmonary bullae.

### Complications

#### Bullae infected

Infected BLD can present with clinical manifestations of fever, cough, purulent sputum production, dyspnea, and pleuritic chest pain. BLD can easily become infected because it is connected to the tracheobronchial tract, for example, due to pyogenic organisms, aspergillus, and fungi, which can develop into mycetoma. Infection of the BLD will result in a reduction in BLD size and fibrotic contraction. Fluid production will cause the connection between the BLD and the airway to close so that, over time, air

will be absorbed, and the air space will disappear. After this kind of infection, BLD usually disappears.<sup>13</sup>

Laboratory findings may include leukocytosis and positive sputum culture. When clinical and radiographic findings suggest an infected BLD, empiric antibiotics should be initiated based on a regimen similar to that used for pneumonia in patients with COPD. Bacterial species that have been identified from infected bullae include methicillin-resistant *Staphylococcus aureus* (MRSA), *Bacteroides*, *Pseudomonas aeruginosa*, and mycobacteria.<sup>13</sup>

Treatment is sometimes prolonged and may require parenteral or intra-BLD administration, as poor bullae drainage inevitably slows the resolution of the disease process. The course of infection should be followed with interval chest radiographs, in part because bullae infections have been associated with bronchogenic cancer. If the patient does not improve with empiric antibiotics, percutaneous bullous fluid aspiration can be performed with CT guidance to identify the antibiotic sensitivity of the infecting organism. Please be aware that percutaneous aspiration increases the risk of pneumothorax and empyema. Most cases of infection can be treated conservatively, and surgery is only performed in refractory cases that require drainage or excision.<sup>13-16</sup>

### **Pneumothorax**

Lung BLD is a predisposing factor for pneumothorax. Pneumothorax in patients with BLD occurs due to BLD rupture. Air originating from the ruptured BLD will move towards the hilus, causing pneumomediastinum. Increased intra-mediastinal pressure, rupture of the parietal pleura in the mediastinal area, and resulting in pneumothorax. This type of pneumothorax should not be treated only by inserting a chest tube. BLD resection, accompanied by closing the air leak gap, is an action to prevent the formation of bronchopleural fistulas, which make it difficult for the lungs to fully expand.<sup>10,21-24</sup>

The recurrence rate for spontaneous pneumothorax from various studies ranges from 16-52 percent, which occurs within a period of 6 months to 2 years after the first pneumothorax. Radiological evidence in the form of pulmonary fibrosis, patient asthenicus, history of smoking habits, and young age were reported as independent risk factors for spontaneous pneumothorax recurrence. The discovery of pulmonary BLD along with pneumothorax apparently cannot be used to predict the possibility of pneumothorax recurrence.

### **Hemoptysis**

Patients who have BLD abnormalities complicated by hemoptysis should undergo bronchoscopy to exclude the possibility of endo bronchial lesions. Likewise, the possibility of a diagnosis of aspergillus superinfection must also be excluded first. Most hemoptysis is associated with infected BLD and can be treated conservatively.<sup>23</sup>

### **Malignancy**

Primary lung cancer has been reported to be associated with bullae. Manifestations that appear include pneumothorax and hemoptysis. 48 The increasing incidence of lung cancer at this time may be due to the fact that lung cancer occurs more often in fibrotic lung disease, which has a tendency to also develop into bullae. Other explanations for the increased incidence of malignancy include dystrophic changes in the lung parenchyma caused by BLD disease.<sup>25,27</sup>

A report noted that multiple cystic air spaces may develop at the site of a previous lung nodule. Based on recent reports, misdetection of lung cancer has been attributed to a failure to appreciate the importance of linking cystic lung disease with bronchogenic carcinoma. The study stated that the patient had a history of giant bullae and a history of smoking. Screening must be carried out through supporting examinations via chest X-ray or CT scan to detect the possibility of lung malignancy. BLD associated with bronchogenic malignancies has an incidence rate of approximately 2.5% and is highest in the 6th decade of life. The results of the BLD histology examination after BLD resection per thoracotomy showed a type 2 pleuro-pulmonary blastoma.<sup>25,27</sup>

### **Non-invasive management**

Complete management for pulmonary BLD is surgery. Asymptomatic cases do not require surgical treatment. In this kind of situation, conservative (non-surgical) therapy is carried out. Conservative therapy is also carried out in patients who refuse to undergo surgery or who have contraindications to surgery.<sup>13,17</sup>

Patients who fall into this category must undergo regular monitoring accompanied by strict pulmonary prophylaxis treatment. Eliminate smoking habits, and if possible, eliminate exposure to other lung irritants, prevent lung infections, and physiotherapy to increase lung functional capacity. If symptoms appear, or if the size of the BLD reaches more than 1/3 of the hemithorax, it is necessary to immediately re-evaluate to assess the need for surgical therapy.<sup>13,17,20</sup>

### **Invasive management: bronchoscopy lung volume reduction (BLVR)**

BLVR is a minimally invasive procedure for patients suffering from severe emphysema. BLVR has been shown to increase functional value and good clinical outcomes with minimal risk of complications. Patients who will be planned for BLVR must be on optimal pharmacological and non-pharmacological treatment. Radiological examination and pulmonary function tests are important things to do beforehand to help identify patients who can undergo BLVR.<sup>21</sup> Various BLVR techniques have been published with different benefits and risks. A system that blocks the entry of inspired air into the treated lobe while air and secretions escape during exhalation. Increasing research reports have suggested that endobronchial therapy may be used to treat bullous disease.<sup>21-23</sup> A 2017 European study, with 27 patients with giant emphysematous bullae undergoing endobronchial valve therapy, 6 did not experience therapeutic collapse. In 21 patients with alveolar collapse, it was found that there was little difference between lung volumes measured with gas dilution techniques compared with whole-body plethysmography. Prospective comparative data are needed to better define this less invasive therapeutic technique.<sup>24-26</sup>

BLVR is categorized as “block” (endobronchial valve [EBV]) and as “non-block” approaches (coil and thermal ablation). The various techniques can also be categorized as definitive (coil and steam) or non-definitive, reversible (removable valve) procedures.<sup>22</sup> BLVR has matured into a treatment option for bullae patients. BLVR has been a treatment option for severe

COPD for many years and can result in improved lung function, exercise tolerance, and quality of life with fewer complications compared with surgical approaches. Further refinement of patient selection and more robust outcome data for endobronchial and steam coils are needed. Long-term follow-up studies will provide further insight into the mortality benefits of bronchoscopic lung volume reduction for specific patient populations.<sup>27</sup>

### **2. Conclusion**

BLD is often associated with spontaneous pneumothorax, but its role as a predisposing factor for recurrent pneumothorax is still not clearly revealed. Many factors are associated with lung BLD, but because cases of BLD are still quite rare, further investigation efforts need to be made to better understand the relationship between predisposing factors and BLD. Diagnosis of BLD by paying attention to the history, physical examination, and appropriate radiological examination is necessary to determine whether surgery is necessary. Current management of BLD has developed with many different therapeutic options. The choice of invasive or non-invasive procedures is adjusted to clinical needs, equipment availability, and medical personnel. Good treatment will, of course, provide satisfactory results, especially in terms of improving the patient's quality of life.

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