Introduction

Bronchiectasis is defined as the permanent dilatation of bronchi that results from a vicious cycle of inflammatory and infectious damage to the bronchial and bronchiolar walls. While cystic fibrosis (CF) is the most common cause of bronchiectasis in childhood in the developed world, non CF bronchiectasis may result from a number of other conditions that include tuberculosis and pertussis squeal, immunodeficiency, connective tissue disorders and allergic bronchopulmonary aspergillosis etc. ***(McShane et al., 2013).***

High-resolution computed tomography (HRCT) is a critical standard investigation for assessing bronchiectasis ***(Woodbine et al., 2010).***

Reid's subtypes of bronchiectasis: cylindrical, varicose and cystic, based upon bronchographic findings are the most commonly used severity classification. Other radiographic scores for quantifying bronchiectasis severity include Bhalla, Nathanson, Reiff and Webb's scores. All use a composite score of various CT scan features, including cylindrical and saccular changes as markers of disease extent and severity ***(Goyal et al., 2016).***

Dominant symptoms and signs of bronchiectasis include productive or wet cough, dyspnea on exertion and other respiratory signs (e.g. clubbing, chest wall deformity,

respiratory noises such as wheeze or crepitations on auscultation). Pulmonary decline may occur over the long-term ***(Pizzutto et al., 2016).***

Patients with Bronchiectasis had significantly higher serum IgG and white blood cells, total lymphocyte, and CD16/56+ cell counts However, these parameters are correlated significantly with age ***(Kostjukovits et al., 2017).***

Interstitial lung disease (ILD) in infants and children represents a heterogeneous group of respiratory disorders, that are mostly chronic and associated with high morbidity and mortality (around 15%) ***(Dinwiddie et al., 2010).***

These disorders are characterized by inflammatory and fibrotic changes that affect alveolar walls. Typical features of ILD include symptoms and signs, the presence of diffuse infiltrates on chest radiograph, and abnormal pulmonary function tests with evidence of a restrictive ventilatory defect (in older children) and/or impaired gas exchange ***(Katzenstein and Myers, 2011).***

A large number of pathological situations can impair gas exchange and contribute to progressive lung damage and ILD. The following diagnostic grouping for pediatric ILD can be considered: exposure-related ILD, systemic disease-associated ILD, alveolar structure disorder-associated ILD and ILD specific to infancy ***(Clement et al., 2010).***

The blood neutrophil to lymphocyte ratio (NLR) is determined by dividing the absolute count of neutrophils by the number of lymphocytes in the complete blood count. NLR has been identified as a potentially useful marker of inflammation that is prognostic of outcome in various disease states, including cardiovascular disease and gastrointestinal cancers. It reflects the balance between neutrophil and lymphocyte levels in the body; it is an indicator of systemic inflammation. NLR, which is calculated from the complete blood count is an easily accessible biomarker and does not require specialized equipment or assays ***(Uthamalingam et al., 2011).***

Multiple studies carried out on adult COPD patients, showed that chronic inflammation was associated with increased blood levels of inflammatory markers and NLR in serum of COPD patients.

However, to our knowledge, there is only one study in the literature that evaluates the role of neutrophil-to-lymphocyte ratio (NLR) in pediatric patients with bronchiectasis and there is no study in literature to evaluate the role of NLR in children with ILD during the stable period and acute exacerbation.

Aim of the Work

1. To evaluate the relationship between NLR as marker of inflammation and the presence of disease (bronchiestasis and ILD) in children.

2. Compare NLR values in stable state and in state of acute exacerbation of the two diseases.

3. To detect correlation between our suggested biomarker and diseases severity as measured by spirometry parameters (FEV1%, FVC%, FEV1/FVC, MMEF% of predicted) and HRCT scoring.

Bronchiectasis

Definition

Bronchiectasis unrelated to cystic fibrosis (CF) is a chronic pulmonary disorder, defined as irreversible dilatation of damaged bronchi presented clinically as chronic "wet" or productive cough accompanied by recurrent pulmonary exacerbations ***(Chang et al., 2015).***

Incidence

The prevalence of bronchiectasis varies with time period and geography, due to differences in antibiotic prescription, availability of vaccinations, and prevalence of associated disorders. Additionally, the doctor's alertness for bronchiectasis and the availability of sensitive diagnostic tools may affect reported prevalence ***(Hacken et al., 2010)***. In 2011 the incidence was 32/100,000 person per year at risk in the UK ***(Quint et al., 2012)***. In New Zealand, the national incidence of bronchiectasis is 3.7/100,000 per year, while in Central Australian indigenous children the estimated prevalence of bronchiectasis is at least 1470/100,000 ***(Chang et al., 2010).*** In the United States, the rate was reported to be as high as 52/100,000 ***(Rademacher and Welte, 2011)***.

Aetiology:

A- Congenital bronchiectasis

1) Congenital anatomic defects

As Mounier-Kuhn syndrome and Williams-Campbell syndrome, pathogenesis is characterized by Atrophy of smooth muscles and elastic tissue in the trachea and main bronchi cause tracheobronchomegaly, can be associated with tracheal and bronchial diverticuli ***(Simon et al., 2014).***

2) Genetic causes

- **Cystic fibrosis:** Illness and death from CF are primarily due to progressively destructive lung disease, resulting in bronchiectasis and respiratory failure. Computed tomography (CT) can detect changes in the lungs associated with bronchiectasis and evidence of structural lung disease in children with cystic fibrosis as young as 11 weeks of age ***(Sly et al., 2013).***

- **Primary ciliary dyskinesia:** an autosomal recessive condition, that Cause impaired mucociliary clearance by structural or functional defects of motile cilia in the airway. Can be associated with infertility and organ laterality defects ***(Horani et al., 2014).***

B- Postinfectious causes

Some infectious agents associated with postinfectious bronchiectasis such as measles, pertussis, adenovirus 21, and

TB, are the principal causative agents of respiratory damage in bronchiectasis. Others are concurrent infections with bronchiectasis such as allergic bronchopulmonary aspergillosis (ABPA), *Pseudomonas aeruginosa*, human immunodeficiency virus and atypical mycobacteria ***(Bonaiti et al., 2015; Fitzpatrick et al., 2014; Park and Olivier, 2015).***

C-Immune dysfunction

By predisposing to recurrent pulmonary infections, congenital and acquired immunodeficiency syndromes can lead to bronchiectasis. Underlying immune-related causes include chronic granulomatous disorders and deficiencies of inflammatory complements or immunoglobulins (Igs) (IgG, IgA, or IgM) ***(Brower et al., 2014).***

Early diagnosis and treatment of primary immunodeficiency disorders, prevent the development or at least the progression of bronchiectasis in children ***(Goyal, 2016; Al-Jahdali, 2017).***

D-Bronchial obstruction

Bronchial obstruction leads to the accumulation of airway secretions which predispose to pulmonary infection. Bronchial obstruction can be due to intraluminal obstruction by foreign bodies, carcinoid tumor, other primary or secondary malignancy or due to extra luminal compression from adjacent enlarged lymph nodes ***(Brower et al., 2014; Ghobadi et al., 2013).***

E-Other disorders

Bronchiectasis is associated with other disorders such as inflammatory bowel disease, α1-antitrypsin deficiency, Marfan's syndrome, Hyper-IgE syndrome (”Job's syndrome”), asthma, COPD, lung fibrosis and connective tissue diseases, especially rheumatoid arthritis and bronchiolitis obliterans ***(Lonni et al., 2015; Al-Jahdali, 2017).***.

In addition, recurrent aspiration and exposure to toxins may cause bronchiectasis. Idiopathic bronchiectasis after excluding secondary causes accounts for <50% of cases ***(Lonni et al., 2015; Al-Jahdali, 2017).***

Pathogenesis of Bronchiectasis: **(Fig.1)**

The underlying mechanism of bronchiectasis is described as a vicious cycle of transmural recurrent infection and subsequent inflammation. Inflammation and infection cause damage primarily to the bronchi and bronchioles. Damaged airways are susceptible to infection with usually colonizing but severely damaging bacterial and fungal microbes such as *Pseudomonas aeruginosa*, *Aspergillus fumigatus* and non-tuberculous mycobacteria***(Moulton and Barker, 2012)***.

Impaired mucociliary clearance leads to the release of phagocytic enzymes and chemokines that erode mucosal barriers and create crevices and microabscesses that harbor potentially pathogenic organisms***(Moulton and Barker, 2012)***.

Damaged airways are then more susceptible to infection, resulting in further damage. Airway damage from inflammation is mediated through both leukocytes and respiratory epithelial cells. Innate immune responses include release of neutrophil elastase (NE) and reactive oxygen species, major histocompatibility complex (MHC) genes involved in cell recognition and activation of complement pathway. Acquired immune responses include antibody production in response to infectious antigens via B cells, T cells and other antigen-presenting cells ***(Moulton and Barker, 2012)***.

Neutrophils play a key role in the development and progression of bronchiectasis. Bronchial biopsies in patients with bronchiectasis have demonstrated tissue neutrophilia, a mononuclear cell infiltrate composed mainly of CD4+ T cells, CD68+ macrophages and increased expression of IL-8 and other chemokines ***(Federico et al., 2015)***.

Neutrophil massive recruitment into the airways in response to infective or inflammatory triggers results in proteolytic enzymes such as neutrophil elastase (NE) and matrix metalloproteinase (MMP) release leading to airway matrix destruction ***(Federico et al., 2015).***

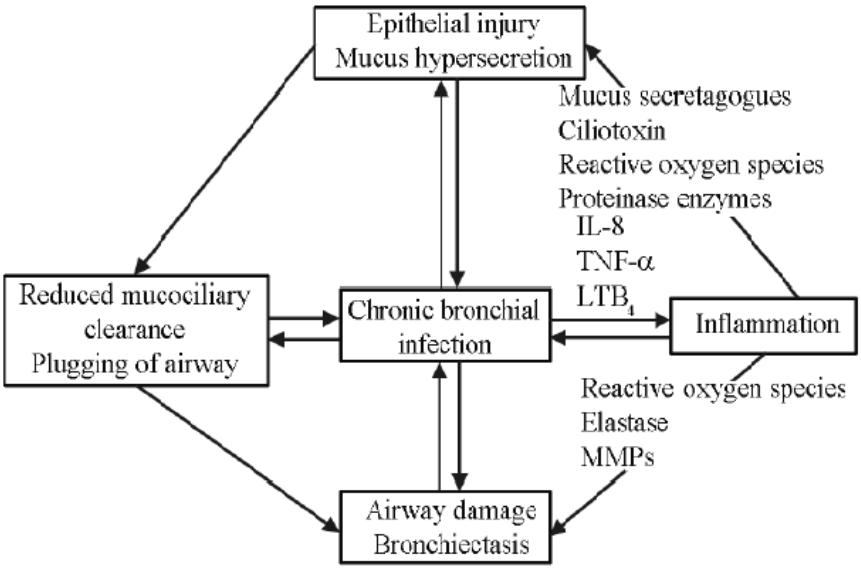

Figure (1): Schematic representation of a vicious circle of events that occur during chronic bronchial infection. IL: interleukin; TNF: tumour necrosis factor; LT: leukotriene; MMP: matrix metalloproteinase ***(Zengli, 2014).***

Reid's subtypes of bronchiectasis that are cylindrical, varicose and cystic, based upon bronchographic findings are the most commonly used severity classification ***(Goyal, 2016).***

Table (1): Morphological types of bronchiectasis

Tubular	Which characterized by smooth dilation of the bronchi; is characterized by uniform dilatation of bronchi, that extends into the lung periphery, without tapering.
Varicose	The bronchi are dilated with multiple indentationsis characterized by irregular and beaded outline of bronchi, with alternating areas of constriction and dilatation.
Cystic	The dilated bronchi terminate in blind ending sacsis the most severe form of the disease. The bronchi dilate, forming large cysts, which are usually filled with air and fluid.
Follicular	Which characterized by extensive lymphoid nodules within the bronchial walls. It usually occurs following childhood infections

(Neves et al., 2012)

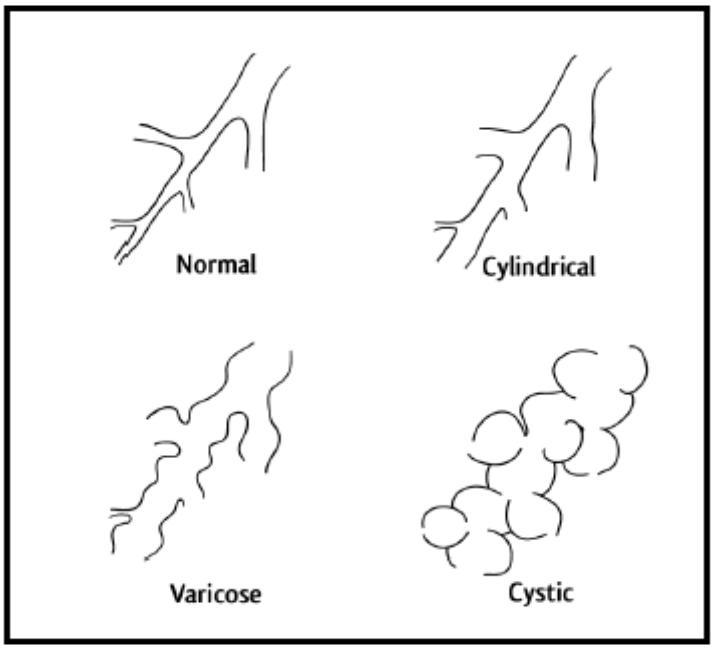

Figure (2): Morphological types of bronchiectasis ***(Neves et al., 2012).***

Clinical Presentation

The most common symptom in children with bronchiectasis is a chronic or recurrent wet cough not responding to antibiotics and especially if accompanied by:

- Exertional dyspnea.
- Recurrent wheezing, although a history of wheeze or asthma like symptoms is reported in 40–74% of children, but asthma itself does not cause chronic wet cough or bronchiectasis.
- Bronchiectasis.
- Chest infections.
- Hemoptysis.
- Digital clubbing.
- Chest wall deformity.

(Chang et al., 2015)

Finally, as bronchiectasis progresses the bronchial artery diameter increases multiplying the risk of hemoptysis ***(Kosar et al., 2014).***

Proposed criteria for defining a pulmonary exacerbation in children with bronchiectasis.

(I) Major criteria

- Significant frequency of cough (median cough score ≥2) over 72h.
- Wet cough for 72 h.

(II) Minor criteria

- Sputum color ≥3 on BronkoTest™.
- Parent/child perceived breathlessness.
- Chest pain.
- Auscultatory crackles.
- Wheeze.
- Hypoxia (oxygen saturation ≤93% by pulse oximetry).

(III) Laboratory criteria

- CRP >3 mg/L on high sensitive testing.
- Serum interleukin-6 >2 ng/L.
- Serum amyloid-A >5 mg/L.
- Raised peripheral blood neutrophil % (age appropriate).

following combinations are considered the best to define an exacerbation:

- (Option-A) *One major* PLUS any *one laboratory criteria* positive [sensitivity 63%, specificity 94%,], OR
- (Option-B) *Two major* criteria positive (sensitivity 92.6%, specificity 75.3%), OR
- (Option-C) *One major* PLUS *any two minor* criteria positive (sensitivity 95%, specificity 75%).

(O'Grady and Grimwood, 2017)

Physical examination

Fatigue and lethargy can be prominent features in some patients and worsen with exacerbations. Crackles and less commonly wheezing may be heard on chest auscultation, but digital clubbing is now rarely present in patients with non-CF bronchiectasis ***(Hayes and Meyer, 2010)***.

Investigations

A) Radiological studies

- **Chest radiograph**

Chest X-ray (CXR) is usually the initial imaging study performed in patients with suspected bronchiectasis. However, a normal CXR does not exclude the presence of bronchiectasis. CXR findings in patients with bronchiectasis vary considerably,

but may raise a suspicion of bronchiectasis and trigger further definitive imaging. These findings include prominence of bronchial markings, rounded or cystic areas of increased radiance, parallel linear densities, tram-track opacities and lobar/lobular atelectasis. The presence of chronic pulmonary infiltrates on repeated CXR should also raise the suspicion of bronchiectasis ***(Perera and Screaton, 2011).***

- **High-resolution CT scan**

HRCT is more sensitive and remains the gold standard test for diagnosis of bronchiectasis. Addition of multiple detection computed tomography to HRCT further increases the diagnostic accuracy**.** Diagnostic features of CT scan include the absence of normal bronchi tapering toward distal airways and increase of the size of inner bronchial walls compared to adjacent arteries by more than 1–1.5 times in adults ***(Al-Jahdali, 2017)***.

A lower bronchoarterial ratio should be used in children. In young children (<5 years of age), the normal bronchoarterial ratio is around 0.5 and in older children (<18 years of age), the upper limit is<0.8 ***(Al-Jahdali, 2017).***