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BRONCHOSCOPY, BRONCHO-ALVEOLAR LAVAGE (BAL) AND TRANS BRONCHIAL LUNG BIOPSY (TBLB)

HISTORY

Bronchoscopy originated in 1897 when Gustav Kilian of Germany used rigid bronchoscope. Chevalier Jackson refined rigid bronchoscope and in 1970 Shigeta Ikeda used flexible bronchoscope

Indications of Bronchoscopy

Bronchoscopy is one of the most common invasive diagnostic & therapeutic procedures in pulmonology. Common indications are:

1. Diagnosis of lung cancer
2. Vocal cord paralysis
3. Occult malignancy (positive sputum cytology)
4. Diagnosis of diffuse lung disease
5. Diagnosis of pulmonary infections
6. Surveillance bronchoscopy for obliterative bronchiolitis in lung transplant patients

Pre-Procedure Workup

Spirometry should be done in patients with suspected COPD. Arterial blood gas analysis is required in severe COPD ($FEV_1 < 40\%$). Prophylactic antibiotics are not indicated except in patients who are asplenic, with heart valve prosthesis, or have a previous history of endocarditis. Bronchoscopy should be avoided within 6 weeks of myocardial infarction. Asthmatic patients should be given bronchodilator prior to the procedure. Clear fluids may be allowed 2 hours prior to the procedure. Patient should be kept nil per-oral for 4 hours after bronchoscopy.

Complications

In a recent retrospective study of 4000 procedures, no death were reported.

Major complications occurred in 0.5% and minor complications in 0.8%.

Major complications included respiratory depression, pneumonia, pneumothorax, cardio respiratory arrest, arrhythmias and pulmonary edema.

Minor complications encountered were vasovagal attack, fever, hemorrhage and airway obstruction.

Complications following TBLB include pneumothorax (1-5%) and hemorrhage (9%) especially in uremic and immunosuppressed patients. In view of low complication rate, hospitalization is not required for TBLB.

Complications of lidocaine (used for local analgesia) include seizures and cardiac depression. Caution should be used in patients with malignancies involving liver (recommended maximum dose 8.2 mg/kg).

Hypoxemia can occur in patients with compromised cardiopulmonary status. Hypoxia is more common if BAL is done. Oxygen supplementation is beneficial in patients with impaired lung function. Oxygen should be given through nasal cannulae at the rate of at least 2 lpm. In high risk hypoxemic patients requiring bronchoscopy and BAL, noninvasive ventilation via face mask can be used.

Monitoring by oximetry should be done if sedation is given or in patients with impaired lung function.

Arrhythmias occur commonly in patients who develop hypoxia (40% in patients with hypoxia). ECG monitoring is recommended in patients who have abnormal pre-operative ECG (in patients with severe cardiac disease) and if hypoxia is refractory to oxygen supplementation. Risk of arrhythmia is particularly high during the passage of bronchoscope through the vocal cords.

Fever may occur in bronchoscopy without BAL in 1.2%, with BAL in (10-30%) and after TBLB in 15%.

Myocardial ischemia is more common in patients over 60 years of age. Continuous ECG monitoring, oxygen supplementation to prevent hypoxia and adequate sedation should be used if ongoing ischemia is present.

Asthma: In a study of 216 patient asthmatic undergoing bronchoscopy 8% of patients developed bronchospasm. Lidocaine exacerbates bronchospasm. Preoperative bronchodilator is beneficial and should be used routinely

BAL

The earliest indication of BAL was therapeutic in the form of removing inspissated secretions in severe asthma. Later this technique was modified and

smaller volumes were used. For obtaining BAL the tip of bronchoscope is wedged in a peripheral small bronchus; either middle lobe/lingula or lower lobe bronchus. Segment is usually selected on the basis of Chest X-Ray abnormality. 20-60 ml of warm buffered saline is injected and gently aspirated. A return of 50-60% is expected in normal persons and lesser in diseased lung

Standardization of BAL

To reduce the problem of variability a standard procedure for BAL is recommended. Standard introduction volume is 100 ml in four equal input aliquots. Standard site of lavage is middle lobe of right lung. If the numbers of ciliated bronchial epithelial cells and squamous epithelial cells present in the BAL samples exceed 5% of the total BAL cells, the lavage sample may be unsatisfactory for alveolar composition.

Precautions

Coughing & trauma are kept to minimum to avoid contamination with blood & mucus. Pre-warmed saline helps in decreasing cough. Lowering aspiration pressure minimizes chances of trauma. Large introduction volume (>300 ml) increases risk of post lavage pyrexia.

Differential Diagnosis from BAL

Lymphocytic BAL is seen in granulomatous diseases, hypersensitivity pneumonitis and drug induced ILDs. Predominance of Neutrophils is seen in IPF, CT-ILD, asbestosis, ARDS and smokers. Haemorrhagic BAL is characteristic of cytotoxic medications like Bleomycin. BAL CD4/CD8 ratio can help in differentiating sarcoidosis from lymphoma and hypersensitivity pneumonitis. This ratio is lowest in lymphomas. In chronic sarcoidosis, BAL lymphocytes may be normal; neutrophils may be increased (usually without eosinophils). Some cases of IPF and ILD associated with Systemic Sclerosis may have increased lymphocytes.

BAL As Prognostic Indicator

IPF with increased numbers of lymphocytes in the BAL fluid, with or without granulocytes, are more likely to respond to steroids. Increased granulocytes without lymphocytes suggested a better responsiveness to cyclophosphamide than to prednisolone. BAL neutrophilia and/or eosinophilia is associated with more extensive disease and a poor prognosis. IPF with increased numbers of lymphocytes in the BAL fluid, with or without granulocytes, are more likely

to respond to steroids. In a study by Haslam et al, increased granulocytes without lymphocytes suggested a better responsiveness to cyclophosphamide than to prednisolone. BAL neutrophilia and/or eosinophilia is associated with more extensive disease and a poor prognosis.

BAL in pneumonia: 40-60% of CAP, HAP & VAP are without etiologic diagnosis. BAL is used in VAP, pneumonia in immuno-compromised and severe CAP. Sensitivity and specificity values of BAL in pneumonia are 72-93% and 65-100% respectively. Results of BAL can help in guiding change of therapy. A lower mortality was seen for patients with VAP who underwent bronchoscopy for BAL. Both groups had similar duration of ICU stay and mechanical ventilation.

In a study by Taylor et al on 1956 newly diagnosed HIV patients (30% of whom underwent bronchoscopy), *pneumocystis* was the most commonly detected organism. Bacteria isolated included *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas spp* and *Haemophilus influenzae*. Mycobacteria were isolates in 8% (most commonly *M. tuberculosis*) and viruses (mainly CMV) in 31%. Endobronchial Kaposi's sarcoma was detected in 15% (detection of HHV8 DNA in BAL is sensitive and specific for pulmonary involvement of Kaposi's sarcoma).

In a recent study, number of bronchoscopies in HIV are decreasing. This decrease correlates with the availability of anti retroviral drugs (era of HAART).

TBLB

TBLB is carried out for bilateral disease. Tip of bronchoscope is wedged into laterally placed peripheral segmental bronchus of lower lobe. Largest possible toothed biopsy forceps are passed. When forceps are seen out, they are opened and advanced till resistance is felt. Forceps are closed and withdrawn. An elastic tug followed by a feeling of 'give' is an indication of satisfactory biopsy. Additionally the lung tissue may be seen to coil backwards. Good piece is a pale fluffy specimen that floats.

Transbronchial lung biopsy in diffuse or peripherally located lung disease without endobronchial lesions is diagnostic in 72%. UIP, DIP, BOOP, pulmonary angitis and granulomatosis may not be diagnosed by TBLB.

For diagnosis of malignancy, endobronchial biopsy (EBBx) is preferred especially if the lesion is visible. In a visible tumor, in order to achieve a probability of

>90% of obtaining a positive malignant biopsy, at least 5 samples should be obtained. If bronchial biopsy is combined with bronchial washing and brushing, yield is increased to 87%. Trans Bronchial Needle Aspiration (TBNA) is more sensitive if submucosal infiltration is present. Otherwise yield is similar to forceps biopsy. It is helpful in friable masses which tend to bleed. TBNA can be used to sample hilar glands if they are adjacent to airways (yield: 38% if radiological evidence of gland enlargement, improved sensitivity if 22 gauge needle is used).

In sarcoidosis, granuloma are usually diffuse, so four samples are sufficient. EBBx should be obtained if the lesion is visible. In Stage II and III sarcoidosis, yield of TBLB is upto 75% while in stage I sarcoidosis, yield is up to 58%.

Pulmonary alveolar proteinosis is usually diagnosed by BAL and TBLB (characteristic PAS positive material in most).

In lymphangitis carcinomatosa, yield is 66%.

In IPF, histology of the disease is sufficiently variable that the larger sampling capability of open lung biopsy is required. Bronchoscopy is certainly not definitive and yield is only upto 27%.

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PULMONARY VASCULITIS

(Part 2 – Vasculitides Other Than Wegener’s Granulomatosis)

2. MICROSCOPIC POLYANGIITIS

It is defined as “*Necrotizing vasculitis with few or no immune deposits affecting small vessels (i.e., capillaries, venules or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*” Key to the Chapel Hill definition is the requirement for few or no immune deposits.

The current definition of classic PAN allows necrotizing inflammation of small and medium arteries, but not of the smallest vessels. The incidence of Microscopic polyangiitis (MPA) is 3-9 patients per million per year with a slight male preponderance. The peak incidence is in the age group of 55 to 74 years. Associations exist with

1. Silica
2. Solvent exposure
3. Drugs like propylthiouracil, hydralazine and penicillamine

Majority of patients with MPA will have ANCA positivity which may be either MPO-ANCA or PR3-ANCA. Patients have a prodromal illness of fever (45%), weight loss (35–60%), myalgia (40%), and arthralgia (30–60%) which precede diagnosis by up to 2 years. Purpuric rash is seen in 30% at diagnosis (leukocytoclastic vasculitis). Renal disease is usually in the form of focal and segmental glomerulo-nephritis (seen in more than 90%, mostly pauci-immune and of varying ages and chronicity).

Pulmonary involvement in MPA most often presents as one or more of the following:

1. Alveolar hemorrhage
2. Pleurisy and pleural effusions
3. Pulmonary fibrosis

Alveolar hemorrhage is seen in up to 30% of patients. Pulmonary fibrosis is an increasingly recognized feature of MPA that is predominantly associated with MPO-ANCA and is a poor prognostic feature. Gastrointestinal features are more common while CNS and ocular involvement is less common than WG.

MPA and WG are both defined as necrotizing vasculitis affecting the small vessels, commonly with glomerulonephritis. Diagnosis of MPA is based on clinical, histological, and serological evidence of a systemic small vessel vasculitis in the absence of marked upper respiratory tract disease. However, evidence is emerging that ANCA specificity does affect course and outcome of the disease.

The 1 and 5 year survival rates are 84% and 76% respectively. Survival was lower in those patients with end stage renal disease (ESRD) being 64% and 53% at 1 and 5 years respectively. Approximately 45% of patients presenting with a creatinine of 5.4 mg/ dl or more go on to ESRD.

Are WG and MPA the same disease or different diseases?

Splitters	Lumpers
Renal lesions seem to depend on the disease (and ANCA type)	Therapy is the same
MPA presents with more indolent lesions chronicity decreases response/ worsens prognosis	Both WG and MPA can be MPO-ANCA positive
Prognosis differs exist	Overlap syndromes exist
Outcome in tendency to relapse differs	

Table 1: Differences and similarities between WG and MPA

3. CHURG-STRAUSS SYNDROME

It has been defined as “*Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia*”

Lanham’s criteria:

- i. Asthma
- ii. Peak peripheral blood AEC > 1.5 x 10⁶/cc
- iii. Systemic vasculitis involving 2 or more extra-pulmonary organs

ARA criteria (requires 4 of the following six findings):

- i. Asthma
- ii. Eosinophilia >10%
- iii. Neuropathy
- iv. Non-fixed pulmonary infiltrates
- v. PNS abnormality
- vi. Extra vascular eosinophils

Three distinct phases are seen:

Phase 1: (prodromal): Long history of rhinitis with nasal polyps and late onset asthma

Phase 2: Increasing peripheral blood and tissue eosinophilia with a waxing and waning course

Phase 3: Systemic vasculitis

Not all patients express a sequential staging of the illness and may present with only one or two manifestations. Respiratory symptoms are common presenting symptoms. Thoracic involvement is seen in all patients over the entire course. Vasculitic process with a varying degree of eosinophilic infiltration cause infiltrates.

4. BEHCET'S DISEASE

Thoracic involvement occurs in 25% and pulmonary manifestations in 5% (1% to 18%) of patients with Behcet's Disease (BD). Data from Japanese autopsy registry show involvement in around 75% of cases

Pulmonary involvement can be classified into 3 groups

- (1) Pulmonary artery aneurysm (PAA)
- (2) Pulmonary parenchymal changes
- (3) Miscellaneous (including pulmonary arterial occlusion, pleural effusion and pulmonary obstructive airway disease)

The pulmonary arteries are the 2nd most common site of involvement, preceded by the aorta. The mean age of presentation is 30.1 years and males form 89% of these patients. Hemoptysis is the predominant symptom. This is due to

1. Rupture of an aneurysm with erosion into a bronchus
2. Development of in situ thrombosis

The mean interval between the diagnosis of BD and the manifestation of PAA is approximately 5.5 years. The aneurysms may be single or multiple, unilateral or bilateral and measure 1 to 7 cm in diameter. Aneurysm formation is more common on the right (59%) and in the lobar arteries (54%). The right lower lobar pulmonary artery is commonly affected (35%) followed by the left lower lobar and main pulmonary arteries. Venous thrombosis or subcutaneous thrombophlebitis is very common (78%). PAA was the only accepted manifestation of BD in two cases. Though deep venous thrombosis (DVT) of lower limbs frequently accompanies pulmonary artery aneurysms, pulmonary thrombo-embolism (PTE) is very rare in BD. Assessment is with CT and MRI. Conventional angiography is not recommended. 1 and 5 year survival rates are 57% and 39% respectively. PAA have a varied course. Hemorrhage can result in focal, multifocal, or diffuse airspace consolidation.

SVC thrombosis is a more prevalent finding than arteritis. Pseudo-aneurysms of the aortic arch as well as the subclavian and coronaries have been described in BD. Mediastinal mass, mediastinitis and chyloptysis have been seen. Cardiac intramural thrombosis is a rare but fatal complication.

Outcomes in BD with PAA

BD patients have a bad outcome with anticoagulation. The patients treated with embolization with or without immunosuppression have a better prognosis. Patients who underwent surgery with or without immunosuppressive therapy had the highest mortality rate. Aneurysmorrhaphy, lobectomy, bilobectomy, pleurectomy, aneurysmectomy and pneumonectomy are procedures that have been used in BD.

5. PULMONARY MANIFESTATIONS OF TAKAYASU'S ARTERITIS

The diagnosis of Takayasu's is clinical and aided by the presence of features outlined by Ishikawa's criteria (or Sharma and Jain's criteria in Indians). Disease occurs in two stages: 'pre-pulseless stage' and 'pulseless stage'. 80% of patients are between 11 and 30 years. Diminished or absent pulses are seen in 84–96% with claudication and blood pressure (BP) discrepancies. Vascular bruits are seen in 80–94% and commonly involve the carotids, subclavian and abdominal vessels. Hypertension is seen in 33–83% of patients while renal artery stenosis (RAS) is seen in 28–75% of patients. Takayasu's retinopathy is seen in

up to 37% of patients. Aortic regurgitation (AR) occurs in 20–24%. Congestive cardiac failure is associated with presence of hypertension, AR and dilated cardiomyopathy. Pulmonary artery involvement is seen in 14–100% of patients. Oligoemic lung fields on plain chest radiograph occur in around one third of cases. The survival rate at 5 years after diagnosis was 80.3% after which the survival curve flattened. Current therapy involves steroids for patients in the inflammatory stage and angioplasties in the stenotic phase. Second line therapies after failure of steroids (approximately half the cases) include methotrexate and azathioprine. Pulmonary artery disease shows little correlation with systemic disease.

6. NECROTIZING SARCOID GRANULOMATOSIS

Pulmonary vascular involvement is common in necrotizing sarcoid granulomatosis (NSG). NSG usually involves small and medium sized muscular arteries and veins. Though considered a variant of sarcoidosis, important differences exist. Patients with NSG rarely have hilar adenopathy. The histopathology of NSG includes granulomatous pneumonitis, “sarcoid-like” granulomas and vasculitis. Widespread regions of coagulative necrosis are the key to histological differentiation of NSG from sarcoid. NSG requires aggressive immunosuppressants. Inadequate treatment is associated with a high mortality rate. Failure to achieve a rapid response from high-dose corticosteroid therapy mandates the addition of a cytotoxic agent.

7. FUNGAL PULMONARY VASCULITIS

Necropsy data on the etiology of fungal pulmonary vasculitis in 23 patients from the author’s institute showed aspergillosis and mucormycosis in 19 and 4 patients respectively. Almost half of these patients had renal failure. Suspicion of a fungal lesion in a febrile patient with nodular lung lesions should occur in the presence of:

1. Prolonged therapy with broad spectrum antibiotics
2. Administration of corticosteroids
3. Renal failure
4. Leukopenia
5. Diabetes mellitus

8. DIFFUSE ALVEOLAR HEMORRHAGE

A detailed description of this entity is beyond the scope of this article. However, broadly it can be approached

as occurring with or without pulmonary capillaritis (see Table 2)

Diffuse Alveolar Hemorrhage without Capillaritis	Diffuse Alveolar Hemorrhage with Capillaritis
Inhalational toxins	
Mitral stenosis	Primary Vasculitis
Severe coagulopathy	ANCA-associated vasculitis
Iatrogenic anticoagulation	Wegener’s granulomatosis
Renal failure polyangiitis	Microscopic
Thrombocytopenia syndrome	Churg-Strauss
Other acquired or autoimmune coagulopathies	Behcet’s disease
Infections	Henoch-Schonlein purpura
Endocarditis	Isolated Pauci-immune pulmonary capillaritis
HIV-assoc	
Neoplasms	Secondary Vasculitis
Lymphangioliomyomatosis	Collagen vascular diseases
Tuberous sclerosis	Systemic lupus erythematosus
Pulmonary veno-occlusive disease	Rheumatoid arthritis
Pulmonary capillary hemangiomatosis	Mixed connective tissue disorder
Diffuse alveolar damage or acute lung injury	Polymyositis
Anti-glomerular basement membrane disease	Primary or secondary APLA
Systemic lupus erythematosus	Drug-induced vasculitis
Idiopathic pulmonary hemosiderosis	
Drugs	

Table 2: Classification of diffuse alveolar hemorrhage

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JOURNAL CLUB

Salpeter SR., Buckley NS, Ormiston TM, Salpeter EE. **Meta-Analysis: Effect of Long-Acting β -Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths.** *Ann Intern Med* 2006; 144: 904-912.

Background: Long-acting β -agonists may increase the risk for fatal and nonfatal asthma exacerbations.

Purpose: To assess the risk for severe, life-threatening, or fatal asthma exacerbations associated with long-acting β -agonists.

Data Sources: English- and non-English-language

searches of MEDLINE, EMBASE, and Cochrane databases; the U.S. Food and Drug Administration Web site; and references of selected reviews through December 2005.

Study Selection: Randomized, placebo-controlled trials that lasted at least 3 months and evaluated long-acting β -agonist use in patients with asthma. All trials allowed the use of as-needed short acting β -agonists.

Data Extraction: Outcomes measured were Peto odds ratio (OR) and risk difference of severe

exacerbations requiring hospitalization, life-threatening exacerbations requiring intubation and ventilation, and asthma-related deaths. The OR for asthma-related deaths was obtained from the Salmeterol Multi-center Asthma Research Trial (SMART).

Data Synthesis: Pooled results from 19 trials with 33,826 participants found that long-acting β -agonists increased exacerbations requiring hospitalization (OR, 2.6 [95% CI, 1.6 to 4.3]) and life threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]) compared with placebo. Hospitalizations were statistically significantly increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and formoterol (OR, 3.2 [CI, 1.7 to 6.0]) and in children (OR, 3.9 [CI, 1.7 to 8.8]) and adults (OR, 2.0 [CI, 1.1 to 3.9]). The absolute increase in hospitalization was 0.7% (CI, 0.1% to 1.3%) over 6 months. The risk for asthma-related deaths was increased (OR, 3.5 [CI, 1.3 to 9.3]), with a pooled risk difference of 0.07% (CI, 0.01% to 0.1%).

Limitations: The small number of deaths limited the reliability in assessing this risk, and 28 studies did not report information on the outcomes of interest.

Conclusions: Long-acting β -agonists have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma related deaths.

Summary

This is a meta-analysis of 19 randomized, controlled clinical trials involving 33,826 asthmatic patients. The results suggest that patients receiving long-acting β -agonists (LABA) are 2.5 times more likely to be hospitalized and about 2 times more likely to have life-threatening asthma attacks than those not receiving the drug. Also, the asthma-related deaths occurred about 3.5 times more in the LABA group.

Limitations

The limitations of the study include the inability to address the possible roles of disease severity, co-

treatments especially the dose and duration of inhaled corticosteroids (ICS), and compliance issues related to prescribed medications. Racial differences might also have contributed to the observed results and the study has not addressed this issue. Retrospective studies have suggested that polymorphism at the 16th amino acid residue of the β 2-adrenergic receptor is associated with adverse effects of β agonist use in asthmatic patients. In one prospective study, patients were stratified by genotype, and it was found that those with the Arg/Arg genotype improved when β agonist therapy was withdrawn and replaced with ipratropium bromide, whereas in those with the Gly/Gly genotype, they were better with regular β agonist therapy than when it was withdrawn. Overall the number of deaths was low and the assessment by the current study of the risk for death is unreliable.

Implications for day-to-day practice

1. Symptomatic treatment of asthma with LABA carries some but significant risk of severe asthma exacerbations and hospitalizations. Hence it is advisable to use ICS as the first line of control of asthma.
2. The use of LABA should be advocated only if the asthma is inadequately controlled despite maximal doses of ICS.
3. The use of LABA as a single agent for the control of asthma should be abandoned.

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