Division of Respiratory Medicine
University Health Network/
Mount Sinai Hospital

RESIDENT’S HANDBOOK

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OF
TORONTO

4th Edition
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Preface to the 1st edition

This first edition of the Respirology Resident Handbook has been prepared with the intention of providing rotating trainees with a quick source of clinically useful information while on their respirology rotation. This handbook has been designed with ease of use in mind. Firstly, it is small enough to be carried in a coat pocket. Secondly, the topics have been arranged in alphabetical order, with headings at the top of each page to facilitate quick reference in the office or on wards.

It is not meant to be a definitive text but rather a collection of approaches to common problems and “pearls”. Reading around subjects from any standard textbook in Internal Medicine or Respirology or from the medical literature is still essential. Nonetheless, the information contained in this handbook will allow residents to get a concise overview on many topics. Emphasis has been placed on the approach to common problems and to those areas with which the rotating resident is least likely to be familiar.

It is my sincere hope that this handbook helps residents to make their time on the Respirology service as rewarding as possible. Suggestions regarding content are always welcome.

I would like to thank Dr. Stephen Lapinsky for his helpful suggestions in the preparation of the clinical material. Particularly, Dr. Lapinsky has asked that all criticism or requests for clarification of the material be directed at him, day or night.

Richard Leung, Respirology Fellow, July 1999

Preface to the 2nd edition

The practice of respiratory medicine is evolving non-stop. While the principles of disease recognition and management espoused in the first edition of “The Handbook” remains sound, some sections have come due for updating. Featured in this second edition are current recommendations for the treatment of community-acquired pneumonia and asthma. A new section on the staging and prognosis of lung cancer has been added, as has a brief section on the peri-operative management of the patient with respiratory disease.

I hope that the second edition manages to live up to the deserved notoriety of the first. As usual Dr. Lapinsky takes full responsibility for its content and requests that he be paged with any questions, day or night.

Michael Miletin, Respirology Fellow, June 2002
Preface to the 3rd edition

Three years after the previous edition of the Respirology Handbook we decided to update the content and expand the topics covered in the Handbook to include all areas of Respirology with special interests at various hospitals in the University of Toronto. To accomplish this we have included multiple new sections including neuromuscular diseases and their impacts on respiratory function, Thromboembolic diseases, Cystic Fibrosis, Hereditary Hemorrhagic Telangetasia (HHT), Mycobacterial infections (Mycobacterium TB and non-Tuberculous Mycobacterial infections), a section on Pulmonary Function Testing and multiple new Practice guidelines.

We are grateful for the help of various staff physicians who reviewed and edited their corresponding topics. Dr. Niroumand oversaw the compilation of this edition of the Handbook which will be distributed in all hospitals of University of Toronto to all trainees rotating Respirology division. We hope to have met the expectations of all with respect to the content and relevance of the material.

Kamyar Soghrati & John Thenganatt, Respirology Fellows, June 2005

Preface to the 4th Edition

This Respirology Handbook represents the fourth update of a practical guide to Pulmonary Medicine at the University of Toronto. It is not intended to be a comprehensive textbook, but rather a quick reference in clinic and for consults on the ward. The guide was originally written in 1999 by Richard Leung and has been expanded and revised by many Pulmonary Fellows over the years. In this edition, several new sections have been added and previous ones updated to conform to current practice guidelines. We tried hard to keep the book concise, in spite of temptation to expand it.

We would like to thank Dr. Thenganatt who oversaw the compilation of this edition. It will be distributed in all hospitals at the University of Toronto to trainees rotating through the Respirology divisions.

Matthew Heffer, Ambrose Lau, Kevin Lumb, Harvey Wong and Jane Yuan, Respirology Fellows, June 2010
INDEX

ASTHMA 1
  General Considerations/Diagnosis 1
  Overview of Management 2
  Drug Therapy 4
    Inhaled Corticosteroids 5
    Long-acting Beta Agonists 6
    Anti-leukotriene Agents 7
    Theophylline 7
    Oral Corticosteroids 8
    Short-acting Beta Agonists 8
    Mast Cell Stabilizing Agents 8
    Anti-IgE Therapy 9
  The Poorly Controlled Asthmatic 10
  Severe Exacerbations of Asthma 11
  Criteria for Admissions 13
  Medical Therapy for Severe Exacerbations 14

COPD 16
  General Considerations 16
  Epidemiology of COPD in Canada 16
  Pathophysiology 16
  Clinical Assessment 17
  Assessment of Severity/Prognosis 18
  COPD vs Asthma 20
  Management of COPD 20
  Non-Pharmacologic Therapy 20
  Pharmacologic Treatment 23
  Exacerbations 25

COUGH 27
  General Considerations 27
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Subsets and Treatment Options</td>
<td>68</td>
</tr>
<tr>
<td>Other Treatment Considerations</td>
<td>69</td>
</tr>
<tr>
<td><strong>HOSPITAL ACQUIRED PNEUMONIA</strong></td>
<td>71</td>
</tr>
<tr>
<td>Definitions</td>
<td>71</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>72</td>
</tr>
<tr>
<td>Treatment</td>
<td>73</td>
</tr>
<tr>
<td><strong>NON-RESOLVING PNEUMONIA</strong></td>
<td>76</td>
</tr>
<tr>
<td>Differential Diagnosis of Non-resolving Air Space Pattern</td>
<td>76</td>
</tr>
<tr>
<td><strong>TUBERCULOSIS</strong></td>
<td>79</td>
</tr>
<tr>
<td>Spectrum of infection and disease</td>
<td>79</td>
</tr>
<tr>
<td>Transmission</td>
<td>81</td>
</tr>
<tr>
<td>Diagnostic Tests</td>
<td>82</td>
</tr>
<tr>
<td>Diagnostic Approach</td>
<td>83</td>
</tr>
<tr>
<td>Treatment of Active Tb</td>
<td>85</td>
</tr>
<tr>
<td>Special Situations</td>
<td>86</td>
</tr>
<tr>
<td>Drug Side Effects</td>
<td>88</td>
</tr>
<tr>
<td>Treatment of Latent TB Infections</td>
<td>89</td>
</tr>
<tr>
<td><strong>LUNG CANCER</strong></td>
<td>91</td>
</tr>
<tr>
<td>General Considerations</td>
<td>91</td>
</tr>
<tr>
<td>Pathology</td>
<td>91</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>92</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>92</td>
</tr>
<tr>
<td>TNM Staging System Table</td>
<td>95</td>
</tr>
<tr>
<td>Approach to Staging</td>
<td>96</td>
</tr>
<tr>
<td>Treatment of Non-small Cell Lung Cancer</td>
<td>98</td>
</tr>
<tr>
<td>Small Cell Lung Cancer</td>
<td>99</td>
</tr>
<tr>
<td>Staging of Small Cell Carcinoma</td>
<td>99</td>
</tr>
<tr>
<td>Treatment of Small Cell Carcinoma</td>
<td>100</td>
</tr>
<tr>
<td><strong>THE SOLITARY PULMONARY NODULE</strong></td>
<td>101</td>
</tr>
<tr>
<td>Background</td>
<td>101</td>
</tr>
<tr>
<td>Predictors of Malignancy</td>
<td>102</td>
</tr>
<tr>
<td>Diagnostic Approach</td>
<td>103</td>
</tr>
<tr>
<td>Investigations</td>
<td>104</td>
</tr>
<tr>
<td><strong>HEMOPTYSIS</strong></td>
<td>105</td>
</tr>
<tr>
<td>Background</td>
<td>105</td>
</tr>
<tr>
<td>Approach</td>
<td>105</td>
</tr>
<tr>
<td>Differential Diagnosis</td>
<td>106</td>
</tr>
<tr>
<td>Role of Bronchoscopy</td>
<td>107</td>
</tr>
<tr>
<td>Massive Hemoptysis</td>
<td>108</td>
</tr>
</tbody>
</table>
Causes of Daytime Hypersomnolence 146
Sleep History 147
Polysomnography - Basics 148
Management of OSA 149

<table>
<thead>
<tr>
<th>NEUROMUSCULAR DISEASES</th>
<th>152</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of Breathing</td>
<td>152</td>
</tr>
<tr>
<td>Muscles of Respiration</td>
<td>153</td>
</tr>
<tr>
<td>Approach to Neuromuscular Disease and Respiratory Failure</td>
<td>153</td>
</tr>
<tr>
<td>Evaluation of Respiratory Strength</td>
<td>155</td>
</tr>
<tr>
<td>Treatment</td>
<td>156</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRONCHOSCOPY</th>
<th>157</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>157</td>
</tr>
<tr>
<td>Contraindications</td>
<td>158</td>
</tr>
<tr>
<td>Complications</td>
<td>158</td>
</tr>
<tr>
<td>Booking a Bronchoscopy</td>
<td>159</td>
</tr>
<tr>
<td>Interventional Bronchoscopy</td>
<td>160</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PULMONARY FUNCTION TESTING</th>
<th>164</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>APPENDIX I: Inhaled Medications</th>
<th>168</th>
</tr>
</thead>
</table>

| APPENDIX II: Inhaler Technique | 170 |
Asthma is characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli. Inflammation and its resultant effects on airway structure are considered the main mechanisms leading to the development and maintenance of asthma (Can Respir J, June 2004). In general some objective measurement of one or both aspects of the definition should be satisfied before making a diagnosis of asthma:

**Diagnosis:**
1) **variable airflow limitation** – assessed by PFT’s with a bronchodilator response
2) **airway hyperresponsiveness** – assessed by bronchoprovocational challenge (e.g. methacholine)

### Pulmonary function tests
1. Bronchodilator response in FEV1 of **>12% and >200cc** in response to Ventolin
2. Improvement in Peak Flow by 20% (min 60l/min) post bronchodilator
3. **Methacholine challenge testing** – increasing concentrations of inhaled methacholine irritates the airways and triggers a bronchospastic response. The concentration at which the patient’s FEV1 is decreased by 20% or more is called the PC20. The PC20 of an asthmatic is significantly lower than that of the general population. Asthma can be ruled out if there is no decrease of more than 20% in FEV1 even at the highest concentration of 16mg/mL.
OVERVIEW OF MANAGEMENT

1. The successful management of patients with asthma relies upon four components:
   - Routine monitoring of symptoms and lung function
   - Controlling factors contributing to asthma severity
   - Pharmacological therapy
   - Patient education

2. Monitoring of asthma with peak flow meters can be used to guide therapy. Many patients who report an absence of symptoms continue to have persistent airflow limitation by objective testing. Patients can be taught to monitor their own symptoms and peak flows, and provided with instructions regarding what steps to take in case of deterioration. In the future, other measurements of airway inflammation, including sputum eosinophilia and exhaled nitric oxide analysis, may play a role in monitoring.

3. Environmental trigger factors must always be addressed. The presence of cigarette smoke, pets and feather pillows or bedding are some of the easiest issues to address. Reducing the humidity in the patient’s home may also be beneficial in reducing contamination by moulds or dust mites. Symptoms suggestive of occupational asthma should be sought.

4. Patient Education about asthma is an important aspect of management. Patients must learn how to monitor symptoms and pulmonary function, avoid or decrease exposure to triggers, and how to use their inhalers. They must also understand what to do in the event of an emergency or in case of a deteriorating condition.
**TABLE 3**

**Asthma control criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Daytime symptoms less than four days per week</td>
</tr>
<tr>
<td>Night-time symptoms less than one night per week</td>
</tr>
<tr>
<td>Normal physical activity</td>
</tr>
<tr>
<td>Mild, infrequent exacerbations</td>
</tr>
<tr>
<td>No absenteeism due to asthma</td>
</tr>
<tr>
<td>Fewer than four doses per week of a fast-acting beta₂-agonist needed*</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 s or peak expiratory flow at 90% of their personal best or greater</td>
</tr>
<tr>
<td>Diurnal variability in peak expiratory flow of less than 10% to 15%</td>
</tr>
</tbody>
</table>

Data from reference 4. *Apart from one dose/day before exercise*

**Figure:** Continuum of Asthma management (Adult Asthma Consensus Guidelines Update 2003)
DRUG THERAPY

- The mainstay of asthma therapy is treatment with **inhaled steroids**. Steroids allow the asthmatic to achieve better long-term control due to the effects of steroids on reducing airway inflammation.

- **Short-acting beta-agonists** (e.g. Ventolin) should be used for

---

TABLE 2

**Overall management of asthma**

<table>
<thead>
<tr>
<th>Suspect asthma</th>
<th>Make differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm the diagnosis and assess initial severity</td>
<td>Evaluate symptoms and measure pulmonary function tests (spirometry or peak expiratory flows)</td>
</tr>
<tr>
<td>Determine possible triggers and inducers of asthma</td>
<td>Perform a questionnaire, allergy tests or other tests (to assess environment, workplace, etc)</td>
</tr>
<tr>
<td>Initiate treatment</td>
<td>Prescribe the medication required to achieve asthma control; treat associated conditions (e.g., rhinitis)</td>
</tr>
<tr>
<td>Initiate education</td>
<td>Provide basic elements and, if possible, refer patients to an asthma educator</td>
</tr>
<tr>
<td>Determine the best results achievable</td>
<td>Check asthma control criteria, including pulmonary function</td>
</tr>
<tr>
<td>Determine the minimum medication needed to keep the asthma controlled</td>
<td>Progressively reduce the medication while checking asthma control</td>
</tr>
<tr>
<td>Devise an action plan for the management of exacerbations</td>
<td>Provide a written document or ask an asthma educator to do so</td>
</tr>
<tr>
<td>Ensure regular follow-up</td>
<td>Regularly check control criteria and pulmonary function</td>
</tr>
</tbody>
</table>

*Data from reference 4*
acute relief of symptoms on a PRN basis.

• The majority of patients will be well controlled with a combination of these two agents. Additional drugs must nevertheless often be utilized to achieve adequate control.

• In a minority of patients, with very mild and intermittent symptoms, a beta-agonist alone may be sufficient therapy.

1. **Inhaled corticosteroids**
   
   – Should be started when persistent symptoms develop:
     
     – Use of bronchodilators >1/wk for relief of symptoms
     – Nocturnal awakening 1 q 2 wks
     – Fluctuations in PEFR of >20%

     – Most asthmatics should be maintained on a dose of 400-1000 mcg/day of beclomethasone (Becloforte) or budesonide (Pulmicort). Higher doses up to 2000 mcg/day may be warranted in severe asthmatics. Fluticasone (Flovent) is considered to be about twice as potent as beclomethasone and is usually prescribed at a dose of 250-500 mcg/day. Severe asthmatics may require up to 1000 mcg/day.

     – Local side effects of inhaled steroid include hoarseness and oral candidiasis. The latter can be prevented by rinsing of the mouth after inhalation. Ciclesonide is a prodrug which is activated in the lung, not in the pharynx, and therefore reduces oral candidiasis.

     – Thinning of the skin and easy bruising is often seen at higher doses, and osteoporosis risk may also be increased at doses exceeding 1000 mcg/day of beclomethasone or 500 mcg/day of fluticasone.
– Every effort should be made to reduce the dose of inhaled steroids to find the lowest possible dose with good asthma control.

– In poorly controlled asthma, despite ICSs, addition of LABA has been found to be better than doubling the dose of ICS

– Insufficient evidence of additional benefit for initial use of combination therapy in mild disease not previously treated with ICSs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose (µg)</th>
<th>Medium Daily Dose (µg)</th>
<th>High Daily Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>200-500</td>
<td>&gt;500-1000</td>
<td>&gt;1000-2000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>200-400</td>
<td>&gt;400-800</td>
<td>&gt;800-1600</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>80-160</td>
<td>&gt;160-320</td>
<td>&gt;320-1280</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>100-250</td>
<td>&gt;250-500</td>
<td>&gt;500-1000</td>
</tr>
</tbody>
</table>

Adapted from GINA 2008

2. Long-acting beta agonists (LABAs)
– Include salmeterol (Serevent) and formoterol (Oxeze). They are generally used in patients who remain poorly controlled despite adequate doses of inhaled steroids. In combination with inhaled corticosteroids, they allow lower steroid dosing and fewer exacerbations.

– When used alone, are less effective than inhaled steroids (NEJM 97, AJRCCM 97)

– They are good choices for nocturnal asthma.
– Salmeterol should never be used as a “rescue” medication and this should be made clear to patients. Formoterol may have an emerging role as a rescue medication, as it has a more rapid onset of action and can be used as a part of the SMART strategy (Symbicort as Maintenance And Reliever Therapy).

– Should **never** be used as monotherapy.

3. **Anti-leukotriene agents**
– Montelukast (Accolate) and zafirlukast (Singulair) are leukotriene receptor blockers.

– These drugs exert anti-inflammatory effects but are less potent than inhaled steroids. They may be valuable in certain circumstances:
  i. patients who are poorly controlled despite adequate doses of inhaled steroids and LABAs
  ii. patients unable to manage steroid inhalers
  iii. patients with a strong atopic history
  iv. patients with exercise-induced asthma
  v. aspirin-sensitive asthma

– Their chief advantage is the fact that they are oral medications, which may result in improved compliance.

– They are inferior to LABAs as add-on therapy to inhaled corticosteroids.

– For patients who cannot or will not use ICSs, LTRAs are alternatives (Level 1), however as monotherapy are less effective than ICS.

4. **Theophylline**
– A weak bronchodilator but there is some recent evidence that it may exert some anti-inflammatory effects as well.
Like long-acting beta agonists, it is mainly used in patients who remain poorly controlled despite adequate doses of inhaled steroids.

The main advantage to theophylline is that it is an oral medication. Disadvantages include its many side effects including GI upset and CNS effects; at toxic doses it can cause seizures or cardiac arrhythmias.

May be used as third therapeutic option (level 2).

5. Oral corticosteroids
   - A two-week course of oral prednisone (e.g., 40mg/day with or without taper) is indicated in moderate to severe exacerbations of asthma.
   - A very small minority of asthmatics may require chronic oral steroid therapy.

6. Short-acting beta agonists
   - These agents are the mainstay of therapy for the acute relief of symptomatic bronchospasm. Agents include salbutamol (Ventolin) and terbutaline (Bricanyl).
   - They should be prescribed on a PRN basis only.
   - A patient’s need for beta-agonist more than 3x/weekly indicates that control of airway inflammation is not optimal.
   - There is some evidence that increased use of inhaled beta-agonists may be associated with excess mortality.
   - Useful in patients with mild intermittent symptoms or in whom triggering can be predicted (e.g., exercise-induced in which
case it should be used 10 minutes prior to exposure)

7. Mast cell stabilizing agents
   – Cromolyn (Intal®) and nedocromi (Tilade®) can be used in exercise-induced bronchoconstriction.
   – Can have additive effect when used in combination with beta agonists.
   – Effective when used prior to exposure but not as “rescue” when symptoms have developed.
   – Less effective than inhaled steroids.

8. Anti-IgE Therapy
   – IgE plays a key role in the pathogenesis of Type 1 hypersensitivity reactions, including allergic asthma.
   – Omalizumab is a humanized monoclonal antibody designed to bind to IgE at its Cε3 domain and forms soluble immune complexes that are cleared by the reticuloendothelial system, thus reducing the amount of free IgE available.
   – Very expensive; may be covered by some private drug plans.
   – Criteria for the use of omalizumab include the following:
     o Age ≥12 years
     o Positive skin test or in vitro reactivity to ≥ 1 perennial aeroallergen
     o Baseline IgE 30-700 U/ml
     o Weight 20-150kg
     o Calculated omalizumab dose < 750mg
     o Severe or inadequately treated asthma as defined by frequent exacerbations and/or the need for daily oral corticosteroids despite appropriate environmental control, smoking cessation (as needed), patient education and consistent therapy with inhaled
corticosteroid at a minimal daily dose of 500µg fluticasone or equivalent plus adjunctive therapy.
(Chapman et al, CRJ 2006)

THE POORLY CONTROLLED ASTHMATIC

Asthmatic patients who continue to be poorly controlled despite what seems to be an adequate therapeutic regimen pose a difficult problem. Long-term use of oral prednisone is one option but is associated with all the usual adverse effects of chronic steroid use. It is worthwhile reviewing the patient’s case in depth to look for other factors contributing to poor control. Many of these cases can be “solved” by taking a thorough history.

Causes of Poor Asthma Control

1. Poor patient compliance – Sometimes the lack of compliance is deliberate; more often, it is not. Many patients confuse their medications and forget that they are supposed to take their inhaled steroid every day, regardless of symptoms. Others do not like carrying their inhalers with them when they are out of the house, particularly if they use an aero-chamber.

2. Poor inhaler technique – A review of the patient’s inhaler technique (see Appendix II) should be routine with every visit, particularly if control has been poor.

3. Environmental factors – Smoking and pets are the most common culprits, but a detailed history should be taken with descriptions of the home and work environment.

4. Drugs – Medications that worsen asthma include salicylates and beta-blockers. Salicylates must be asked about specifically because many patients do not consider aspirin to be a medication. The same applies to beta-blocker eye drops.
5. **Comorbid disease** – Those that worsen asthma include gastroesophageal reflux disease (GERD), sinusitis, allergies, and congestive heart failure (“cardiac asthma”).

6. **Complications of asthma** – These include allergic bronchopulmonary aspergillosis (ABPA), Churg-Strauss syndrome and chronic eosinophilic pneumonia.

7. **Psychosocial factors** – Psychosocial factors, stresses and a poor home environment can lead to deterioration of asthma control through unclear mechanisms.

8. **Wrong diagnosis** – Is it absolutely certain that the patient has asthma? Some conditions are frequently misdiagnosed as asthma, among them vocal cord dysfunction (“pseudo-asthma”), COPD, upper airway obstruction including subglottic stenosis and airway tumours.

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**SEVERE EXACERBATIONS OF ASTHMA**

**Assessment of Disease Severity**

The first step in the management of a life-threatening exacerbation of asthma is identifying it as such. The majority of asthmatics who present to the emergency room are in no danger of death. A swift determination of the severity of the attack and the risk of deterioration is crucial.

**History**

Predictors of subsequent deterioration include:

- a past history of severe attack requiring intubation
- symptoms of long duration
- poor response to intensive outpatient therapy (e.g. already on prednisone)
- sleep deprivation

**Physical examination**

The general appearance of the patient is the best guide to severity. Worrisome signs include:
- altered level of consciousness
- sitting up
- inability to speak
- diaphoresis
- severe respiratory distress with accessory muscle use and abdominal paradox
- a “quiet chest”. Chest auscultation commonly reveals high-pitched polyphonic wheezes; beware of the patient with a “quiet chest” in whom airflow may have diminished to the point that it cannot even generate a wheeze.
- **Pulsus paradoxus** indicates the presence of wide intrathoracic pressure swings and indicates a severe attack. Note that as the patient fatigues, respiratory muscle strength may be insufficient to generate a pulsus paradoxus, so absence of this sign does not mean that the attack is a mild one.

**Peak flows** are an objective measure of disease severity. A peak flow reading less than 30-50% of the patient’s previous best or less than 120 L/min indicates a severe exacerbation. Failure of these values to improve over the next 2-4 hours is even more ominous.

**Arterial blood gases** have little role in mild episodes but are useful in severe attacks. Asthmatic patients in the midst of a severe attack will typically be hypocapnic. Hypercapnia (or even normocapnia) is an ominous sign indicating respiratory muscle fatigue. Acidemia may occur as a result of hypercapnia as well as metabolic acidosis
(lactic, starvation ketosis). However, hypercapnia alone is not an indication for intubation, as even these patients will often improve dramatically with therapy.

**CXR** has not been found to be a very useful test in the management of acute asthma. A number of studies have found routine CXR to have an extremely low yield for finding abnormalities, even in severe asthmatics requiring hospitalization. Still, a CXR is probably indicated to rule out pneumothorax or pneumonia and to serve as a baseline in case of admission.

**Criteria for admission**

Patients should usually be treated and observed for at least 4-6 hours in the emergency room before deciding on disposition. Decisions made based on periods of observation shorter than this are associated with a higher relapse rate. Based on **post-treatment peak flows**, patients can be divided into three groups:

- **Improvement in symptoms, physical exam and peak flow > 70% predicted** – these patients could safely be discharged on appropriate medication.

- **Patients with persistent severe symptoms and findings, and peak flow < 40% predicted after bronchodilators or <25% predicted on arrival in emergency department** – these patients may require admission to the intensive care unit.

- **Patients with persistent moderate symptoms and findings and peak flow 40-70% predicted** – these patients should continue to be treated in the emergency room until further improvement occurs or be admitted to the general medical ward.
Medical therapy for severe exacerbations

1. **Oxygen** – Hypoxemia is common but generally quite mild in acute asthma and easily corrected with modest flows of oxygen (1-3L by nasal prongs).

2. **Beta-agonists** – Inhaled beta agonists are the drugs of choice for treatment of acute bronchospasm. Commonly, initial treatment consists of salbutamol (Ventolin) 2.5-5mg in 2-5cc NS by nebulizer. Dosing can be as frequent as every 15 min or even continuously, limited only by the appearance of side effects (tremulousness, tachycardia, arrhythmias). Studies have shown that metered-dose inhalers with an aero-chamber are just as effective as nebulizers, but most clinicians still prefer nebulizers in the acutely distressed patient.

3. **Anticholinergics** – These produce less bronchodilation than beta agonists, but there is evidence that the combination of the two agents may have additive effects and reduce the need for admission. Side effects are few, so 0.5-1.0 mg of ipratropium (Atrovent) is generally added to the nebulized mixture of salbutamol.

4. **Corticosteroids** – IV corticosteroids should be administered in every case of severe asthma exacerbation. A meta-analysis of 30 randomized controlled trials concluded that steroids were effective, and that dose and frequency of administration did not matter as long as patients received the equivalent of 30 mg of prednisone q6h or more. There is one study indicating that 125mg of Solumedrol q6h resulted in more rapid initial clinical improvement than 40mg q6h, and both of these doses were much superior to 15mg q6h.

5. **Theophylline** – Theophylline is a weak bronchodilator with a significant risk of toxicity. There is conflicting evidence
regarding its usefulness in this setting, but in general, use of theophylline does not seem to confer additional benefit beyond the above medications.

6. **Magnesium** - IV magnesium was reported to be a useful therapy for acute asthma based on small studies and case series but larger prospective studies have not confirmed this. There is no good evidence in favor of magnesium use in asthma, but this therapy carries little risk.
COPD

GENERAL CONSIDERATIONS

**Chronic obstructive pulmonary disease (COPD)** is defined by the Canadian Thoracic Society (CTS) as a respiratory disorder caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations.

**Chronic Bronchitis** is defined clinically as the presence of productive cough for three months in each of two successive years.

**Emphysema** is defined pathologically as abnormal permanent enlargement of airspaces distal to the terminal bronchioles accompanied by destruction of their walls.

### Epidemiology of COPD in Canada

- *Fourth leading cause of death in men and women*
- Mortality rates for women have increased by 117% from 1988 to 2003 and will likely surpass the number of deaths in men in the near future
- 4.4% of Canadians over the age of 35 have probable COPD
- $467$ million were spent on hospital care and drugs for COPD in Canada
- Total costs per year are estimated to be ~ $1.7 billion

### Pathophysiology

- Chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature
- Macrophages, T lymphocytes, and neutrophils are increased in various parts of the lung
- Smoking is the main inflammatory trigger
- Mucosal inflammation, edema, mucous hypersecretion, and airway remodeling cause increased airway resistance
- Destruction of lung parenchyma reduces lung elastic recoil and airway tethering
- Result is expiratory airflow limitation with air trapping and lung hyperinflation – the hallmark physiologic change in COPD
- In advanced disease, gas exchange is impaired, resulting in hypoxemia, and, later on, hypercapnia

**Clinical Assessment**

**Diagnosis** should be considered in any patient who has cough, sputum production, or dyspnea, and/or history of exposure to risk factors for the disease. The disease is confirmed by an objective measure of airflow limitation

**Table 5 - Key Indicators for Considering a Diagnosis of COPD**

Consider COPD and perform spirometry if any of these indicators are present. These indicators are not diagnostic by themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

<table>
<thead>
<tr>
<th>Chronic cough:</th>
<th>Present intermittently or every day. Often present throughout the day; seldom only nocturnal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic sputum production:</td>
<td>Any pattern of chronic sputum production may indicate COPD.</td>
</tr>
<tr>
<td>Dyspnea that is:</td>
<td>Progressive (worsens over time). Persistent (present every day). Described by the patient as: “increased effort to breathe,” “heaviness,” “air hunger,” or “gasper.”</td>
</tr>
<tr>
<td>History of exposure to risk factors,</td>
<td>Worse on exercise. Worse during respiratory infections.</td>
</tr>
<tr>
<td>Tobacco smoke. Occupational dusts and chemicals. Smoke from home cooking and heating fuels.</td>
<td></td>
</tr>
</tbody>
</table>
Pulmonary Function
- To identify patients earlier in the course of their disease, spirometry should be performed in those who have chronic cough and sputum production and a history of exposure to risk factors, even if they do not have dyspnea.
- The presence of a post-bronchodilator FEV1 < 80% and an FEV1/FVC ratio < 70% confirms the presence of airflow limitation that is not fully reversible.

Assessment of Severity
- *CTS guidelines suggest basing management decisions on assessment of dyspnea and disability rather than on FEV1.*
- Stratification based on FEV1 not proven to be of particular value.
- CTS advocates using a system based on Medical Research Council (MRC) dyspnea scale.

---

Assessing Disability in COPD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breathless with strenuous exercise</td>
</tr>
<tr>
<td>2</td>
<td>Short of breath when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>3</td>
<td>Walks slower than people of the same age on the level or stops for breath while walking at own pace on the level</td>
</tr>
<tr>
<td>4</td>
<td>Stops for breath after walking 100 yards</td>
</tr>
<tr>
<td>5</td>
<td>Too breathless to leave the house or breathless when dressing</td>
</tr>
</tbody>
</table>

*Figure 1) Medical Research Council dyspnea scale. COPD Chronic obstructive pulmonary disease. Data from reference 1*
Prognosis

- BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index is better than the FEV1 alone at predicting death from respiratory cause and any cause in patients with COPD.

<p>| Canadian Thoracic Society chronic obstructive pulmonary disease (COPD) classification by symptoms/disability* |</p>
<table>
<thead>
<tr>
<th>COPD stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk (does not 'yet' fulfill the diagnosis of COPD)</td>
<td>Asymptomatic smoker, ex-smoker or chronic cough/sputum, but postbronchodilator FEV1/FVC&lt;0.7 and/or FEV1&lt;80% predicted</td>
</tr>
<tr>
<td>Mild</td>
<td>Shortness of breath from COPD† when hurrying on the level or walking up a slight hill (MRC 2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Shortness of breath from COPD† causing the patient to walk slower than people of the same age on the level or stop after walking about 100 m (or after a few minutes) on the level (MRC 3-4)</td>
</tr>
<tr>
<td>Severe</td>
<td>Shortness of breath from COPD† resulting in the patient to breathlessness to leave the house, or breathlessness after dressing/undressing (MRC 5), or the presence of chronic respiratory failure or clinical signs of right heart failure</td>
</tr>
</tbody>
</table>

*Postbronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) less than 0.7 and FEV1 less than 80% predicted are both required for the diagnosis of COPD to be established; †In the presence of non-COPD conditions that may cause shortness of breath (eg, cardiac dysfunction, anemia, muscle weakness, metabolic disorders), symptoms may not appropriately reflect COPD disease severity. Classification of COPD severity should be undertaken with care in patients with comorbid diseases or other possible contributors to shortness of breath. MRC Medical Research Council.

### Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points on BODE Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% of predicted)†</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>≥65</td>
<td>50–64</td>
</tr>
<tr>
<td>Distance walked in 6 min (m)</td>
<td>0–1</td>
</tr>
<tr>
<td>≥350</td>
<td>250–349</td>
</tr>
<tr>
<td>MMRC dyspnea scale‡</td>
<td>0–1</td>
</tr>
<tr>
<td>0–1</td>
<td>2</td>
</tr>
<tr>
<td>Body-mass index§</td>
<td>&gt;21</td>
</tr>
</tbody>
</table>

(Celli, NEJM 2004)
Clinical differences between asthma and COPD

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Usually &lt; 40 years</td>
<td>Usually &gt; 40 years</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Not causal</td>
<td>Usually &gt; 10 pack years</td>
</tr>
<tr>
<td>Sputum production</td>
<td>Infrequent</td>
<td>Often</td>
</tr>
<tr>
<td>Allergies</td>
<td>Often</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Disease course</td>
<td>Stable (with exacerbations)</td>
<td>Progressive worsening (with exacerbations)</td>
</tr>
<tr>
<td>Spirometry</td>
<td>Often normalizes</td>
<td>May improve but never normalizes</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>Intermittent and variable</td>
<td>Persistent</td>
</tr>
<tr>
<td>Airway Inflammation</td>
<td>Eosinophilic</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Role of exercise</td>
<td>Rarely formally used</td>
<td>Essential therapy</td>
</tr>
<tr>
<td>training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-of-life discussion</td>
<td>Rarely necessary</td>
<td>Often essential</td>
</tr>
</tbody>
</table>

O’Donnell, CTS COPD Recommendations 2007 Update

MANAGEMENT OF COPD

Non-Pharmacologic Treatment

1. Smoking Cessation
   - Cigarette smoking is the single most important cause of COPD.
   - 1/6 smokers will develop clinically significant COPD.
   - Quitting smoking reduces the rate of decline in FEV1 to that of
Smoking cessation is the **only** means of reducing the risk of developing COPD and slowing its progression.

## Pharmacologic Aids to Smoking Cessation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Duration, use and advantages</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine gum</td>
<td>2mg if &lt;25 cig/d, 4mg if ≥25 cig/d</td>
<td>1 piece q1h prn x ≥ 12 weeks. Chew 2-3 times and park gum between gingival and cheek for 30-60s, repeat x 30 min. Do not eat 15 minutes before or after.</td>
<td>Recent MI, unstable angina, severe cardiac arrhythmia, recent stroke, patients &lt; 18 years old, pregnancy and breastfeeding</td>
<td>Burning, jaw pain, hiccups</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>7mg, 14mg, 21mg/24 hrs</td>
<td>2-4 weeks. Tapering and duration should be individualized.</td>
<td></td>
<td>Local skin reaction, vivid dreams</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>10mg /cartridge/ 20 min, 6-12 cartridge / day</td>
<td>Use up to 12 weeks, and then decrease progressively over 6-12 weeks.</td>
<td></td>
<td>Mouth and throat irritation, cough, rhinitis, broncho-spasm</td>
</tr>
<tr>
<td>Buproprion</td>
<td>150mg q am x 3 d, then 150mg BID. Decrease with hepatic or renal failure.</td>
<td>7-12 weeks. Smoking cessation advised between days 8-14. Longer treatment in smokers subject to mood swings or who continue to experience strong urges.</td>
<td>Current seizure disorder, current or previous anorexia nervosa or bulimia, undergoing withdrawal from alcohol or benzodiazepines, current use of MAO inhibitors or thioridazine within 14 d of discontinuation, severe hepatic impairment</td>
<td>Insomnia, dry mouth, tremors, skin rashes, serious allergic reactions</td>
</tr>
<tr>
<td>Varenicline</td>
<td>0.5mg od for days 1-3, 0.5mg bid for days 4-7, 1g bid for days 8 to end.</td>
<td>12 weeks. Stop smoking after 7 days. Those who are abstinent at 12 weeks may continue for another 12 weeks.</td>
<td>Allergy to varenicline; end stage renal disease; pregnancy and breastfeeding; patients&lt;18 years; caution in combination with smoking cessation aids due to lack of data</td>
<td>Nausea, abnormal dreams, constipation, vomiting, flatulence,</td>
</tr>
</tbody>
</table>
2. Vaccinations
- Annual influenza vaccination reduces morbidity and mortality from the disease significantly.
- Data for pneumococcal vaccination is limited, however, it is still recommended by the CTS every 5-10 years.

3. Rehabilitation
- Principal goals are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities.
- Physiological benefits include improved strength and endurance of ventilatory capacity, improved breathing pattern and ventilatory capacity, improved strength and endurance of peripheral muscles and, finally, cardiovascular effects.
- A meta-analysis of 23 RCTs looking at pulmonary rehabilitation for COPD showed significant improvement in dyspnea, exercise endurance and quality of life compared with standard of care.
- The benefits of pulmonary rehabilitation have been shown to be sustained for several months.
- Patients must be clinically stable with symptomatic COPD despite optimal pharmacologic intervention. Patients must have quit smoking and have no active ischemic heart disease.

4. Oxygen therapy
- Oxygen therapy for ≥ 15 hrs/day is the only treatment that has been shown to improve mortality in COPD.
- No evidence for nocturnal or ambulatory oxygen.
- Indications for long term oxygen therapy:
  i. \( \text{PaO2} < 55 \text{ mmHg or SaO2} < 89\% \)
  ii. \( \text{PaO2} \text{ 55 – 59 mmHg in the presence of cor pulmonale or polycythemia} \)
  iii. \( \text{PaO2} \text{ 55-59 mmHg with O2 desaturation (<88%) on} \)
exercise for 2 minutes or O2 desaturation (<88%) for more than 30% of the night during an overnight oximetry assessment

5. Lung Transplantation
- Refer when BODE score = 5
- Transplant may be considered if ≥ 1 criteria: FEV1<25% pred (no reversibility), PaCO₂>55mmHg, elevated pulmonary arterial pressures with progressive deterioration.

Pharmacologic Therapy
- Pharmacotherapy is used to prevent and control symptoms, reduce frequency and severity of exacerbations, improve health status, and improve exercise tolerance.
- No drug has been shown to modify the long-term decline in lung function.

1. Bronchodilators (key points)
- Central to the symptomatic management of COPD.
- 3 major classes: anticholinergics, beta2-agonists, and methylxanthines.
- Short-acting bronchodilators (Ventolin/Atrovent) have been shown to improve pulmonary function, dyspnea, and exercise tolerance.
- Long-acting anticholinergic Tiotropium bromide has been shown to reduce hyperinflation, increase inspiratory capacity, and improve dyspnea. It has also been shown to improve lung function, quality of life and exacerbations during a 4 year period.
- Long-acting beta2-agonists (LABA) provide sustained improvements in pulmonary function, chronic dyspnea, and quality of life compared to short-acting bronchodilators. TORCH: salmeterol alone was associated with decreased frequency and severity of exacerbations.
- Oral theophylline may offer benefit to some patients on maximal
bronchodilators.

2. Inhaled Corticosteroids (ICS)
   - Unlike in asthma, ICS should not be used as first-line or monotherapy in COPD.
   - Regular use of ICS in combination with a LABA and LAAC should only be initiated in those with moderate-severe COPD who have recurrent exacerbations (≥1/year x 2 consecutive years).
### Acute Exacerbations

- Rule out other cause of dyspnea and cough (i.e. PE)
- Bronchodilators: combined short-acting beta₂-agonist and anticholinergic
- Corticosteroids: in moderate or severe exacerbations. Equivalent of 30-40mg/day for 10-14 days.
- Antibiotics: consider in purulent exacerbations. Antibiotic choice depends on underlying risk factors.
- Non-invasive positive-pressure ventilation (NIV): reduces mortality in acute exacerbations. Indications for use in respiratory distress (respiratory rate > 25 /minute and use of accessory muscles), and respiratory acidosis (pH<7.35, and PaCO₂>45mmHg).
NIV not indicated for those with respiratory arrest, hemodynamic instability, high risk for aspiration, impaired mental status, or otherwise unable to cooperate.
Coughing can cause a number of very bothersome complications including exhaustion from paroxysms, musculoskeletal pain, hoarseness, urinary incontinence and social embarrassment.

In many patients, the cause of cough is multi-factorial, but can be the sole manifestation of asthma, gastroesophageal reflux disease (GERD), or post-nasal drip syndrome (PNDS) / upper airway cough syndrome (UACS). These three entities are responsible for the majority of cases of chronic cough in those who are non-smokers, not on an ACE inhibitor, and have a normal chest x-ray.

Eliciting possible symptoms of each of these entities should be a major focus of the history in the chronic cough patient.
- Cough occurs through the stimulation of a complex reflex arc.
- It is initiated by stimulation of cough receptors located in the epithelium of the upper and lower respiratory tracts, pericardium, esophagus, diaphragm and stomach.
- Receptors are most numerous on the posterior wall of the trachea, main carina and at branching points of the large airways.
- Impulses are relayed to the cough center located in the medulla and efferent impulses are transmitted via the phrenic nerve, spinal motor nerves to the respiratory musculature and larynx.

### Assessment of Chronic Cough

1. A reasonable first step is to establish that the cough is actually chronic. A **post-viral cough** following a viral URTI may persist for up to a month. Reassurance is usually adequate for these patients with open-ended follow-up if the cough persists longer than a month. Symptomatic treatment with inhaled steroids or bronchodilators are of questionable benefit but may be used in select patients with acute bronchitis and wheezing.

2. A thorough history and physical examination should be performed to rule out serious underlying diseases such as **congestive heart failure**, **chronic bronchitis**, **bronchiectasis** or **interstitial lung disease**. As always, the smoking history is relevant.

3. **ACE inhibitor** use should be asked about. These agents have about a 10% incidence of cough, probably secondary to irritant effects of bradykinin in the lung. Patients who have had cough on one ACE-inhibitor generally do not benefit from switching to another. Switching to an ARB may be an alternative to an ACE inhibitor. The cough usually resolves within five days of discontinuing the drug.
4. **CXR** should be performed to assess for possible underlying infection, fibrosis, bronchiectasis or malignancy.

---

**Common Causes of Chronic Cough**

**Upper Airway Cough Syndrome (formerly Post-Nasal Drip Syndrome):**
- Most common cause of chronic cough.
- Related to allergic rhinitis, nasopharyngitis, and sinusitis.
- Cough is caused by mechanical stimulation of the afferent limb of the cough reflex in the upper airway by secretions from the nose or sinuses.
- Patients complain of a sensation of liquid dripping into the back of the throat, frequent throat clearing, a tickle in the throat, nasal congestion, or nasal discharge.
- A minority of patients will have “silent” post-nasal drip.
- Clues include a history of URTI prior to onset and “cobblestone” appearance of nasal mucosa on physical exam.
- A definitive diagnosis cannot be made simply on history or physical exam because the symptoms and signs are non-specific.
- Empiric therapy may be instituted with nasal steroid for 2-4 weeks, especially if allergic rhinitis is suspected. Alternatively, a first generation antihistamine/decongestant such as Drixoral™ can be considered.
- Imaging of the sinuses is usually not warranted unless there is failure of empiric therapy.

**Asthma:**
- Generally reported as the second most common cause of chronic cough.
- Accompanied by episodic wheezing, dyspnea, history of atopy, and family history of asthma.
- Cough can be the sole manifestation and is called “cough variant
Asthma-related cough may be seasonal, triggered by an URTI, worsen with cold exposure.
- PFTs may demonstrate normal spirometry, but the methacholine challenge is positive.
- The treatment should be the same as with asthma presenting with other symptoms.
- Corticosteroids with a beta-agonist should be initiated to relieve acute symptoms.

**Eosinophilic Bronchitis**
- Increasingly recognized cause of cough.
- Characterized by a predominance of eosinophils in sputum, cough, and importantly, no airway hyper-responsiveness.
- Bronchial mucosal biopsies demonstrating airway eosinophils and basement membrane thickening are required to make the diagnosis.
- Findings are indistinguishable from asthma, with the only difference being airway hyper-reactivity.
- Patients respond well to inhaled corticosteroids, and rarely require oral steroids.
- Evaluation for possible environmental allergens, including occupational exposures followed by avoidance is useful.

**GERD**
- Third most common cause of persistent cough, occurring in 30-40% of patients.
- Many patients complain of heartburn or a sour taste in the mouth, epigastric or retrosternal discomfort.
- Cough is worse upon lying down, after meals, or after bending at the waist.
- Between 50-75% of patients have no reflux symptoms.
- Cough is thought to be stimulated by aspiration of gastric contents, stimulation of receptors in the URT, or through
receptors in the distal esophagus.
- Laryngeal symptoms such as dysphonia, hoarseness and a sore throat are also prominent, especially with microaspiration.
- The gold standard of diagnosis is 24 hour esophageal pH monitoring but an acceptable alternative strategy is a trial of moderate dose proton pump inhibitor for 4-6 weeks with documented improvement in cough.

**Post-Infectious Cough**
- Cough following viral or bacterial upper respiratory tract infection can persist for more than eight weeks.
- During outbreaks of obvious infection with *Mycoplasma* and *Bordetella* pertussis infections, the frequency of post-infectious cough has ranged from 25-50%.

**Bordetella**
- Adults complain of SOB and a tingling sensation in the throat.
- Cough is spasmodic and occurs more frequently at night.
- Usually lasts for 4-6 weeks.
- The characteristic “whoop” is often absent.
- Diagnosis is based on acute serum IgA antibodies by ELISA or isolation of the organism by culture.
- In cases of pertussis, treatment with a macrolide for the patient and prophylaxis to close contacts has been found to be effective in decreasing the severity and transmission if given in the first eight days of infection.
- Prednisone at 30-40 mg a day for 2-3 weeks can be tried in those with protracted and persistently troublesome cough.

**Angiotensin-Converting Enzyme Inhibitor-Induced Cough**
- Non-productive cough is a well-recognized complication occurring in up to 15% of patients.
- Cough usually commences within one week of starting therapy, but the onset may be delayed up to six months.
- Typically resolves in 1-4 days of discontinuing therapy, but can
take up to four weeks.
- It generally recurs with a re-challenge, is more common in women, and does not cause airflow obstruction.
- Treatment is discontinuation of the drug.

**Lung Cancer**
- A feared, but uncommon cause of chronic cough
- Malignancies presenting with cough are usually within the large airways
- May present with focal wheezing or airway obstruction
- Should be considered in smoking patients, and those with a history of hemoptysis or new worsening cough in patients with smoking related chronic bronchitis.
Bronchiectasis is an anatomical description referring to dilatation of airways. This results in and from impaired mucous clearance, recurrent infection, chronic inflammation and chronic pathogen colonization of the airways. Clinically, this may present with chronic productive cough, hemoptysis, dyspnea and airflow obstruction due to increased airway collapsibility. The plain CXR may show dilated and thickened airways (“tram-tracking”). On CT scan, failure of the airways to taper peripherally, and airway diameter 1.5x that of its accompanying blood vessel are the hallmarks of bronchiectasis.

Cystic Fibrosis has served as the model from which the basic principles for the management of bronchiectasis have evolved. These include maintenance of adequate nutrition, techniques for secretion drainage, pharmacological management of mucous, aggressive treatment of acute exacerbations and chronic suppression of challenging pathogenic colonizers.

One approach to determining the etiology of bronchiectasis is to divide the causes into those that cause focal versus diffuse bronchiectasis. Focal causes are typically those that cause chronic inflammation due to focal infection or chronic obstruction of an airway resulting in distal dilation due to impaired secretion drainage. Systemic disease or a diffuse infectious process typically causes diffuse bronchiectasis.
<table>
<thead>
<tr>
<th><strong>FOCAL</strong></th>
<th><strong>DIFFUSE</strong></th>
</tr>
</thead>
</table>
| **Post-obstructive:** | - Cystic Fibrosis  
- Primary Ciliary Dyskinesia  
- Young’s Syndrome (possibly CF with unrecognized mutations)  
- Alpha-1 antitrypsin deficiency  
- Immunodeficiency (CVID, HIV)  
- Non-tuberculous mycobacteria  
- Allergic Bronchopulmonary Aspergillosis  
- Systemic inflammatory diseases (RA, Sjogrens, IBD)  
- Miscellaneous (Yellow nail and Marfan’s syndromes) |
| - Foreign body aspiration  
- Endobronchial tumour  
- Extrinsic airway compression (e.g. lymph node – classic example is TB) |  |
| **Post-infectious** |  |
| - Severe childhood pulmonary infection (egg Pertussis)  
- Necrotizing pneumonia  
- Tuberculosis  
- Non-tuberculous mycobacteria |  |
CYSTIC FIBROSIS

BACKGROUND

Cystic fibrosis (CF) is a multi-system disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel that influences other ion channels. Abnormalities in this transmembrane channel affect hydration of secretions, causing thick, viscous secretions in the lungs, pancreas, liver, intestine, and vas deferens, and increased salt content in sweat gland secretions. The most common inheritance is autosomal recessive in Caucasians, but many other mutations have been identified with variable penetrance in all ethnicities.

CLINICAL MANIFESTATIONS

1. **Respiratory tract involvement**- Inadequate clearance of thick secretions cause airflow obstruction and hyperinflation. Chronic infection and intermittent acute exacerbations results in bronchiectasis resulting in chronic cough, dyspnea, purulent sputum production and weight loss. Clubbing is found in patients with moderate to severe disease. Colonization of the airways with pathogenic bacteria occurs early in disease (see following table).

<table>
<thead>
<tr>
<th>Childhood</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Hemophilus influenzae</em></td>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td></td>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
<tr>
<td></td>
<td><em>Alcaligenes xylosoxidans</em></td>
</tr>
<tr>
<td></td>
<td><em>Atypical mycobacterium</em></td>
</tr>
</tbody>
</table>

2. **Sinus disease**- Radiographs reveal panopacification of the paranasal sinuses in 90-100% of patients. Nasal polyps are seen in 10-30% of patients.
3. **Pancreatic disease** – 85% of people with CF will have pancreatic insufficiency (implying >98% destruction of the pancreas), which leads to malabsorption of fat (with steatorrhea). Failure to thrive is a presenting sign in many infants and children. These problems can be reversed with oral supplementation of pancreatic enzyme extracts. Fat-soluble vitamins A, D, E and K deficiency occurs and is treated with vitamin supplementation. Of those with pancreatic sufficiency, 20% develop acute recurrent pancreatitis, which does not occur in pancreatic insufficient patients. Glucose metabolism is variable. Those with pancreatic sufficiency have normal insulin secretion and responsiveness. Those with pancreatic exocrine insufficiency may have decreased insulin secretion, but normal glucose tolerance due to increased hepatic glucose production and increased peripheral utilization. When these mechanisms fail (impaired peripheral glucose utilization or hepatic insulin responsiveness), impaired glucose tolerance and overt diabetes may develop. Amongst adults with CF, 25% will have diabetes that requires insulin and prevalence increases with age.

4. **Meconium ileus and distal ileal obstruction syndrome (DIOS)** – Meconium ileus is the presenting problem in 10-20% of newborns. DIOS occurs in 15% of adults with CF and is usually associated with pancreatic insufficiency. DIOS is a syndrome of chronic partial and complete SBO caused by thick viscous secretions in the small bowel. The diagnosis is based on abdominal pain, palpable mass in the RLQ and AXR showing stool in the right colon.

5. **Biliary disease**- Biliary cirrhosis and symptomatic portal hypertension may occur in 5% of patients with CF. Asymptomatic liver disease may present with mild elevations in serum alkaline phosphatase and GGT. Cholelithiasis has been reported in up to 12% of patients resulting from excess loss of
6. **Infertility**- Despite adequate spermatogenesis, congenital bilateral absence of vas deferens is responsible for infertility in at least 98% of males. Incidence of female infertility is hard to estimate but may be as high as 20%. This is due both to secondary amenorrhea (due to malnutrition) and production of abnormal cervical mucus. When CF patients become pregnant, maternal and fetal outcomes are generally favorable if the pregnancy FEV1 exceeds 50% of predicted values and there is adequate weight gain during pregnancy.

7. **Musculoskeletal disorders**- Reduced rate of bone formation and accelerated rate of bone loss causes high prevalence of low bone mineral density and increased risk of fractures, although the relationship between bone density and fractures is not clear. Hypertrophic osteoarthropathy is characterized by abnormal proliferation of osseous tissue at the distal parts of the extremities, with periosteal new bone formation. Clubbing may also be present in moderate to severe cases.

**HISTORY AND PHYSICAL EXAM OF THE CF PATIENT**

Inquires should be made in history-taking to ascertain severity of disease, extent of complications as well as the recent events leading to hospital admission.

**HISTORY**

Degree of lung disease:
- bronchiectasis: cough, sputum (amount, thickness, purulence), hemoptysis
- presence of airway reactivity (dyspnea, wheeze, PND)
- use of oxygen
Degree of pancreatic insufficiency:
- weight, change in weight
- steatorrhea
- appetite, what do they eat
- use/dose of pancreatic enzyme supplements
- use of nutritional supplements and gastrostomy feeding tube

Complications:
- hemoptysis
- pneumothorax
- allergic bronchopulmonary aspergillosis
- sinusitis/nasal polyps
- diabetes
- DIOS (distal intestinal obstruction syndrome)
- cirrhosis
- GE reflux
- cholelithiasis
- arthropathy

4. Assessment of therapy
- medications (type, compliance)
- exercise (type, frequency)
- physiotherapy (technique used, frequency)

5. The clinic chart should be reviewed to look for:
- previous weight
- previous lung function
- previous ABG
- most recent sputum culture and sensitivity
PHYSICAL EXAMINATION

General Condition: BP, Pulse, Respiratory Rate, Temperature

Things to look for in addition to lung disease:

- clubbing
- cyanosis
- sinusitis
- nasal polyps
- cor pulmonale, pulmonary hypertension
- hepatomegaly
- splenomegaly
- arthropyathy

INVESTIGATIONS ON ADMISSION

- CBC
- ESR
- lytes, creat, BUN, glucose
- AST, alk phos., GGT
- protein, albumin, INR
- Oximetry (at rest, sleep and exercise)
- ABG’s (on room air) do if:
  - previously hypoxic
  - on O₂ therapy at home
  - FEV₁ <1.0 L
  - O₂ saturation on oximetry <92%
  - “sick”
  - CXR
  - sputum C&S
- blood C&S (only if temperature >38.5 C or patient appears septic)
- if diabetic: HbA.C, 24 hour urine for protein, creatinine clearance

### DIAGNOSTIC TESTS

The diagnosis of CF is based on clinical findings with biochemical or genetic confirmation. The sweat chloride test is the mainstay confirmation, although other tests including specific mutations, nasal potential difference or immunoreactive trypsin may also be useful in certain cases.

1. **Sweat chloride** - This test is performed by collection of sweat with pilocarpine iontophoresis and by chemical determination of chloride concentration. A sweat chloride value greater than 60mEq/L distinguishes most patients with CF. Intermediate response (40-60 mEg/L) may be seen in 1-5% of patients with CF, who may have unusual genotypes. Hypoproteinemic edema and untreated hypothyroidism can cause a false negative test.

2. **Molecular diagnosis** – This is carried out by direct mutation analysis, and identification of specific known mutations in the nucleotide sequence of the CFTR gene. The Cystic Fibrosis Mutation Database lists over 1300 different mutations in the CFTR gene (www.genet.sickkids.on.ca/cftr). The current screening panel included 39 of the most common mutations.

3. **Nasal potential difference measurements** - Abnormalities in epithelial chloride secretion can be demonstrated in most CF patients by evaluating the nasal transepithelial potential difference in the basal state, after nasal perfusion with amiloride and after nasal perfusion with a chloride-free
solution. Presence of nasal polyps or inflammation may result in false negative results.

4. **Immunoreactive trypsinogen** - Infants with CF have elevated blood levels of immunoreactive trypsin, which can be quantitated by radioimmunoassay or enzyme-linked immunoassay. IRT levels fall rapidly during infancy, and is not informative after eight weeks of age. Newborn trypsinogen screening was introduced in Canada in 2008. All newborns with a positive screen go on to have a limited 2-mutation screen. All detected homozygotes are referred to a CF centre.

### TREATMENT OF ACUTE EXACERBATIONS

*Intermittently, patients develop an acute pulmonary exacerbation which is defined clinically as any of the symptoms or signs below:*

- increase in the amount, thickness or purulence of sputum
- increasing dyspnea
- hemoptysis
- fever
- weight loss
- increase in WBC
- increase in ESR
- fall in PFTs
- infiltrate on CXR

Treatment for an acute exacerbation is usually with oral antibiotics as an outpatient. For failure of oral therapy or severe exacerbation, hospital admission is required for parenteral antibiotic therapy, physiotherapy and nutritional therapy.

**INFECTION CONTROL**
Due to the risk of person-to-person transmission of bacteria, no CF patient is put in the same ward-room as another CF patient, even if they appear to grow the same bacteria. Ambulatory clinics are divided into “cepacia positive” and “cepacia negative” clinics. All patients are put in a clinic room as soon as they arrive in clinic to reduce chance of contact with other CF patients.

**NUTRITIONAL CARE**

Most patients are pancreatic insufficient and require pancreatic enzymes with meals/snacks and a high caloric diet to prevent malnutrition. Vitamin supplements are needed to prevent fat-soluble vitamin deficiencies. Occasionally, patients with malnutrition and acute weight loss are given IV lipids (intralipid 20% 500 ml overnight) to provide additional calories for weight gain.

**General Principles of IV Antibiotics in CF**

1. Combination antibiotic therapy is usually used.

2. The dose of antibiotics is higher than the usual doses because of the increased drug clearance and increased volume of distribution in patients with CF (see table below).

3. The choice of antibiotics is based upon the most recent sputum culture and sensitivity results available, in combination with clinical experience with that patient. Sputum C&S are done at each clinic visit. Burkholderia cepacia is often resistant to many or all antibiotics but a clinical response is usually seen with antibiotic therapy. Thus, clinical improvement occurs even though in vitro sensitivity results show resistance. Multiple antibiotic combination testing (“synergy studies”) is done for patients with multi-resistant bacteria to help guide therapy.
4. The duration of therapy is usually 10 to 14 days and is determined by clinical response (decrease in the thickness and purulence of sputum, weight gain, improvement in PFTs, resolution of hypoxia, etc.). If patient responds well initially and has adequate supports, they can often finish a course of IV antibiotics at home (Home-Care referral).

5. The dose of aminoglycosides is adjusted according to pre (trough) and post (peak) antibiotic levels. Aim for pre levels of <2 and post levels of 8 to 10. Sputum concentrations of antibiotics are much lower than blood levels, so we aim for high serum levels.

6. New Antibiotics are generally changed if there is no clinical improvement after seven days.
INTERSTITIAL LUNG DISEASE

APPRAOCH TO INTERSTITIAL LUNG DISEASE

- Diffuse parenchymal lung diseases (DPLD) are often collectively referred to as interstitial lung diseases (ILDs) and encompass a wide variety of disease processes.
- The term interstitial is misleading, since many of these processes are also associated with alveolar and airway abnormalities.
- ILDs may be secondary to infection, neoplasm, environmental and occupational exposure, drugs, and connective tissue disease.
- Idiopathic ILDs are referred to as the Idiopathic Interstitial Pneumonias.
- The nomenclature can be confusing, but it is important to distinguish pathological patterns (UIP, NSIP, DIP, RB-ILD, BOOP) from the disease entities with the same name.

DIFFERENTIAL DIAGNOSIS OF ILD

**Idiopathic Interstitial Pneumonias (alphabet soup!):**
1. Idiopathic Pulmonary Fibrosis / Usual Interstitial Pneumonia (IPF/UIP) – see section below
2. Non-Specific Interstitial Pneumonia (NSIP) – IPF not otherwise specified
3. Desquamative Interstitial Pneumonia (DIP) – smoking related, responds well to smoking cessation & steroids
4. Respiratory Bronchiolitis-associated Interstitial Lung Disease (RBILD) – similar to DIP, smoking related
5. Acute Interstitial Pneumonia (AIP) – acute, fulminant IPF
6. Lymphocytic Interstitial Pneumonia (LIP) – HIV associated, cystic lung disease
7. Cryptogenic Organizing Pneumonia (COP) – airspace disease, aka idiopathic BOOP
Inflammatory
- Rheumatological Diseases - Scleroderma (not CREST), Rheumatoid arthritis, Polymyositis/Dermatomyositis, Sjogren's Syndrome, Mixed Connective Tissue Disease, Ankylosing Spondylitis, SLE (rarely)
- Other “Inflammatory” Conditions - Sarcoidosis, lymphangioleiomyomatosis (LAM), pulmonary Langerhans’ cell histiocytosis (PLCH)

Exposures:
- Organic Antigens – plant products, animal products, aerosolized microorganisms, organic chemicals (hypersensitivity pneumonitis – “Farmer’s lung”, “Bird Fancier’s lung” etc.)
- Inorganic dusts - asbestosis, silicosis, berylliosis (Pneumoconioses)
- Drugs: nitrofurantoin, amiodarone, methotrexate
- Thoracic radiation

Infections: viruses, parasites, fungi, TB
Malignancy: lymphangitic carcinomatosis
Fluid: pulmonary edema, ARDS

See organizational flow chart next page
Diffuse Parenchymal Lung Disease

Rule out infections, malignancy, fluid
Ix: cultures, cytology/biopsy, echocardiogram

Idiopathic Interstitial Pneumonias
Ix: biopsy (open lung)

“Known” cause

Inflammatory

Rheumatological Disease
- Scleroderma
- RA
- DM/PM
- Sjogren’s Syndrome
- MCTD
- Ankylosing Spondylitis
- SLE (rare)

Other
- Sarcoidosis
- LAM
- PLCH

Ix: ANA, RF, autoABs
BAL fluid analysis

Exposures

Organic Antigens
(Hypersensitivity Pneumonitis)

Inorganic Antigens
(Pneumoconioses)
- Asbestos
- Beryllium
- Silica

Drugs

Radiation

Ix: History!
CLINICAL PRESENTATION

Radiologic, laboratory and even pathologic investigations are often nonspecific, so the key to reaching a diagnosis in these patients is taking a thorough history. Some key points to include are:

Age: Most patients with IPF are over the age of 50. Patients with Sarcoidosis, connective tissue disease-associated ILD, LAM, and PLCH usually present between the ages of 20 and 40.

Gender: LAM and pulmonary involvement in tuberous sclerosis occur in premenopausal women.

Smoking History: PLCH, DIP, IPF, RBILD occur in current or ex-smokers.

Medication Use: A detailed history of prior medication use is needed to exclude the possibility of drug-induced lung disease. Common examples include nitrofurantoin, bleomycin, methotrexate, and amiodarone.

Occupational History: Chronological listing of prior employment, specifically focusing on exposures to dusts, gases, and chemicals.

Environmental Exposures: Hypersensitivity pneumonitis (extrinsic allergic alveolitis) is often temporally related to the workplace (farmer’s lung), or to a hobby (pigeon breeder’s disease). Symptoms may disappear after the patient leaves the exposure for several days and often reappear with repeat exposure.

Symptoms: The symptoms of insidious onset shortness of breath and dry cough are common for most disease processes and are non-
specific. Important symptoms are those of connective-tissue disease (arthritis, rash, Raynaud’s, photosensitivity, dry eyes etc…). Hemoptysis is uncommon and usually indicates an underlying vasculitic process, LAM, or malignancy.

**Physical Examination** - commonly reveals:
- Tachypnea
- Reduced chest expansion
- Diffuse end-inspiratory (“velcro”) crackles
- Clubbing (esp. in IPF)
- Signs of pulmonary hypertension and cor pulmonale in advanced disease

**Diagnostic Tests**

After one has narrowed the differential diagnosis as much as possible by taking a thorough history, additional investigations are often still necessary.

**Chest X-ray**
- The chest x-ray is the first method of detecting a diffuse lung process, however, in > 10% of cases, the CXR may look normal
- Most common findings are reticular, nodular, or mixed alveolar and interstitial changes.
- Certain diseases tend to favour an upper lobe predominance, while others tend to have a lower lobe predominance. There are mnemonics to help you remember the list of diseases associated with diseases favouring the upper lobes.
Upper lobes: “HASTEN”

Hypersensitivity Pneumonitis
Ankylosing Spondylitis
Sarcoidosis, silicosis
Tuberculosis
Eosinophilic Granulomatosis (aka PLCH)
Neurofibromatosis

*Remember that the commonest causes of an "interstitial pattern" on CXR are Congestive Heart Failure and Infection

CT Scan

- High-Resolution CT (HRCT) examines 1 mm slices at 10mm intervals and provides greater anatomic detail than conventional CT.
- More precisely defines the appearance and distribution of the disease, which can be helpful in narrowing a diagnosis or guiding attempts at biopsy.
- May also detect disease that may not be present on CXR, as in early hypersensitivity pneumonitis and lymphangitic carcinomatosis.
- Also useful in determining disease activity and response to therapy. In IPF, ground glass changes are more responsive to therapy than reticular changes and honeycombing.
- HRCT and clinical history together can yield a diagnosis in cases of IPF, LAM, PLCH, and Hypersensitivity Pneumonitis.

Pulmonary Function Tests

- PFT’s for most of these diseases show a restrictive pattern (reduced TLC and FVC).
- FEV1 is decreased but this is proportional to the decreased lung
volume, therefore FEV1/FVC remains normal, or even increased.
- The DLCO will be reduced (the earliest abnormality).

**Bronchoscopy and Transbronchial Biopsy**
- Bronchoscopy is particularly useful in the diagnosis or exclusion of infection. The latter may be an important consideration if high dose steroid or immunosuppressive therapy is being considered.
- In terms of making a definitive diagnosis, transbronchial biopsy has a poor yield for most ILDs. One exception to this rule is sarcoidosis, in which transbronchial biopsy is diagnostic in 80-90% of cases, by demonstration of non-caseating granuloma.
- TBB may also be helpful in lymphangitic carcinomatosis, hypersensitivity pneumonitis, and eosinophilic pneumonia.

**Open lung biopsy**
- Open lung biopsy is considered the gold standard for the diagnosis of ILD.
- Diagnostic yield is greater than 90%, but it is not without morbidity (6 – 19%) and mortality.
- Video-assisted thorascopic surgery is preferred method due to improvements in morbidity compared to traditional open thoracotomy.
- The degree to which this test should be utilized is a highly controversial issue in Respirology. Certainly, there are many cases in which open lung biopsy is not necessary because a firm diagnosis can be made on clinical grounds (e.g., ILD in a patient with rheumatoid arthritis). On the other hand, there are many cases in which the diagnosis is not clear and an open lung biopsy is needed.
### IDIOPATHIC PULMONARY FIBROSIS (IPF)

**Definition:** IPF or cryptogenic fibrosing alveolitis (CFA) is a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of usual interstitial pneumonia (UIP) on surgical lung biopsy.

### EPIDEMIOLOGY

- Population studies demonstrate a prevalence of 30/100,000 males and 15/100,000 females, giving IPF a distinct male preponderance.
- Patients are often middle-aged, with 2/3 of patients being over the age of 60 and a mean age of diagnosis of 66.
- There is no known geographical distribution.

### RISK FACTORS

- Smoking has been identified as a potential risk factor, with odds ratios ranging from 1.6-2.9 for the development of IPF in smokers.
- Chronic aspiration secondary to GERD has been implicated in the development of IPF.
- There is no clear evidence linking environmental factors or infectious agents as a cause of IPF.

### PATHOLOGY

- Pathologic findings of idiopathic pneumonias first described by Liebow and Carrington in 1969. Katzenstein and Myers revised this scheme in 1998 and described four histologic patterns for
idiopathic interstitial pneumonias – UIP, DIP/RBILD, NSIP, AIP.
- UIP is the most common idiopathic pneumonia accounting for 50-60%.
- It is characterized by a heterogeneous, predominantly subpleural distribution. Temporal heterogeneity is seen, with areas of end-stage fibrosis and honeycombing abutting areas of active proliferation of fibroblasts (fibroblastic foci are essential for the pathological diagnosis of UIP).

**DIAGNOSIS**

- IPF is a diagnosis of exclusion and requires exclusion of systemic disorders, environmental/occupational causes, drug exposures, and other causes described above.
- Symptoms are those of insidious onset of dyspnea over 1-2 years. Non-productive cough and weight loss are common.
- Chest exam reveals Velcro crackles. About 2/3 of patients with IPF will develop clubbing. Many will also go on to develop cyanosis and signs of secondary pulmonary hypertension and right heart failure.
- ATS and ERS have published a consensus statement describing major and minor criteria for the clinical diagnosis of IPF (see below). The presence of all 4 major and ¾ minor criteria has a high specificity for the diagnosis of IPF.
- In the absence of surgical lung biopsy findings, the diagnosis of IPF remains unproven.
RADIOLOGY

**CXR:** Peripheral reticular opacities, most profuse at the lung bases. Opacities are usually bilateral, asymmetric and associated with decreased lung volumes.

**HRCT:** Patchy, basilar, subpleural reticular opacities. Absent or limited “ground glass” changes. Traction bronchiectasis and “honeycombing” are also seen. *Atypical findings* include extensive ground-glass changes, upper lobe predominance, and significant hilar or mediastinal lymphadenopathy.

ROLE OF LUNG BIOPSY

- Most recent studies of HRCT have demonstrated specificities of 90-97% for the confident diagnosis of IPF.
- Combined clinical and histopathological specificity for the diagnosis of IPF is >95%.
- Therefore, several experts have argued that histologic confirmation is not necessary in every patient with suspected IPF.
If patients do not meet the major and minor criteria listed by the ATS, or if the HRCT is predominantly ground-glass appearing, then surgical biopsy should be done to assess for an alternative diagnosis.

Diagnostic Algorithm for IPF
1. There is a great deal of variation in the management of IPF.

2. The difficulty lies in the fact that only 10-20% of patients will have a significant response to immunosuppressive therapy and that initiating therapy commits the patient to at least three months of **high dose steroids** and/or **cytotoxic agents**.

3. Because the majority (80-90%) of patients will not respond to therapy, many clinicians try to identify the subgroup of patients who are more likely to respond. In general, patients whose lungs are undergoing a lot of active inflammation are more likely to respond to therapy. A number of investigations can be performed in an attempt to identify these patients:

   i. **HRCT** - “Ground glass” is thought to represent active inflammation, whereas “honeycombing” represents end stage fibrotic lung. The amount of fibrosis predicts lack of steroid response better than ground glass predicts a steroid response. Patients with > 25% fibrosis have the worst prognosis and will likely progress despite treatment.

   ii. **BAL and open lung biopsy** – Findings on BAL or open lung biopsy have not been useful in predicting response to treatment.

**Treatment Recommendations:**
- 6 months of combined oral prednisone and azathioprine.
- If the patient is found to be improved or stable (based on symptoms, HRCT, PFTs, ABGs) then the patient should continue with the regimen, with re-evaluation at 12 months and 18 months.
4. **Lung Transplant** should be considered in all patients with progressive disease, unresponsive to treatment. Transplant should be considered for patients with FVC < 60% predicted, resting hypoxemia or signs of pulmonary hypertension, and progression while on medical therapy. Rapid and unexpected deterioration in IPF is not uncommon, so early referral for lung transplant assessment is recommended.
SARCOIDOSIS

GENERAL CONSIDERATIONS

- Sarcoidosis is an idiopathic systemic granulomatous disease.

- Although virtually any organ system can become involved, the lungs or intrathoracic lymph nodes are involved in 90% of patients. Sarcoid patients are usually cared for by Respirologists.

- Sarcoidosis typically presents around age 30-40. There is a slight female predominance and the disease may be more common and aggressive in Blacks.

SARCOID LUNG DISEASE

Sarcoid most commonly manifests as asymptomatic intrathoracic nodal disease, which is discovered on a routine CXR. The pattern of bilateral hilar adenopathy (BHL), with or without right paratracheal nodes, is classic for sarcoid.

Lofgren’s Syndrome is an acute presentation of sarcoid consisting of the triad of BHL, arthralgias and erythema nodosum. The prognosis for spontaneous remission for patients with Lofgren’s Syndrome is particularly good – about 90%.

Sarcoid also causes an interstitial disease of the lung. There is a staging system based on the CXR appearance. The importance of the staging system is that it predicts the likelihood of spontaneous remission. This was developed by Wurm and Scadding more than 40 years ago.
Patients with sarcoid most commonly present with asymptomatic disease.

More severe parenchymal lung disease is associated with symptoms of dyspnea, cough and, sometimes, unusual chest pains.

Auscultation of the chest may reveal fine crackles but often there is a surprising lack of adventitious sounds in the chest when compared to degree of abnormality of the CXR. Pleural effusions are rare.

Extrapulmonary symptoms and findings are referable to the organ system involved (see chart on following page):

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Manifestation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Anterior uveitis, posterior uveitis, conjunctivitis</td>
<td>Topical steroid or systemic steroid</td>
</tr>
<tr>
<td>Skin</td>
<td>Erythema nodosum, lupus pernio, skin nodules</td>
<td>Topical or intralesional steroid</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Mononeuritis, brain parenchymal lesions, cranial nerve palsy</td>
<td>Absolute indication for systemic steroids</td>
</tr>
<tr>
<td>Heart</td>
<td>Arrhythmias, blocks, restrictive CM</td>
<td>Absolute indication for systemic steroids</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td></td>
<td>Hydration, reduction in PO calcium and</td>
</tr>
<tr>
<td>Condition</td>
<td>Diagnosis</td>
<td>Treatment</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Acute or chronic polyarthritis</td>
<td>NSAID’s</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Diabetes insipidus, pituitary insufficiency</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Cholestatic hepatitis</td>
<td>Mild transaminitis does not require treatment</td>
</tr>
<tr>
<td>Spleen</td>
<td>Anemia</td>
<td>Steroids</td>
</tr>
<tr>
<td>Fever</td>
<td>FUO</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Renal failure rare, usually secondary to hypercalcemia</td>
<td></td>
</tr>
</tbody>
</table>

### Chance of Spontaneous Remission Based on CXR

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Chance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>BHL without lung involvement</td>
<td>80%</td>
</tr>
<tr>
<td>II</td>
<td>BHL with diffuse lung involvement</td>
<td>50%</td>
</tr>
<tr>
<td>III</td>
<td>Lung involvement without BHL</td>
<td>20%</td>
</tr>
</tbody>
</table>

At the time of diagnosis most patients present with stage 1 to 3. **Stage IV** is sometimes used to denote irreversibly fibrotic lung.

- Pulmonary function tests show a restrictive or mixed restrictive/obstructive pattern. Sarcoidosis is one of the few diseases that give this mixed picture.
The key to diagnosis of sarcoid is the demonstration of noncaseating granulomas on tissue biopsy in the right clinical context.

Other granulomatous diseases like TB and chronic fungal infections must also be excluded, as they may have similar histology. (Also think about other causes of granulomatous reactions such as in Beryllium exposure, reaction to cancer, or lymphoma)

In some instances, when a presentation is very classic (e.g., Lofgren’s syndrome), tissue diagnosis may not be necessary.

The yield of transbronchial biopsy for the diagnosis of sarcoid is excellent: 70-100% depending on the stage of disease.

OTHER FEATURES THAT SUPPORT DIAGNOSIS OF SARCOIDOSIS:

- Gallium scan showing lambda and panda sign (scan takes three days to complete).
- BAL showing increased lymphocytes or CD4:CD8 ratio.
- Increased ACE level (positive in 65% of patients with acute disease, less frequently elevated in chronic disease; up to 10% of elevated ACE caused by non-sarcoidosis related conditions.
- Elevated serum calcium.
- In patients that bronchoscopy has failed to make a diagnosis, open-lung biopsy or mediastinoscopy can be considered.
The mainstay of therapy of sarcoid is a prolonged course of moderate to high doses of systemic steroids.

The decision of when to initiate therapy is controversial for two reasons:
- Many cases of sarcoidosis will undergo spontaneous remission
- Lack of evidence that steroids actually alter the natural history of the disease.

In general, Stage I sarcoidosis is not treated.

Stage III is usually treated.

Stage II may be treated if the patient is symptomatic or if there has been a decline in pulmonary function tests or CXR.

In meta-analysis by Cochrane group of corticosteroids therapy, authors concluded that steroids were of benefit for pulmonary disease, that they would lead to resolution of CXR abnormalities and improvement in DCO, but unclear whether they would change the natural history of disease.

Steroid therapy often lasts for two or more years. In one study, 90% of patients who stopped therapy early required reinstitution of systemic therapy.

Long-term use of steroids is associated with significant toxicity. Alternatives to steroids are summarized in the following table:
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Antimetabolite, inhibits dihydrofolate reductase</td>
<td>-can be used as steroid sparing agent (Baughman 2000)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Purine analog, effects synthesis of RNA and DNA</td>
<td>Pacheco 1985, Sharma 1971 -Improved in symptoms and CXR in small group of patients</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Antimalarial with immunomodulating properties</td>
<td>Improvement in symptoms, PFT’s, ACE levels, and lung gallium scan BTA 1967, Baltzan 1999</td>
</tr>
</tbody>
</table>

Other potential agents: Pentoxifylline, Infliximab (a-TNF)

**Disease Activity**

Assessments of the degree of active inflammation are sometimes used to guide therapeutic decisions. The main ones are:

1. **Serum ACE** (angiotensin converting enzyme) level
2. **Gallium scanning**
3. **High Resolution CT scan** to look for “ground glass” areas of inflammation
4. **Bronchoalveolar lavage** to look for lymphocytosis.

The evidence supporting the predictive value of these tests is generally poor.
COMMUNITY ACQUIRED PNEUMONIA

General Considerations

- Community-acquired pneumonia (CAP) guidelines were last issued by the Canadian Thoracic Society in 2000 and by the American Thoracic Society/Infectious Diseases Society of America in 2007. The topics addressed included: admission and discharge criteria, diagnostic testing, pneumococcal resistance, and prevention of CAP.
- Compared to the CTS guidelines, further patient variables were incorporated in the treatment options.

Site-of-Care Decision

The ATS/IDSA Guideline proposes a set of clinical predictors to define severe pneumonia, recommending that patients with these features be admitted directly to the ICU/High-intensity Unit if resources allow.

<table>
<thead>
<tr>
<th>Major Criteria (&gt;0)</th>
<th>Minor Criteria (≥ 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure requiring mechanical ventilation</td>
<td>RR ≥ 30</td>
</tr>
<tr>
<td>Septic shock requiring vasopressors</td>
<td>PiO₂/FiO₂ ≥ 250</td>
</tr>
<tr>
<td></td>
<td>Multilobar infiltrates</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>BUN ≥ 7mmol/L</td>
</tr>
<tr>
<td></td>
<td>WBC &lt; 4</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt; 100</td>
</tr>
<tr>
<td></td>
<td>Temperature &lt; 36°C</td>
</tr>
<tr>
<td></td>
<td>Hypotension requiring aggressive IVF resuscitation</td>
</tr>
</tbody>
</table>

A disease severity score (British Thoracic Society Criteria aka CURB-65) or prognostic score (Pneumonia Severity Index) may be used to help guide physicians on patient disposition for treatment,
but should not negate clinical judgment if there is a suspicion that out-patient management is not appropriate.

The CURB-65 score has the advantage of simplicity and ease of use, but was validated in a cohort of 214 patients, therefore lack the statistical validity of the PSI. Concurrent validation of the CRB-65 score showed very similar mortality division, and can be applied where urea is not routinely measured.

<table>
<thead>
<tr>
<th>CURB-65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Urea &gt; 7 mmol/L</td>
</tr>
<tr>
<td>Respiratory Rate &gt; 30</td>
</tr>
<tr>
<td>Blood pressure &lt; 90 systolic or &lt; 60 diastolic</td>
</tr>
<tr>
<td>Age &gt; 65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Class Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features Present</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Admit</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>
**Pneumonia Severity Index (Pneumonia Outcomes Research Team - aka PORT score)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points Assigned*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic factor</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Age (yr)</td>
</tr>
<tr>
<td>Women</td>
<td>Age (yr) - 10</td>
</tr>
<tr>
<td>Nursing home resident</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Coexisting illnesses†</strong></td>
<td></td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>+30</td>
</tr>
<tr>
<td>Liver disease</td>
<td>+20</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
</tr>
<tr>
<td>Renal disease</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Physical-examination findings</strong></td>
<td></td>
</tr>
<tr>
<td>Altered mental status‡</td>
<td>+20</td>
</tr>
<tr>
<td>Respiratory rate ≥30/min</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 90 mm Hg</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt; 35°C or ≥40°C</td>
<td>+15</td>
</tr>
<tr>
<td>Puls ≥125/min</td>
<td>+10</td>
</tr>
<tr>
<td><strong>Laboratory and radiographic findings</strong></td>
<td></td>
</tr>
<tr>
<td>Arterial pH &lt; 7.35</td>
<td>+30</td>
</tr>
<tr>
<td>Blood urea nitrogen ≥30 mg/dl (11 mmol/liter)</td>
<td>+20</td>
</tr>
<tr>
<td>Sodium &lt; 130 mmol/liter</td>
<td>+20</td>
</tr>
<tr>
<td>Glucose ≥ 250 mg/dl (14 mmol/liter)</td>
<td>+10</td>
</tr>
<tr>
<td>Hematocrit &lt; 30%</td>
<td>+10</td>
</tr>
<tr>
<td>Partial pressure of arterial oxygen &lt; 60 mm Hg$</td>
<td>+10</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>+10</td>
</tr>
</tbody>
</table>

### Risk Class Score

<table>
<thead>
<tr>
<th>Class</th>
<th>Points</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>II</td>
<td>&lt; 70</td>
<td>0.6</td>
</tr>
<tr>
<td>III</td>
<td>71-90</td>
<td>0.9</td>
</tr>
<tr>
<td>IV</td>
<td>91-130</td>
<td>9.3</td>
</tr>
<tr>
<td>V</td>
<td>&gt; 130</td>
<td>27.0</td>
</tr>
</tbody>
</table>

- Class I-III: outpatient care
- Class IV-V: admit to hospital
Sampling for Bacteriology

- Sputum gram stain and culture lack sensitivity and specificity and are not recommended for routine use in outpatient management.
- Patients with severe pneumonia should have blood cultures and sputum culture prior to initiation of antibiotics, provided a suitable sputum specimen can be obtained. Obtaining specimens for culture should not delay treatment. Consider nasal secretion sampling for respiratory viruses in time of seasonal activity.
- In patients admitted to the ICU, a concerted effort should be made to obtain lower airway specimens for culture, and urinary antigen testing for *Legionella pneumophila* and *Streptococcus pneumoniae* should be done.
- Specific patient modifiers are proposed by the ATS/IDSA Guidelines to guide microbiological sampling (see below)
- When a specific pathogen is identified, specific tailoring of therapy is debated because of the co-existence of typical and atypical pathogens
Consideration for specific pathogens

**Beta-lactam-Resistant and Drug (FQ or Macrolide)-Resistant Streptococcus pneumoniae (DRSP)**
- Age > 65 yr (or < 2)
- Antibiotic use in last 3 mos
- Alcoholism
- Immunosupression
- Multiple Medical Comorbidities
- Exposure to a child at a daycare centre

**Enteric gram-negatives**
- Residence in a nursing home
- Underlying cardiopulmonary disease
- Multiple medical comorbidities
- Recent anti-biotic therapy
**Pseudomonas Aeruginosa**
- Structural lung disease
- Corticosteroid therapy
- Broad-spectrum antibiotics for > 7 day in last month
- Malnutrition

### Patient Subsets and Associated Pathogens

<table>
<thead>
<tr>
<th>Patient Variables</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients + previously healthy + no recent antibiotics</td>
<td>Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Hemophilus influenzae, respiratory viruses</td>
</tr>
<tr>
<td>Outpatients + previously healthy + no recent antibiotics</td>
<td>Above + drug-resistant Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Co-morbidities or risk factors for DRSP, or risks for enteric gram negatives, or aspiration</td>
<td>Above + enteric gram negatives, Moraxella catarrhalis, Legionella spp., anaerobes</td>
</tr>
<tr>
<td>ICU</td>
<td>All of the above + Staphylococcus aureus, Pseudomonas, TB, fungi</td>
</tr>
</tbody>
</table>

The ATS/IDSA document includes a table which outlines less common pathogens and their associated risk factor(s).

### Patient Subsets and Empiric Treatment Options

#### Outpatients

<table>
<thead>
<tr>
<th>Patient Variable</th>
<th>Preferred Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously Healthy, no risk factors for DRSP</td>
<td>A macrolide¹ or doxycycline</td>
</tr>
<tr>
<td>Comorbidities (COPD, diabetes, renal or congestive heart failure, malignancy, alcoholism, immunosuppression) or use of antibiotics in previous 3 months</td>
<td>A respiratory fluoroquinolone² alone, an advanced macrolide plus high-dose amoxicillin, or an advanced macrolide plus high-dose beta-lactam</td>
</tr>
<tr>
<td>Regions with high rates of macrolide-resistant pneumococcus, regardless of patient modifiers</td>
<td>A respiratory fluoroquinolone² alone, an advanced macrolide plus high-dose amoxicillin, or an advanced macrolide plus high-dose beta-lactam</td>
</tr>
</tbody>
</table>

1. Erythromycin, azithromycin, or clarithromycin
2. Moxifloxacin, gatifloxacin, levofloxacin 750
3. Azithromycin or clarithromycin
4. Amoxicillin 1g tid or amoxicillin-clavulanic acid 2g bid
## Inpatients

<table>
<thead>
<tr>
<th>Patient Variable</th>
<th>Preferred Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Ward</strong></td>
<td>A respiratory fluoroquinolone alone or an advanced macrolide plus a b-lactam(^1)&lt;br&gt;Carbopenem + doxycycline for select patients as alternative macrolide</td>
</tr>
<tr>
<td><strong>ICU</strong></td>
<td>Beta-lactam plus either an advanced macrolide or a respiratory fluoroquinolone</td>
</tr>
<tr>
<td>Pseudomonas is not an issue</td>
<td>Antipseudomonal beta-lactam(^2) plus ciprofloxacin or levofloxacin 750 OR&lt;br&gt;Antipseudomonal beta-lactam plus an aminoglycoside plus respiratory fluoroquinolone OR&lt;br&gt;Antipseudomonal beta-lactam plus an aminoglycoside plus advanced macrolide</td>
</tr>
<tr>
<td>Risk for Pseudomonas</td>
<td>Add Vancomycin or linezolid</td>
</tr>
<tr>
<td>Risk factor for MRSA</td>
<td></td>
</tr>
<tr>
<td>If Influenza A is a consideration</td>
<td>Add oseltamivir or zanamivir if presentation is within 48hr symptom onset ** Evidence more recent to publication of guidelines suggests wide resistance to oseltamivir in wild-type influenza A and possible emerging resistance in novel H1N1 influenza A. Refer to Canada FluWatch (<a href="http://www.phac-aspc.gc.ca/fluwatch/index-eng.php">http://www.phac-aspc.gc.ca/fluwatch/index-eng.php</a>) for current reports on influenza activity and resistance profiles.</td>
</tr>
<tr>
<td>Nursing Home Patient</td>
<td>Same as for medical ward and ICU</td>
</tr>
<tr>
<td>Pleuropulmonary abscess or risk of gross aspiration (loss of consciousness, seizure, esophageal dismotility) with evidence of periodontal disease</td>
<td>Addition of anaerobic coverage (metronidazole or clindamycin)</td>
</tr>
</tbody>
</table>

1. Second or third generation cephalosporin, high dose amoxicillin-clavulanic acid<br>2. Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime.

### Other Treatment Considerations

#### Time to First Antibiotic Dose
Retrospective studies have suggested that mortality is reduced if first antibiotics are administered within 4 to 8 hours of presentation in the ED. Prospective studies have failed to confirm this benchmark.
Transition from IV to oral antibiotics and hospital discharge

Transition to oral antibiotics (same drug or drug class) is suggested when clinical stability improves. It is not clear if meeting all criteria is required before switching to oral, but no more than one should be unmet prior to discharge. In addition to clinical stability, there should be no other active medical issue, a safe discharge environment and assured follow-up prior to discharge.

Duration of Treatment

There is a surprising lack of evidence in support of treatment of any particular duration. ATS/IDSA suggests 7-10 days, with a minimum of 5 days, with no more than one stability criterion not met, and afebrile for 48-72 hours prior to discontinuation of treatment. Treatment decisions should be guided by severity of the pneumonia and response to therapy.

Prevention

- Hand and respiratory hygiene practices
- Annual Influenza vaccination in persons over the age of 50, with risk factors for influenza complications, house-hold contacts of high-risk persons, and health-care workers.
- Pneumococcal polysaccharide vaccination in persons over the age of 65, and those at risk of complicated pneumococcal disease.
- Vaccination status assessment at the time of hospitalization for all patients
- Smoking cessation
- Public health notification of particular pneumonia cases (Legionella, psitticosis, SARS, H1N1)
HOSPITAL-ACQUIRED PNEUMONIA/VENTILATOR-ASSOCIATED PNEUMONIA/HEALTHCARE-ASSOCIATED PNEUMONIA (HAP/VAP/HCAP)

**DEFINITIONS**

Hospital-acquired pneumonia (HAP)
Pneumonia that occurs more than 48 hours following admission to hospital and did not appear to be incubating at the time of admission. Also known as nosocomial pneumonia. HAP is the leading cause of death among hospital-acquired infections.

Ventilator-associated pneumonia (VAP)
A type of HAP that develops more than 48-72 hours after endotracheal intubation. Incidence 9-27% of ventilated patients with mortality of 25-50%.

Healthcare-associated pneumonia (HCAP)
Pneumonia that occurs in a non-hospitalized patient with extensive healthcare contact:
- Intravenous therapy, wound care, or chemotherapy within 30d
- Residence in a nursing home or long-term care facility
- Hospitalization in an acute care hospital for ≥2d in prior 90d
- Attendance at a hospital or hemodialysis clinic within prior 30d

**PATHOGENESIS**

- Related to the number and virulence of microorganisms
entering the lower respiratory tract via micro-aspiration (primarily from oropharyngeal colonization and GI tract to a lesser extent) and the host immune response.

- Wide variety of pathogens, can be polymicrobial and may be due to MDR pathogens

### DIAGNOSIS

Presence of a new or progressive radiographic infiltrate plus at least 2/3 of: fever >38C, leukocytosis or leukopenia, or purulent secretions.

The Clinical Pulmonary Infection Score (CPIS) can be used help improve the specificity of clinical diagnosis of VAP. A CPIS score of ≥6 is suggestive of pneumonia and has been evaluated as a threshold to start antibiotics. Some patients with a low clinical suspicion of VAP (CPIS<6) can have antibiotics safely discontinued after 3 days if the subsequent course suggests that the probability of pneumonia is still low.

**Modified Clinical Pulmonary Infection Score (CPIS) (AJRCCM 2003)**

<table>
<thead>
<tr>
<th>CPIS Points</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tracheal secretions</strong></td>
<td>Rare</td>
<td>Abundant</td>
<td>Abundant + purulent</td>
</tr>
<tr>
<td><strong>CXR infiltrates</strong></td>
<td>No infiltrate</td>
<td>Diffuse</td>
<td>Localized</td>
</tr>
<tr>
<td><strong>Temperature (C)</strong></td>
<td>≥36.5 and ≤38.4</td>
<td>≥38.5 and ≤38.9</td>
<td>≥39 and ≤36</td>
</tr>
<tr>
<td><strong>WBC</strong></td>
<td>≥4 and ≤11</td>
<td>&lt;4 or &gt;11</td>
<td>&lt;4 or &gt;11 + bands (≥0.5)</td>
</tr>
<tr>
<td><strong>PAO2/FiO2</strong></td>
<td>&gt;240 or ARDS</td>
<td></td>
<td>≤240 and no evidence of ARDS</td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
<td>Negative</td>
<td></td>
<td>Positive</td>
</tr>
</tbody>
</table>
Figure: Management strategies for a patient with suspected HAP, VAP, HCAP. The decision about antibiotic discontinuation may differ depending on the type of sample collected (PSB, BAL, or endotracheal aspirate), and whether the results are reported in quantitative or semiquantitative terms.

**ATS HAP/VAP/HCAP guidelines 2005**

**TREATMENT**

HAP, VAP and HCAP are commonly caused by aerobic gram-negative bacilli, such as *P. aeruginosa, K. pneumoniea*, and *Acinetobacter* species, or by gram-positive cocci, such as *S. aureus*, including MRSA. Anaerobes are an uncommon cause of VAP. Prevalence of MDR pathogens varies by patient population, hospital, and type of ICU, which underscores the need for local surveillance data.

**Risk factors for MDR pathogens**
- Antimicrobial therapy in preceding 90d
- Current hospitalization of 5d or more
- High frequency of antibiotic resistance in the community or the specific hospital unit
- Presence of risk factors for HCAP or family member with MDR pathogen
- Immunosuppressive disease and/or therapy

**Initial empiric antibiotic therapy in patients with no known risk factors for MDR pathogens and early onset (<5 days) – ATS/IDSA 2005**

<table>
<thead>
<tr>
<th>Potential pathogens</th>
<th>Recommended antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em> †</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>or</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (MSSA)</td>
<td>Levofloxacin, moxifloxacin</td>
</tr>
<tr>
<td>Antibiotic-sensitive enteric gram-negative bacilli</td>
<td>or</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Ampicillin/sulbactam, amoxicillin/clavulanic acid</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>or</td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td>Ertapenem</td>
</tr>
<tr>
<td><em>Proteus species</em></td>
<td></td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td></td>
</tr>
</tbody>
</table>

**Initial empiric therapy in patients with late-onset (≥5 days) disease or risk factors for MDR pathogens – ATS/IDSA 2005**

<table>
<thead>
<tr>
<th>Potential pathogens</th>
<th>Recommended antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>As above plus</td>
<td>Antipseudomonal cephalosporin (cefepime, ceftazidime)</td>
</tr>
<tr>
<td>MDR pathogens</td>
<td>or</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Antipseudomonal carbepenem (imipenem, meropenem, doripenem)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> (ESBL+)†</td>
<td>or</td>
</tr>
<tr>
<td><em>Acinetobacter species</em>†</td>
<td>β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam)</td>
</tr>
<tr>
<td></td>
<td><strong>plus</strong></td>
</tr>
<tr>
<td></td>
<td>Antipseudomonal fluoroquinolone† (ciprofloxacin or levofloxacin)</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td><em>Legionella pneumophila</em>†</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>or Aminoglycoside (amikacin, gentamycin, or tobramycin)</td>
<td><em>plus</em> Linezolid or vancomycin‡</td>
</tr>
</tbody>
</table>

† If an ESBL+ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbepenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

‡ If MRSA risk factors are present or there is a high incidence locally.

- Initial antibiotic therapy should be given promptly because delays in administration may add to excess mortality.
- Intravenous therapy should be administered to all patients, with a switch to oral/enteral therapy in selected patients with a good clinical response and a functioning intestinal tract.
- When results of lower respiratory tract cultures are known, antibiotics should be tailored to monotherapy in the absence of resistant pathogens. Aerosolized antibiotics have not been proven to have value in the therapy of VAP but may be useful as adjunctive therapy in patients with MDR pathogens who are not responding to systemic therapy.
- If patients receive an initially appropriate antibiotic regimen with a good clinical response, a duration of 7 days is adequate unless infection is with *P. aeruginosa* or *Acinetobacter* species (at least 14 days required). Non-response to therapy is usually evident by day 3. Non-responding patients should be evaluated for non-infectious mimics of pneumonia, drug-resistant organisms, extrapulmonary sites of infection and complications of pneumonia and its therapy.

HAP is typically caused by gram-ve pathogens including *Pseudomonas* as well as *S. aureus*. The choice of the initial empiric antibiotic regimen should provide coverage for these “core
organisms”. In addition, the regimen should be modified according to the presence of various risk factors.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Likely pathogens</th>
<th>Antibiotic choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild—moderate HAP AND No-risk factors</td>
<td>Core organisms (S. aureus, Gram-ve’s, Pseudomonas)</td>
<td>Cefazolin + aminoglycoside OR 2nd gen cephalosporin OR 3rd gen cephalosporin</td>
</tr>
<tr>
<td>Aspiration, poor dentition, abdominal surgery</td>
<td>Core organisms + anaerobes</td>
<td>Add metronidazole or clindamycin</td>
</tr>
<tr>
<td>Chronic corticosteroids</td>
<td>Core organisms + Legionella</td>
<td>Add macrolide</td>
</tr>
<tr>
<td>ICU stay, chronic lung disease, prior broad spectrum antibiotics OR Severe HAP</td>
<td>Core organisms + Pseudomonas</td>
<td>Broad-spectrum Beta-lactam with anti-pseudomonal activity (piperacillin, ceftazidime, imipenam/cilastin, ticarcillin/clav) OR Antipseudomonal fluoroquinolone AND Aminoglycoside</td>
</tr>
</tbody>
</table>
THE “NON-RESOLVING PNEUMONIA”

A number of diseases commonly present in the following fashion:

A patient develops some combination of cough, SOB, malaise and fever. CXR confirms the presence of an **airspace infiltrate** and the patient is treated with a course of antibiotics for a presumed community-acquired pneumonia. However, the symptoms persist and the CXR fails to improve. Ultimately, the patient may receive several courses of antibiotics.

It is at this point that the Respirologist becomes involved…

**Differential Diagnosis of Nonresolving Airspace Pattern:**

**Bacterial pneumonia**
- Inappropriate antibiotics
- Post-obstructive (often secondary to malignancy)
- Aspiration
- Empyema

**Tuberculosis, other infections**

**Malignancy**
- Bronchoalveolar cell carcinoma
- Lymphoma

**Eosinophilic pneumonia**

**BOOP**

**Pulmonary alveolar proteinosis**

**Drug-induced pneumonitis**

**Bacterial pneumonia** – the longer the patient’s course, the less likely it becomes that the disease is in fact caused by a bacterial pneumonia. *The CXR may take up to eight weeks to clear in older individuals or those with comorbidities (alcoholism,*
diabetes, COPD, CHF). Nonetheless, it is worthwhile confirming that there are no obvious reasons why the patient’s pneumonia might have not responded to therapy. Inappropriate antibiotic choices may lead to partial therapeutic success and a “lingering” course. The presence of endobronchial obstruction or recurrent aspiration may be other explanations. Lastly, any effusion should be sampled to rule out the presence of empyema.

If bacterial pneumonia is excluded, the remainder of cases will usually be the result of one of six diseases:

1. **Tuberculosis** – should always be considered. Remember that the CXR appearance of tuberculosis can look like almost anything. At a bare minimum, sputum should be sent for AFB and TB culture, and bronchoscopy may be indicated for further investigation, particularly if the patient is at epidemiologic risk.

   a) **Other infections** - good history taking may provide clues, i.e., "where have you been and what do you do?"
   - fungal pneumonia (caves, chicken coops, renovations)
   - Q fever (parturient cats, sheep, goats, abattoirs)
   - tularemia (rabbit hunters)
   - leptospirosis (rat urine)
   - hantavirus

2. **Drug-induced pneumonitis** - especially amiodarone, Nitrofurantoin, methotrexate

3. **Malignancy** – Bronchoalveolar cell carcinoma (BAC) is a subtype of adenocarcinoma, which commonly presents as airspace disease on CXR. The reason is that the tumour cells tend to grow along the alveolar surfaces and may literally fill the alveoli, simulating a pneumonia. BAC may even display air bronchograms. Lymphoma is another pulmonary malignancy, which can present in this fashion. Other bronchogenic carcinomas are less likely to simulate airspace disease.
4. **Eosinophilic pneumonia** – is an idiopathic inflammatory disease associated with eosinophilia, both in the serum and in bronchoalveolar lavage fluid. About 50% of cases occur in asthmatics. The CXR pattern classically (but only in a minority) displays a bilateral peripheral pattern that has been described as the “photographic negative of pulmonary edema”. There is generally a very good response to steroids.

5. **BOOP (Bronchiolitis obliterans organizing pneumonia)** - should not be confused with BO (Bronchiolitis obliterans). BOOP is characterized by inflammatory cells and granulation tissue filling alveoli and obstructing small bronchioles. Some authorities prefer the name COP (Cryptogenic organizing pneumonia). The CXR shows focal airspace infiltrates, which may disappear, only to reappear somewhere else. The majority of cases of BOOP are idiopathic, but it is also associated with connective tissue disease, infection, organ transplant and some drugs. There tends to be a good response to steroids.

6. **Pulmonary alveolar proteinosis (PAP)** – is a flooding of the alveoli with a granular lipoprotein, which is probably derived from surfactant. The CXR typically shows bilateral perihilar infiltrates. There may be striking air bronchograms, which are best appreciated on CT scan. PAP has been associated with hematologic malignancies and treatment with Busulfan. Hypoxemia may be profound, with cyanosis and clubbing. Bronchoalveolar lavage returns a distinctive milky fluid. Treatment is with therapeutic whole lung lavage with large quantities (up to 50L) of saline.
Primary Infection

Mycobacterium tuberculosis is transmitted by inhaled droplet nuclei, and therefore site of primary infection is typically mid and lower lung zones.

The majority of such infections will be contained by the host macrophage mediated immune response and subsequently, T-cell mediated delay-type hypersensitivity develops (Latent TB infection). There may be a mild self-limited febrile illness, and in a small minority, hypersensitivity phenomena (erythema nodosum, conjunctivitis). Evidence of previous primary infection may be seen on the CXR as calcified granulomata (“Ghon's foci”) alone, or with calcified lymph nodes (Ghon's complex).

Primary Disease

A small minority (5%) of immunocompetent hosts will develop symptomatic primary disease within the first 18-24 months of initial infection. This risk is much greater in immunocompromised hosts (e.g. 10%/year in HIV+ individuals), which includes extremes of age, diabetes, renal failure and use of immunosuppressing medication.

Classic primary disease manifests with febrile respiratory illness, with patchy mid-lower zone infiltrates, hilar/mediastinal adenopathy, which is often unilateral and/or pleural effusion (“TB pleurisy”). Patient with isolated adenopathy or pleural effusion are unlikely to be infectious. This spectrum of TB is typically thought of as a disease of childhood in endemic countries, but is seen more...
commonly now in adults in regions where exposure to TB in childhood is uncommon.

A sub-group of these individuals will progress to severe destructive disease with cavitation and abscess formation ("primary progressive disease").

**Reactivation ("Post Primary") Tuberculosis**

Reactivation tuberculosis is the appearance of active disease years after the initial infection. The lifetime risk of reactivation TB is about 10% (Most of that risk appears to be upfront within 1-2 years of seroconversion). Risk factors for reactivation are similar to those mentioned above for primary disease.

Pulmonary disease is by far the most common site for reactivation with a predilection for the upper lung zones, likely due to higher oxygen tension and reduced lymphatic drainage.

Typical presentation is that of chronic dry cough, anorexia, weight loss, fevers, night-sweats. Dyspnea and hypoxia are not common. Productive cough and hemoptysis are features of more advanced disease.

**Non-Respiratory ("extra-pulmonary") Tuberculosis**

Reactivation is believed to be the mechanism for non-respiratory TB following hematogenous seeding of organs at the time of primary infection. Although any system can be affected, superficial lymph nodes and the genito-urinary tract are the most common, followed by pericardial, meningeal, bone, and abdomen. Disseminated (miliary) disease may include all of these sites including lung. These forms of TB are not transmissible with the exception of disseminated, unless focal areas of infection are disrupted (e.g. Operating room, laboratory).
Transmission

As mentioned, TB is transmitted via inhalation of respiratory micro-nuclei and droplet secretions. Patients with active pulmonary disease are those who can transmit the disease to others. The likelihood of transmission is determined by patient factors, environmental factors and host factors.

1. Patient factors: The presence of coughing or sneezing increased the aerosolization of infectious particles. The concentration of bacilli per droplet increases with higher burden of disease (33% transmission rate for smear-positive cases) Cavitary disease is known to bear a high burden of bacilli. From a public health perspective, patients are thought to be non-infectious when serial sputum cultures are negative. A patient with serial negative AFB smears may still transmit disease if cultures are positive, though the risk is much lower (17% transmission rate) than with positive smears. Finally, smears may occasionally be positive with negative cultures, indicating that the bacilli seen on the smear were not viable.

2. Environmental factors: Typically, prolonged (months) close contact with an index case is required for transmission. Evidence of this is the relatively low attack rate (25%) of close household contacts. Poor ventilation settings increase the risk of transmission, and therefore minimum total air exchange standards are recommended for high risk settings (shelters, prisons, hospitals). The *Mycobacterium tuberculosis* bacilli do not survive well on fomites.

3. Host factors: Despite the above considerations, there are known cases of transmission with low risk exposures, and therefore there are host factors that influence individual susceptibility.
### Diagnostic Tests

1. **Tuberculin skin testing** (PPD or Mantoux) is a test for latent infection. Delayed hypersensitivity reaction to the antigen cause erythema and induration at the site of dermal implantation. The test is read at 48-72 hours and should record the greatest diameter of induration only. It has little role in the diagnosis of active disease, as a positive test indicates previous exposure only and a negative test may be falsely so on the basis of anergy from the current systemic illness. The test may be falsely negative in other forms of immunosuppression (HIV, medications). The main causes of false positives are previous Bacillus Calmette-Guérin (BCG) vaccine and previous exposure to non-tuberculous mycobacteria (NTM).

2. **Interferon-Gamma Release Assay** is a novel screening blood test that detects patient T-cell response to TB antigen *in vitro*. It is not currently widely available and is not covered under the provincial health insurance. At present, the main advantage is that it is not influenced by BCG vaccine or NTM exposure.

3. **AFB Staining** is the direct visualization of acid fast bacilli under light microscopy following preparation with one of several acid fast stains. Manual quantification is reported from absent to numerous. Hospital labs with often report a preliminary smear (unconcentrated) which has poor sensitivity. The concentration of the specimen requires additional precautions and is performed at Toronto Public Health Laboratories. Decisions should be made based on the concentrated smear. False positives may occur with non-tuberculous mycobacteria and less commonly, non-mycobacterial organisms (e.g. *Nocardia sp.*).

4. **Nucleic Acid Amplification** are techniques used to rapidly determine if the organisms seen on an AFB preparation are in fact *Mycobacterium tuberculosis*. Toronto Public Health Laboratories uses the commercial assay AMTD (Amplified Mycobacterium Tuberculosis Direct Test). This is an RNA based test, which has the advantage of only detecting viable organisms (unlike DNA
based PCR techniques).

5. **Mycobacteria Culture** is the gold standard for diagnosis. *Mycobacterium tuberculosis* typically grows within about 3-4 weeks but cultures are not reported until 8 weeks to allow for the slower growing NTMs. Sensitivities for the four first line drugs are routinely performed on positive TB cultures, and can be performed for alternative drugs upon request (this is done in Winnipeg).

6. **Genotyping** is currently in use at the public health level for tracing outbreaks.

---

**Diagnostic Approach to Common Clinical Scenarios**

1. *Does this symptomatic patient with an abnormal CXR have active pulmonary TB?*

   *When in doubt, isolate* – negative pressure room, N95 for others, surgical mask for patient. If a patient with a high index of suspicion is being worked up as an outpatient, then they should remain in the home, use a surgical mask in common living space and if they leave the home. House hold contacts should be assessed, and consideration for removal of the patient from the home (e.g. hospital admission) made if there are high risk persons in the home (immunocompromised, children < 5)

   *What are the symptoms?* (fever, night-sweats, weight loss, cough, symptoms of non-respiratory TB?)

   *Has this patient had or been treated for tuberculosis in the past?* Can any details be obtained? Often the details of previous treatment are not obtainable. Important for decisions about empiric therapy if drug resistance is a possibility.

   *What are the risk factors for exposure?* (known contact of active case, high risk settings such as immigration from an endemic...
country, prisons, shelters, reserves, hospitals, long-term care facilities).

**Physical examination:** Typically normal in respiratory TB. May have findings of consolidation, or findings of non-respiratory disease. If clinical suspicion is high, AMTD can be requested for negative smears for increased sensitivity.

**CXR:** Upper zone infiltrates or fibro-cavitary disease increases the probability but may seen opacities elsewhere only. Whenever possible, compare to old films.

**Sputum Sampling:** Patients with cough productive of copious sputum can often give spontaneous sputum sample for AFB and culture with good yields. In less advanced disease, spontaneous sputum is less sensitive (in keeping with the lesser degree of infectivity). Two induced sputa have a higher sensitivity than bronchoscopy, but this is not available in all centers. To increase yield, sputa should be collect post-bronchoscopy as well (effectively, induced sputa).

Treatment initiated if AFB (and AMTD) + or if very high pre-test probability.

**2. Does this asymptomatic patient with an abnormal CXR have active pulmonary TB?**

Same approach as for Scenario 1., but an asymptomatic patient does not require isolation. A very common scenario in Toronto is a patient referred from Immigration Canada with an abnormal CXR, often showing either changes consistent with previous primary infection (granulomata, calcified lymph nodes) or previous TB disease (apical fibrotic changes). Once again, comparison to previous films is very useful if available. Long standing, unchanged abnormalities excludes the possibility of active disease. If no
previous films are available, then negative induced sputum culture (ideally 2 specimens), followed by serial clinical and CXR surveillance for 2 years with no change excludes active disease.

3. This patient was exposed to a case of active respiratory TB
If there is no clinical or radiographic evidence of active disease, and the patient is not in a high risk group (e.g. HIV), then a two step-skin TB skin test is performed, with the second part done at least 8-weeks after the end of contact with the index case. If the test remains negative then no further investigation is required. If the skin test known to be previously positive, then recent seroconversion cannot be detected, and the patient should have clinical and CXR surveillance for 2 years.

Treatment of Active Tuberculosis

1. Initiation of four first-line drugs: **INH, rifampin, pyrazinamide and ethambutol**, given for two months followed by INH and rifampin for four months is the preferred treatment for patient with fully sensitive organisms. Ethambutol can be discontinued if the organism is fully sensitive. Pyrazinamide is highly bacteriocidal against slowly dividing/dormant bacilli, therefore its inclusion in the regimen for 2 months allows for shortened overall duration of therapy to 6 months.

2. Alternatively, a nine-month regimen of INH and rifampin is acceptable for patients who are intolerant of pyrazinamide. Again, ethambutol should be included in the initial regimen, pending susceptibility studies.

3. Baseline and follow-up evaluations:
   - Microscopic examination and mycobacterial cultures (three sputum specimens) and baseline and q monthly until two
consecutive specimens are negative on culture (AFB can be used for infectiousness).

- Counseling and testing for HIV infection.
- AST, ALT, ALT, Bili, CR, PLT count at baseline, but routine testing throughout therapy not necessary unless abnormal baseline or increased risk of hepatotoxicity.
- Monthly testing of visual acuity and red-green color discrimination when EMB being used.
- Clinical evaluations at least monthly to identify possible adverse effects of the medication and assess adherence.

4. Consideration should be given to treating all patients with directly observed therapy (DOT).

5. Children should be managed in essentially the same way as adults with appropriate dosage adjustments.

6. Extrapulmonary TB should be managed in essentially the same way as pulmonary TB with the exceptions of patients with meningeal, miliary, bone or joint TB who should receive at least 12 months of therapy, and consideration given to the use of IV medications if poor absorption is a consideration (e.g. cachectic patient)

7. The major determinant of the outcome of treatment is strict adherence to the drug regimen.

**Special Situations**

1. **HIV infection:** Generally treatment is similar with exception of:
   a. Drug interactions
   b. Immune reconstitution using antiretroviral therapy may cause worsening signs and symptoms such as high fevers, adenopathy, and worsening lung infiltrates. Therefore, TB treatment is usually initiated first for several weeks to
decrease the bacillary burden, followed by HAART therapy. NSAIDS or prednisone may be used to control such inflammation.

2. **Extrapulmonary disease:** Fully sensitive TB is treated with the same medications, but for longer durations: 6-9 months for TB adenitis, 12 months for disseminated, meningitis, pericarditis, and bone. Addition of glucocorticoids recommended for meningitis and pericarditis (1mg/kg for 4 weeks, tapered over 8 weeks).

3. **Pregnancy and breast-feeding:** because of the risk of TB to the fetus, treatment should be initiated whenever the probability of disease is moderate to high. Initial regimen should include INH, RIF, and EMB. There is little data on the use of PZA in pregnancy. Streptomycin can cause congenital deafness in the fetus. Breastfeeding can continue. Pyridoxine should be given to all pregnant or breastfeeding women.

4. **Drug Resistance**
   Isolated INH resistance is the most commonly seen due to its widespread use.
   Multi-drug Resistance TB (MDR-TB) is defined as a strain resistant to INH and RIF. This may include resistance to other drugs.
   Extensively Drug Resistant TB (XDR-TB) is defined as a strain resistant to INH, RIF, FQ and one injectable agent (i.e. aminoglycoside).

   General principles:
   a. Never add a single drug to a failing regimen.
   b. Request consultation.
   c. Patients should receive DOT therapy.
   d. Attempt to add at least three new drugs with in vitro susceptibility.
   e. Intermittent therapy should not be used.
   f. Consider role of surgery.
<table>
<thead>
<tr>
<th>Pattern of Drug Resistance</th>
<th>Suggested regimen</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>RIF, PZA, EMB</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>(may add FQN if extensive disease)</td>
<td></td>
</tr>
<tr>
<td>MDR: INH and RIF</td>
<td>FQ, PZA, EMB, IA +/- alt agent</td>
<td>18-24 months</td>
</tr>
<tr>
<td>MDR: INH, RIF, EMB, PZA</td>
<td>FQ (EMB pr PZA if active), IA, 2 alt agents</td>
<td>24 months</td>
</tr>
<tr>
<td>RIF</td>
<td>INH, EMB, PZA, FQ</td>
<td>9-12 months</td>
</tr>
</tbody>
</table>

IA: Injectable agent: aminoglycoside (streptomycin, amikacin, or kanamycin)
Alt agent: Ethionamide, cycloserine, P-amnosalicylic (PAS), clofazamine, clarithromycin, clavulin, linezolid

**Adverse Effects of First Line Drugs**

**INH**
Hepatotoxicity is the major adverse effect with INH. It is rare in patients < 20 y/o and seen in 2% of patients >50 y/o. Other risk factors for hepatitis must be considered when quoting this risk. Practice for monitoring transaminases varies, but should be done at baseline in all patients, and monthly in patients with history of or risk factors for liver disease. Patients should be counseled to stop INH and seek medical attention if signs/symptoms of hepatitis develop. INH should be stopped if transaminases rise to five time ULN without symptoms or 3 time ULN with symptoms.

Peripheral neuropathy is the second major adverse effect and its risk is minimized by the addition of pyridoxine (vitamin B6) 25 mg (up to 100 mg in patients with risk factors for neuropathy such as diabetes)

**Rifampin**
Hepatotoxicity and drug interactions are the importance adverse effects of rifampin. Important interactions exist with HIV medications and the birth control pill.

**Ethambutol**
Optic neuropathy is the major consideration with ethambutol. Baseline and monthly visual acuity and colour vision testing should
be performed in addition to a baseline ophthalmology assessment. Risk of optic neuropathy increases with cumulative dose and impaired renal function, and is usually reversible with discontinuation.

Rash and GI symptoms are common with all TB medications

**Latent Tuberculosis Infection**

TBST should only be used if the *a priori* decision has been made to treat LTBI if the test is positive. Therefore, its use should be limited to situations where the risk of active disease is high:

1. Recent exposure* or immigration from an endemic country within the last 2 years
2. Impaired immunity (HIV, Diabetes, Renal failure, immunosuppressing medications including TNF-alpha inhibitors, pulmonary silicosis)
3. Radiographic evidence of old healed active TB (i.e. Fibronodular changes) but no prior treatment.

*Annual testing in healthcare workers is a means of detecting recent sero-conversion in a population at higher risk of exposure.

Induration cut-offs are set to emphasize high specificity in patients at lower risk of developing active disease (i.e. Large induration) and sensitivity in patients at high risk (i.e. Small induration).
Interpreting the TBST in a patient with previous BCG vaccine is challenging. When given before the age of 1, the BCG has little impact on the TBST. After the age of 1, it should be considered an important cause of false positive test. There is an online calculator that helps predict the risk of active disease, taking into consideration the BCG status:

http://meakins.mcgill.ca/meakins/NEW%20TST%20Calculator/homeE.htm

Standard treatment for LTBI is INH 5mg/kg (max 300mg) daily for 9 months, decreasing the risk of developing active disease by about 80%.

Alternative regimens include RIF for 4 months, INH+RIF for 6 months. RIF+PZA has been shown to increase the risk of hepatotoxicity.

<table>
<thead>
<tr>
<th>TST Reaction Size (mm induration)</th>
<th>Situation in Which Reaction is Considered Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>HIV infection with immune suppression AND the expected likelihood of TB infection is high (e.g. patient is from a population with a high prevalence of TB infection, is a close contact of an active contagious case, or has an abnormal x-ray)</td>
</tr>
<tr>
<td>5-9</td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>Close contact of active contagious case</td>
</tr>
<tr>
<td></td>
<td>Children suspected of having tuberculosis disease</td>
</tr>
<tr>
<td></td>
<td>Abnormal chest x-ray with fibronodular disease</td>
</tr>
<tr>
<td>≥ 10</td>
<td>Other immune suppression: TNF-alpha inhibitors, chemotherapy</td>
</tr>
<tr>
<td></td>
<td>All others</td>
</tr>
</tbody>
</table>
LUNG CANCER

General Considerations

- Most common cause of cancer mortality in the world.
- In the US, the number of deaths caused by lung cancer exceeds the mortality from colon, breast, and prostate combined.
- Unfortunately, lung cancer is recognized late and the five-year mortality from the time of diagnosis is 85-90%.
- This is exemplified by the fact, that more than 90% of patients are symptomatic at the time of diagnosis.

Pathology

- Lung cancer can be divided into small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), and neuroendocrine tumours.

NSCLC:
- 3 types: Adenocarcinoma, Squamous Cell Carcinoma, Large Cell Carcinoma

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Squamous:</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-40%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Bronchoalveolar</td>
<td></td>
</tr>
<tr>
<td>carcinoma (BAC)</td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td></td>
</tr>
<tr>
<td>Acinar</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large Cell:</td>
</tr>
<tr>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>
The greatest risk factor for lung cancer is smoking, with a 10-30 times higher risk as compared to a non-smoker.

Other risk factors for lung cancer include: second-hand smoke, asbestos, radon, arsenic, ionizing radiation, and haloethers.

90% of patients diagnosed with lung cancer are symptomatic at presentation.

Minority of patients have symptoms related to the primary tumour.
Most have symptoms related to intra-thoracic spread or distant mets.

Symptoms Related to Primary Tumour:

**Cough**: Non-specific symptom seen in most smokers with COPD. A change in a chronic cough should raise suspicion for malignancy.

**Dyspnea**: Again, may be related to underlying COPD. Lung cancer itself may cause dyspnea secondary to airway obstruction, post obstructive atelectasis, lymphangitic spread of tumour, or pleural effusion.

**Hemoptysis**: Seen in 25-50% of patients. Rarely massive -- usually manifests as streaking of sputum.

**Chest pain**: Occurs in 25-50% of patients. A dull, intermittent pain usually occurs on the side of the tumor. It is unrelated to breathing or coughing.
**Wheezeing:** Uncommon and if present consider obstruction of a major airway.

**Symptoms Related to Intrathoracic Spread**

**Neurologic:**

*Recurrent Laryngeal Nerve:* More common with left-sided lesions and causes hoarseness in up to 15% of patients

*Phrenic Nerve:* If present, usually noted on chest radiograph as elevated hemi-diaphragm

*Pancoast Tumour:* Lesion involving posterior segment of upper lobe. If involving brachial plexus, common routes involved are C8, T1, and T2. Symptoms include pain, muscle wasting, and temperature perception changes. Involvement of the sympathetic chain may cause Horner’s syndrome (miosis, ptosis, anhydrosis).

**Chest Wall:** This pain may be severe and or localized reflecting extension of the tumour into the chest wall or ribs. Tenderness may be elicited at site of tumour extension.

**Pleura:** Pleural involvement occurs in up to 15% of patients. It may cause characteristic “pleuritic” chest pain or even pleural effusion. Effusion may be caused by direct extension of tumour into pleural space, obstruction of lymphatics, or mediastinal lymph node enlargement impairing drainage.

**SVC Obstruction:** Most commonly associated with small cell carcinoma. Caused by direct invasion of the SVC or by compression by paratracheal lymph nodes. Symptoms include facial swelling, dilated veins on upper chest, and plethora.
**Pericardium:** Metastases to the heart can cause a pericardial effusion. It rarely causes tamponade.

**Symptoms Related to Extrathoracic Spread/Distant Metastases**

**Bones:** Vertebrae are most commonly involved, but any bone may be involved. Most common symptom is pain and is present often at presentation.

**Liver:** Common site of involvement. Symptoms are weakness and fatigue. Liver enzymes rarely elevated until metastases are large and numerous.

**Adrenals:** Most commonly occurs with small cell tumours and often found during staging. Usually does not cause adrenal insufficiency.

**Brain:** 10% of patients will have brain lesions at presentation. Symptoms include headache, nausea, vomiting, and focal neurologic deficits. Confusion, personality changes, and seizures may also occur.

**Paraneoplastic Syndromes:**
A large number of paraneoplastic syndromes are associated with lung cancer.

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Neurologic:</th>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Eaton-Lambert</td>
<td>Clubbing</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome</td>
<td>Hypertrophic</td>
</tr>
<tr>
<td>Cushing Syndrome</td>
<td>Peripheral Neuropathy</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Mononeuritis multiplex</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Subacute sensory neuropathy</td>
<td>Lactic Acidosis</td>
</tr>
<tr>
<td></td>
<td>Cerebellar degeneration</td>
<td></td>
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</tbody>
</table>
The 7th edition of the TNM staging system is the most recent version, replacing the 6th edition as of January 1, 2010. The major change in the 7th edition is the reclassification of malignant pleural effusions and separate tumor nodule(s) (previously called satellite nodules). Other changes include new size cut-offs and new subdivisions of the T1 (into T1a and T1b), T2 (into T2a and T2b), and M1 (into M1a and M1b) descriptors.

TNM Staging System

<table>
<thead>
<tr>
<th>Stage groupings</th>
<th>T1a-T1b</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIA:</td>
<td>T1a, T1b, T2a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB:</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA:</td>
<td>T1a, T1b, T2a, T2b</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB:</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III:</td>
<td>T4</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV:</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a or M1b</td>
</tr>
</tbody>
</table>

General Approach to Staging

**History and Physical:**
- A full history and physical focusing on the possible effects of the tumour as described above (local, intrathoracic, extrathoracic).

**Blood Tests:**
- American Thoracic Society (ATS) guidelines recommend that all patients have a CBC, electrolytes, creatinine, calcium, ALP, AST, ALT, albumin, and bilirubin done at baseline.
- Elevations in liver function or enzymes should prompt evaluation of the liver with ultrasound or CT.
- Increased calcium and ALP should prompt evaluation for bone mets.

**CT Chest:**
- All patients with lung cancer should have a CT of the chest and abdomen to include the adrenals.
- Allows for accurate measurement of tumour size and assessment of atelectasis and the presence of an effusion.
- Unfortunately, CT is not as good at diagnosing metastatic spread of tumour to mediastinal and hilar nodes.
- The reported sensitivity and specificity for assessing mediastinal nodes is 60% and 81% respectively.
- The CT is used as a guide for further assessment via mediastinoscopy or fine needle biopsy.

**Brain Imaging:**
- The ATS does not recommend the routine use of MRI or CT brain for staging of lung cancer patients.
- Imaging should be guided by positive findings on history or physical.
- However, most oncologists and surgeons will order either CT or MRI on their patients.
- The American Society of Clinical Oncology recommends the
routine use of brain imaging for patients with Stage III NSCLC, who will be undergoing aggressive treatment.

**Bone Scan:**
- Should be ordered based on clinical grounds, but often is ordered on all patients pre-operatively.

**Positron Emission Tomography (PET) Scanning:**
- PET scanning is currently available at PMH as part of a research trial.
- Several reports thus far indicate improved detection of local and distant metastases as compared to CT.
- Further studies are needed to help define how PET should be used in the context of lung cancer staging.

**Invasive Staging:**
- The presence of mediastinal lymph nodes has a significant impact of the choice of therapy.
- CT has inadequate test characteristics for accurate staging.
- Mediastinoscopy is the gold standard for assessment of mediastinal lymph nodes.
- It is done in the OR under general anaesthesia.
- Patients are usually discharged home the same day.
- An incision is made at the supra-sternal notch and biopsies can be made of the left and right paratracheal nodes, pre-tracheal nodes, and anterior subcarinal nodes.
- Assessment of posterior sub-carinal, inferior mediastinal, AP window, and anterior mediastinal nodes cannot be assessed
- The approximate sensitivity is 80-85%.
- Patients with abnormal lymph nodes on CT, but no distant metastases should have a mediastinoscopy.
- As well, patients with normal lymph nodes on CR, and no distant metastases should also undergo mediastinoscopy because of the high false negative rate of CT.
Treatment of Non-Small Cell Lung Cancer:

- Treatment is based on tumour type (non-small cell versus small cell) and staging.
- NSCLC Stages I and II have relatively high cure rates using combination surgery and adjuvant chemotherapy.
- The use of adjuvant chemotherapy has only in the last year been demonstrated to be effective in prolonging survival, with much of the results coming from work at Princess Margaret Hospital (PMH).
- Stage III and IV lung cancer have very poor median survival rates.

Stages IB and II:

- Treatment involves combination surgery (resection of involved lobe or pneumonectomy) and now adjuvant chemotherapy.
- The NCIC BR1-10 Trial conducted at PMH involved 459 patients with resected IB or II disease. Patients were randomly assigned to surgery alone or surgery followed by four cycles of vinorelbine and cisplatin.
- 5-year relapse-free survival was 61% versus 48% favouring the adjuvant arm.
- Overall survival advantage with chemotherapy was 69% versus 54%.

Stage IIIA:

- Treatment options depend on respectability of the tumour and the patient’s overall health status:
  1. If the tumour is resectable and the patient can tolerate surgery, resection plus adjuvant chemotherapy is the preferred treatment option.
  2. If the tumour is unresectable, then two options remain:
     i) Conventional chemotherapy and radiation
     ii) Neoadjuvant chemotherapy followed by surgery
Stage IIIB:
- Treatment is with concurrent chemotherapy and radiation.
- Etoposide plus cisplatin is used initially with radiation followed by further chemotherapy.
- Possible cure can be achieved, with 5-year survival in the range of 15-20%.

Stage IV:
- Primarily managed with palliative chemotherapy and radiation therapy.
- Chemotherapy with cisplatin plus vinorelbine/gemcitabine improves one-year survival from approximately 15% with no treatment to 35-35% with treatment.
- Median survival is extended by from 6 months to approximately 10-11 months.
- Palliative radiotherapy to lungs is considered for large bulky tumours, hemoptysis, lobar collapse, or for bony metastases.

Small Cell Lung Cancer

- Small cell accounts for about 20% of lung cancer and is much more rapidly growing, requiring a different staging system and management approach. Patients commonly present with bulky disease and distant metastases.

Staging of Small Cell Carcinoma

**Limited disease:** confined to one hemithorax and ipsilateral supraclavicular nodes.

**Extensive disease:** spread beyond the confines above.
Treatment of Small Cell Carcinoma

- Response rates to chemotherapy are high (60 - 90%) but relapse rate is also very high. Chemotherapeutic agents used include etoposide, cisplatin, carboplatin, cyclophosphamide, ifosfamide.

**Limited Disease:**
- Treatment is with combination radiation and chemotherapy.
- Cure is achievable, with 5-year survival rates of 10-20%.
- Median survival is 16-18 months with treatment.

**Extensive Disease:**
- Chemotherapy is the treatment of choice, with median survival of 9 months and 2 yr survival less than 10%.
- Cure is generally not achievable.
THE SOLITARY PULMONARY NODULE

BACKGROUND

1. This is an extremely common Respirology referral. By definition, a solitary pulmonary nodule is
   - a lesion seen on CXR which is < 3cm in diameter
   - surrounded by normal lung parenchyma. There should be no associated abnormalities (e.g. atelectasis, adenopathy or effusions).
   - Major question is whether the lesion represents a benign or malignant process.

2. **Granulomas** and **hamartomas** make up more than 50% of all SPNs and the vast majority (90%) in those less than 35 years of age. However in older patients, and particularly those with a smoking history, the majority of SPNs will be **malignant**.

<table>
<thead>
<tr>
<th>Causes of Solitary Pulmonary Nodule</th>
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<tbody>
<tr>
<td><strong>Benign causes (60%)</strong></td>
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<tr>
<td>Granuloma  54%</td>
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<tr>
<td>Hamartoma   4%</td>
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<tr>
<td>Many others</td>
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<tr>
<td><strong>Malignant (40%)</strong></td>
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<tr>
<td>Lung CA (BAC and large cell most common) 33%</td>
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<tr>
<td>Carcinoid    3%</td>
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<td>Metastasis  4%</td>
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Under age 35:  90% of SPNs are benign
Over age 70:  70% of SPNs are malignant
Infectious granulomas- TB, endemic fungi (histoplasmosis, coccidiodomycosis), atypical mycobacterium, PCP in HIV.

Hamartomas- Benign tumors of the lung. Can have variety of components, including cartilage (with scattered calcification), fat, muscle, and myxomatous and fibroblastic tissue.

<table>
<thead>
<tr>
<th>PREDICTORS OF MALIGNANCY</th>
</tr>
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<tbody>
<tr>
<td>1. Patient age- chance of malignancy increases with increasing age, 3% ages 35-39, 15% ages 40-49, 43% ages 50-59, 50% &gt;60 years of age.</td>
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<tr>
<td>2. Presence of underlying risk factors- Exposure to smoking, asbestos, occupational carcinogens, previously diagnosed malignancy. All increase the likelihood of malignancy.</td>
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<tr>
<td>3. Size of lesion- lesions greater than 3 cm particularly likely to be malignant.</td>
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<tr>
<td>4. Border characteristics of lesion- Calcification in a diffuse, laminar, central or “popcorn” pattern indicates that the lesion is secondary to a remote inflammatory process and is benign. Eccentric calcification is not helpful, and can be associated with malignancy.</td>
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<tr>
<td>5. Growth of lesion- A “doubling time” less than one month usually means the lesion is due to an infectious process. A “doubling time” refers to doubling of the volume of the lesion and corresponds to an increase in diameter of $1/3$. Malignant lesions have a DT 20-400 days.</td>
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<tr>
<td>6. CT appearance- Smooth border is indicative of a benign lesion in 80% of cases; irregular border is indicative of a malignant lesion in 80% of cases.</td>
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</table>
1. The first step in evaluation of the solitary pulmonary nodule is to obtain a good history and physical examination and make every effort to obtain old CXRs for comparison.
2. Documentation of lack of change in size over a two year period rules out malignancy with a high degree of confidence, and can follow with yearly CXR
3. Other radiologic characteristics of the nodule may be helpful
For the above algorithm, likelihood ratios based on clinical features (age, smoking history, etc), as well as patient preference should be considered to guide direction of investigations.

**INVESTIGATIONS**

If the benignity of the lesion is in doubt, there are a number of possible approaches based on the degree to which the patient is at risk for having a malignancy.

1. **Serial CXRs** – this would be an acceptable approach in a young non-smoker who is at low risk. CXRs can be performed every three months for the first year, then every six months for the second year. If the lesion remains stable, then it is benign.

2. **Bronchoscopy** – overall, the yield of bronchoscopy to diagnose malignancy is low (about 40%), but rises if the patient has a cough or hemoptysis or if the lesion is located medially, close to the bronchial tree, and is greater than 2 cm in diameter (yield up to 70%).

3. **Transthoracic CT guided biopsy** – this is particularly well suited for peripheral lesions near the chest wall. The overall yield is about 2/3.

4. **Surgical resection** – generally speaking, this procedure is reserved for those patients who remain undiagnosed after the one or both of the above.
HEMOPTYSIS

BACKGROUND

Expectoration of blood can range from blood streaking of sputum to presence of gross hemoptysis. Blood can arrive from two possible sites. Virtually the entire cardiac output crosses the capillary bed from the low-pressure pulmonary arterial system. In contrast, the bronchial arteries are under much higher systemic pressure but only carry a small portion of the cardiac output. The bronchial arteries are generally a more important source of hemoptysis than the pulmonary circulation. In addition to being at higher pressure, they also supply the airways and lesions within airways. In bronchiectasis, the bronchial circulation becomes hyperplastic and tortuous, and can be a source of massive hemoptysis.

APPROACH TO HEMOPTYSIS

1. The first step in the evaluation of hemoptysis is to distinguish it from hematemesis, which patients sometimes cannot differentiate. A history of epistaxis should also be sought, as aspiration of blood from the nasopharynx is a common, benign cause of hemoptysis.

2. The differential diagnosis of hemoptysis is quite large and includes bleeding from virtually any anatomic site in the upper or lower respiratory tract.
DIFFERENTIAL DIAGNOSIS

Infections
- Mycobacteria, particularly tuberculosis
- Fungal infections (mycetoma)
- Lung abscess
- Necrotising pneumonia (Klebsiella, Staphylococcus, Legionella)

Iatrogenic
- Swan-Ganz catheterisation
- Bronchoscopy
- Transbronchial biopsy
- Transtracheal aspiration

Parasitic
- Hydatid cyst
- Paragonimiasis

Trauma
- Blunt/penetrating injury
- Suction ulcers
- Tracheoesophageal fistula

Neoplasm
- Bronchogenic carcinoma
- Bronchial adenoma
- Pulmonary metastases
- Sarcoma

Evaluation of Hemoptysis
- CXR, HRCT
- CBC (magnitude and chronicity of bleeding)
- Urinalysis/Renal function (pulmonary-renal syndrome)
- INR/PTT
- Sputum (cytology, AFB, fungal, C+S)
- Bronchoscopy (localize site, visualization of pathology and biopsy)
- Consider Serology (ANA, ANCA, C3, C4, anti-GBM

Vascular
- Pulmonary infarct, embolism
- Mitral stenosis
- Ateriobronchial fistula
- Ateriovenous malformations
- Bronchial telangiectasia
- Left ventricular failure

Coagulopathy
- Von Willebrand’s disease
- Haemophilia
- Anticoagulant therapy
- Thrombocytopenia
- Platelet dysfunction
- Disseminated intravascular coagulation

Vasculitis
- Behcet’s disease
- Wegener’s granulomatosis

Pulmonary
- Bronchiectasis (including cystic fibrosis)
- Chronic bronchitis
- Emphysematous bullae

Miscellaneous
- Lymphangioleiomatosis
- Catametal (endometriosis)
- Pneumoconiosis
- Broncholith
- Idiopathic

Spurious
- Epistaxis
- Haematemesis
3. In general, it is not necessary to pursue the cause of hemoptysis with bronchoscopy in every case. Younger nonsmokers with transient hemoptysis do not require further investigation beyond a CXR. It is likely that many of them had hemoptysis secondary to an acute bronchitis. The priority is to look for serious underlying causes (especially malignancy) and to identify potential sources of massive hemoptysis.

Role of Bronchoscopy

Hemoptysis is one of the most common indications for bronchoscopy.

1. Studies have generally agreed that in patients older than 40 years or with a greater than 40 pack year smoking history, and a normal CXR, bronchoscopy has a yield of 5-10% in discovering malignancy.

2. All patients with hemoptysis and a localizing abnormality on CXR should also undergo bronchoscopy.

3. Patients who fail to meet the above criteria (patients under 40 years old with less than 40 pack years and normal CXR) do not need routine bronchoscopy.

4. In the presence of a normal CXR, CT scan of the chest rarely contributes much to the evaluation of hemoptysis and should not be routinely performed. An exception would be the patient in whom there is a clinical suspicion of bronchiectasis, for which a high-resolution CT scan is the test of choice.
MASSIVE HEMOPTYSIS

Massive hemoptysis is defined as the coughing up of >600cc of blood in 24 hours. It is a life-threatening situation and the greatest risk to patients is usually from impairment of gas exchange due to blood in the alveoli rather than the effects of blood loss.

The most common causes of massive hemoptysis:
- Bronchiectasis
- Lung abscess
- Bronchogenic carcinoma
- Tuberculosis
- Aspergilloma

Management of massive hemoptysis

1. **Airway control** – sometimes this may require selective bronchial intubation with a double lumen tube to isolate the bleeding lung

2. **Breathing** – supplemental O2. The patient should be positioned with the bleeding lung in the dependent position to prevent spillover to the opposite side.

3. **Circulation** - Fluid resuscitation with crystalloid or blood products. Any coagulopathy should be corrected.

4. **Thoracic surgery** should be consulted early when bleeding is identified to be massive.

5. **Bronchoscopy** (early) can be useful in localizing the bleeding site if the source is unclear. **Rigid bronchoscopy** in the OR allows for better suctioning and airway control and may be preferable to the flexible bronchoscope in some circumstances.
6. **Bronchial artery embolization** can stop bleeding in patients who are relatively stable, particularly if the bleeding is due to bronchiectasis (the most common cause). Infarction of the anterior spinal artery is a feared complication of this procedure.

7. **Surgical resection** is indicated in cases of hemodynamic instability or severe respiratory compromise, or when the bleeding lesion is unlikely to be successfully treated by embolization (e.g., aspergilloma).
PULMONARY EMBOLISM

General Considerations

- Pulmonary embolism (PE) occurs in 1-2 persons per 1000 annually in the United States
- 10% of symptomatic PE are fatal in the first hour of presentation; 5-10% of patients present in shock and 50% have evidence of right ventricular dysfunction
- Without treatment, 50% of patients with symptoms of PE or deep venous thrombosis (DVT) will have recurrence at three months
- Treatment of PE results in 50% resolution of perfusion defects by 2-4 weeks; complete resolution is expected to occur in two-thirds of patients

Clinical Presentation

- Diagnosis of PE is challenging because of the wide range of symptoms and signs that may be attributed to PE

<table>
<thead>
<tr>
<th>Common Symptoms:</th>
<th>Common Signs:</th>
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<tbody>
<tr>
<td>Shortness of Breath</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>Tachypnea</td>
</tr>
<tr>
<td>Cough</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Fever</td>
</tr>
<tr>
<td>Syncope</td>
<td>Loud P2</td>
</tr>
<tr>
<td></td>
<td>Right-sided heart failure</td>
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</tbody>
</table>
**Investigations**

- **ABG** - may show hypoxemia, hypocapnia, and respiratory alkalosis.
- **Chest Radiography** - may show elevated hemi-diaphragm, unilateral pleural effusion, plate-like atelectasis, or be normal.
- **EKG** – sinus tachycardia, non-specific t-wave changes, right bundle-branch-block, or S1Q3T3 pattern.
- **D-dimer** – degradation product of cross-linked fibrin. Quantitative ELISA tests have good sensitivity and negative predictive value but poor specificity and positive predictive value. Level>500ng/ml is abnormal.
- **Troponin** – elevated in 30-50% of pts with moderate to large PE likely due to right heart overload
- **BNP** – predicts RV dysfunction and mortality, but poor specificity and sensitivity.
- **Echocardiogram** – signs in PE include increased RV size, decreased RV function and tricuspid regurgitation. Useful in massive PE to justify use of thrombolytics.

**Clinical Prediction Rules**

- Once PE has been raised as a possible diagnosis, the clinical likelihood can be defined using one of many clinical prediction rules.
- Pre-test probability assessment categorizes patients into subgroups, such as low, intermediate, or high.
- The Simplified Wells Scoring System is one model that has been validated to categorize patients into low, moderate, or high probability based on seven variables.
- The Wells prediction rule has been assessed prospectively and prevalence of disease for each of the groups was demonstrated to be 1.3%, 16.2%, and 40.6% respectively.
The Simplified Wells Scoring System

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
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<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of deep veins)</td>
<td>3.0</td>
</tr>
<tr>
<td>No alternate diagnosis is more likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in last 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous history of PE or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer actively treated within last 6 months</td>
<td></td>
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</tbody>
</table>

Pretest probability calculated as follows: Total Points

<table>
<thead>
<tr>
<th>Points</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Moderate</td>
<td>2-6</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 2</td>
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</tbody>
</table>

Diagnostic Algorithms:

- Several diagnostic algorithms have been studied for investigation of suspected PE.
- All patients first must have their clinical pretest probability.
- If a patient is “low probability” and has a negative D-dimer test, this excludes the diagnosis of PE without any need for V/Q or spiral CT.
CT based Algorithm (Christopher Study, JAMA 2006)

PE unlikely if Modified Wells Score $\leq 4$
PE likely if Modified Wells Score $> 4$
Which Imaging Modality to Begin With?

**Choose V/Q Scan**
- Normal CXR
- No known lung disease
- Spiral CT is contraindicated (allergy/renal failure)
- Pregnant

**Choose Spiral CT**
- Abnormal CXR
- Known respiratory disease
- Critical care patient
- Suspected massive PE
For patients with objectively diagnosed non-massive PE, subcutaneous low molecular weight heparin, IV unfractionated heparin, or factor Xa inhibitor can be used.

At the same time, oral anticoagulation using warfarin should be started to achieve a target INR of 2-3.

Initial treatment should be overlapped with warfarin for at least five days and until the INR is therapeutic.

For patients with a first episode of PE secondary to a transient risk factor: anticoagulation for 3 months.

Patients with a first episode of unprovoked PE: anticoagulation for 3 months and then reassess

Recurrent PE: indefinite anticoagulation

**Thrombolytic Therapy in Acute PE (Todd Chest 2009)**
PULMONARY HYPERTENSION

DEFINITION

Pulmonary hypertension is defined by a mean pulmonary artery pressure (mPAP), which exceeds **25mmHg at rest** with a pulmonary artery capillary or left atrial pressure **< 15 mm Hg.**

**Exercise hemodynamics have been removed from the definition.**

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pulmonary hypertension is simple if one thinks of the pulmonary circulation as a circuit with the blood flowing as follows:

- **Pulmonary artery**
  - Lungs
  - Pulmonary veins
  - Left atrium
  - Mitral valve
  - Left ventricle

Diseases that cause obstruction to the flow of blood anywhere in the circuit can cause increased pressure “upstream” and lead to pulmonary hypertension.
Evaluation of Pulmonary Hypertension

With the above differential diagnosis in mind, the evaluation of pulmonary hypertension becomes very straightforward.

Clinical History
1. Presenting Symptoms:
   - Asymptomatic in the early stages, followed by:
     - Exertional dyspnea
     - Non-specific fatigue, weakness
     - Dyspnea at rest
     - Anginal chest pain
     - Palpitations, syncope
2. Symptoms of Related Conditions:
PH is associated with a variety of comorbid conditions, and thus, symptoms of related illnesses should be considered.

- Clues suggestive of underlying lung or heart disease
- Symptoms of pulmonary emboli/DVT
- Prior use of anorexigens
- Risk factors for HIV
- History of connective tissue disease or cirrhosis
- Family history may be relevant as PPH runs in some families (~5%)
- History of snoring
- Chronic sough/sputum production

3. Physical Examination:
Signs of PH on physical examination may be subtle and overlooked. No rigorous analysis of the sensitivity and specificity of findings on physical examination has been performed.

- Loud P2
- Palpable left parasternal lift produced by he impulse of the hypertrophied RV
- Right-sided S4
- Prominent CV wave in the JVP
- Holosystolic murmur of TR
- Peripheral edema

In addition, look for signs of associated comorbid disease such as:

- Crackles pointing to CHF or fibrosis
- Wheezing, prolonged exhalation time
- Obes., kyphoscoliosis
- Rashes, nail-fold capillary abnormalities, arthritis
- DVT
- Signs of chronic liver disease
4. **Tests** which are commonly performed include:

**ECG**
- Right-axis deviation.
- RVH with strain pattern (tall R wave and small S wave with R/S ratio >1).
- Right atrial enlargement (a tall P wave >2.5mm in lead II).

**CXR**
- Enlarged main and hilar pulmonary arterial shadows with concomitant pruning of peripheral pulmonary vascular markings.
- Right pulmonary artery may be dilated (upper limit of normal is 16mm in males and 14mm in females).
- Right ventricular enlargement.
- Any signs of related diseases (COPD, CHF, PE, IPF).

**Echocardiogram**
- **RVSP (right ventricular systolic pressure)** approximates the pulmonary arterial systolic pressure and can be calculated echocardiographically from the velocity of a tricuspid regurgitant jet.
- RVSP calculated from the TR jet should normally be less than 40mmHg.
- Assess for anatomic abnormalities such as right atrial enlargement, right ventricular enlargement, pericardial effusion.
- Look for systolic and diastolic dysfunction, valvular heart disease, intra-cardiac shunting.
PFTs/ABGs
- Performed in all patients to assess for presence of lung disease.
- Findings in IPAH include lung restriction and reduced diffusing capacity.
- DLCO is particularly important in systemic sclerosis to improve detection of pulmonary vascular or interstitial disease.

V/Q scan
- Rule out chronic thromboembolic disease.
- In patients with V/Q scan suggestive of embolic disease, pulmonary angiogram should follow.

High-Resolution CT Scan
- R/O ILD

5. If all of the above investigations (along with the history and physical examination) do not turn up any secondary causes, only then should IPAH be diagnosed.

### IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

Idiopathic Pulmonary Arterial Hypertension (IPAH) is a rare disease and a diagnosis of exclusion.

**Pathogenesis**
- Disease of small pulmonary arteries causing increased vascular resistance.
- Three factors thought to be related to increased resistance: vasoconstriction, remodeling of pulmonary vessel walls, and thrombosis in situ.
Prognosis

- IPAH is associated with a poor prognosis. The mean survival is about 2.5 years and the 5 year survival only about a third (based on NIH registry 1985).
- Treatment has improved survival, with one-year, three-year, and five-year survival increased to 87%, 63%, and 54% respectively (based on epoprostenol data).

Treatment

_Basic Therapy: Warfarin, Supplemental O2, Diuretics, Digoxin_

Anticoagulation

- The rationale behind anticoagulation is that patients with IPAH may have their condition aggravated by in situ thrombosis in the pulmonary vessels, which is a common finding on autopsy.
- Target INR 1.5 to 2.5.
- Anticoagulation of patients with connective tissue disease and congenital heart disease is controversial.

Oxygen

- Hypoxemia is a potent vasoconstrictor and can contribute to progression of IPAH.
- Important to maintain SaO2 > 90%.

Diuretics

- Indicated in patients with evidence of right-sided heart failure.
- Maintaining near euvolemia with diuretics and careful dietary restriction of sodium and fluid intake is considered important.
Pulmonary Vasodilator Therapy

- Three targeted pathways: endothelin, nitric oxide (NO), and prostacyclin
- Calcium channel blockers (CCB) only to be used in patients with an acute vasodilator response

Endothelin-Receptor Antagonists (ERAs)
- Endothelin-1 stimulates the proliferation of vascular smooth-muscle cells, induces fibrosis, and acts as a pro-inflammatory mediator.
- The effects of endothelin-1 are mediated through $\text{ET}_A$ and $\text{ET}_B$.
- Both selective ($\text{ET}_A$) and non-selective ($\text{ET}_{A+B}$) ERAs are available
- In Canada, Bosentan, Sitaxsentan, and Ambrisentan are approved for use.

Phosphodiesterase Inhibitors
- Cyclic guanosine monophosphate (cGMP) involved in vascular smooth muscle vasodilation.
- Degraded by phosphodiesterases.
- **Sildenafil and Tadalafil** are a potent phosphodiesterase-5 inhibitors approved for use in Canada
- Contraindication are concomitant use of nitrates.

Prostacyclin Therapy
- Prostacyclin is a metabolite of arachadonic acid produced in the vascular endothelium.
- It induces relaxation of vascular smooth muscle by stimulating production of cyclic AMP and inhibits platelet aggregation.
- Studies with **Epoprostenol** have shown benefit in exercise tolerance, hemodynamic improvement, and survival.
- Also been shown to be of benefit in the scleroderma population.
- Generally reserved for the sickest PPH patients.
- It is delivered continuously due to its short half-life intravenously via a pump connected to a Hickman line.
- Accidental disruption of drug infusion may result in rebound symptoms and severe right heart failure.
- Side effects include jaw pain, diarrhea, joint pains and systemic hypotension. Line sepsis is not common.
PULMONARY ARTERIOVENOUS MALFORMATION

General Considerations

Pulmonary arteriovenous malformations (PAVMs) are direct artery-to-vein connections in the pulmonary circulation, without any intervening capillary network. In approximately 80% of PAVM cases, Hereditary Hemorrhagic Telangiectasia (HHT) is the underlying cause. The remaining 20% are idiopathic.

HHT is an autosomal dominant disorder characterized by vascular malformations, which can be small (telangiectasia) or large (arteriovenous malformations, AVMs). HHT is caused by mutations in the Endoglin or ALK-1 genes (HHT 1 or HHT 2). More recently, mutations of MADH4 gene (coding for the SMAD4 protein) have been described a small proportion of HHT patients with a rare syndrome of combined familial juvenile polyposis (JP) and HHT but can also rarely occur in HHT patients without JP. Genetic testing is now available for HHT families for all of these genes but is only 80% sensitive. There appears to be at least two gene loci not yet identified but involved in patients with HHT.

As both Endoglin and ALK-1 are TGF-beta co-receptors, they may be involved in angiogenesis, vascular differentiation, induction of endothelial cell mitogens, interplay between cells, matrix and external factors, but the mechanisms for development of arteriovenous malformations in HHT remain unclear.

CLINICAL MANIFESTATIONS OF HHT

Symptoms:

1. Epistaxis (80-90% of adults)
2. Gastrointestinal bleeding (upper>lower) occurs in 20% of adults, usually after age 50 years, due to telangiectasia in the GI tract, especially stomach and small bowel.

3. **Dyspnea on exertion/exercise intolerance:** found in only 50% of patients with PAVMs. This is especially common in patients whose PAVM are large, multiple, bilateral, or diffuse. **Platypnea,** defined as improvement in dyspnea upon reclining, occurs in a small number of patients. This is believed to be due to decrease in blood flow through PAVMs in the dependent portions of the lungs upon assuming the supine position (may also be seen in hepatopulmonary syndrome, atrial septal defects).

4. **Hemoptysis:** Typically massive and life-threatening, occurring in 10-15% of patients with untreated PAVMs. Minor hemoptysis is usually due to laryngeal or tracheobronchial telangiectasia, rather than PAVMs.

5. **Chest pain:** Unilateral chest pain occurs if the patient develops a spontaneous hemothorax, complicating a PAVM. Otherwise, PAVMs do not cause chest pain.

6. **Neurologic symptoms:** Patients with PAVMs are at risk for neurologic complications such as TIA, stroke and cerebral abscess (see below). In addition, the prevalence of migraine, particularly with aura, is approximately 40% in patients with PAVMs.

7. **Liver vascular malformations** (telangiectasia and sometimes confluent vascular malformations) can be detected in 50-70% but are symptomatic only with massive involvement (approximately 5% of people with HHT). When symptomatic, liver vascular malformations can cause high-output heart
failure, portal hypertension, biliary necrosis or mesenteric steal.

Signs:

1. **Mucocutaneous telangiectasia** (80-90% of adults)

2. **Pulmonary bruit:** over the site of the PAVM (found in approximately 10% of patients). Bruits are loudest during inspiration and when the PAVM is in the gravitationally dependent position.

3. **Cyanosis and Clubbing:** Only present in most severe cases (approximately 10%) with diffuse PAVMs or multiple bilateral large PAVMs.

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**HHT DIAGNOSTIC CRITERIA**

Currently, HHT is a clinical diagnosis based on the presence of recurrent epistaxis, mucocutaneous telangiectasia, arteriovenous malformations involving visceral organs, and family history of HHT. HHT patients were identified using the **International Clinical Diagnostic (Curaçao) Criteria**, in which the diagnosis of HHT is definite when at least 3 out of the 4 of the above criteria are present, suspected when 2 criteria are present, and unlikely when only 1 criterion is present.

**Diagnostic Approach:**

If any suspicion of PAVMs, or if the patient has HHT and, therefore, requires screening for PAVMs, it is generally recommended to screen with **contrast echocardiography and chest x-ray**. If either suggests the diagnosis of PAVMs, then **confirmatory CT thorax** should be done.
Diagnostic Modalities:

1. **Shunt fraction measurement**: can be assessed by 100% oxygen method, which assesses SaO2 and PaO2 after breathing 100% O2 for 15-20 min. A shunt fraction of >5% is considered abnormal. The sensitivity of this test for PAVMs is approximately 65-75%.

2. **Contrast echocardiography**: Sensitive tool for detection of small right-left shunts, by visualizing echocontrast in the right atrium with a delay of 3-8 cardiac cycles (which distinguishes it from an intracardiac shunt with a delay of one cardiac cycle). The sensitivity of this test for PAVMs is approximately 93%.

3. **Radionuclide perfusion lung scanning**: can also be used to estimate shunt fraction.

4. **Computed tomography**: likely highly sensitive test, when using multidetector CT, for detecting PAVMs; in fact, increasingly accepted as the current gold standard. Contrast enhancement NOT required, in fact generally avoided due to risk of air embolism during rapid injection.
Complications

PAVMs can be associated with a variety of complications, some of which are life threatening:

1. **Stroke:** mechanism likely of paradoxical embolization, of thrombus (from asymptomatic DVT or in situ thrombus in PAVM), as the filtering function of the pulmonary capillaries is bypassed. At diagnosis of PAVMs, 30% of patients (usually young adults) have already had a stroke.

2. **Cerebral abscess:** mechanism likely of paradoxical embolization of bacteria, as the filtering function of the pulmonary capillaries is bypassed. Risk appears to be greatest after bacteremic procedures. At diagnosis of PAVMs, 10% of patients (usually young adults) have already had a cerebral abscess.

3. **Spontaneous hemothorax or massive hemoptysis:** Due to rupture of PAVM, can be life-threatening. Highest risk during pregnancy, especially T2 and T3. At diagnosis of PAVMs, 15% of patients (usually young adults) have previously had massive hemoptysis or spontaneous hemothorax.

4. **Other complications** – Polycythemia is rare, occurring in only the severely hypoxemic patients.

MANAGEMENT

The current recommendation is to treat all PAVMs with a feeding artery diameter of 3 mm or greater, regardless of symptoms or
previous complications. Since most PAVMs occur in patients with HHT, with appropriate screening and treatment, PAVM complications could be largely eliminated. The treatment of choice is transcatheter embolotherapy. Surgical resection is no longer required, except for the rare case of massive hemorrhage in a center without embolization experience.

1. **Transcatheter Embolotherapy** – Angiographic occlusion of the feeding arteries to a PAVM, with steel coils, platinum coils or detachable balloons. Multiple PAVMs may be embolized during a single session. This technique has a very high success rate (approximately 90%). Unsuccessful cases, where PAVMs are shown to be reperfused, can be retreated with the same technique. The only frequent complication is transient pleuritic chest pain. Rare complications include: transient symptoms from air embolization, pulmonary infarction, DVT, paradoxical embolization of device (1%).

2. **Other treatment measures** –

   a. **Antibiotic prophylaxis** prior to dental and surgical procedures to avoid bacteremia and cerebral abscess, even once all detectable PAVMs treated (as there are usually other small ones which are not detectable on CT/angio)

   b. **IV air filter**: care should be taken to avoid introduction of air when there is IV access, due to risk of air embolism. Use of in-line air filters is ideal.

   c. **Avoid SCUBA**: patients with PAVMs should be advised to avoid SCUBA diving, due to expected increased risk of complications of decompression.
ADMISSIONS FOR PATIENTS WITH PULMONARY ARTERIOVENOUS MALFORMATIONS

1. Patients will be admitted under Dr. Faughnan
2. Patients usually have diagnostic CT angiogram on the same day as the embolization, before admission.
3. Transferred to the floor after embolization, usually around 4PM.
4. Ibuprofen 400mg q 4hrs if chest pain (once started should take regularly for at least 48 hours, then taper over 7-10 days)
5. Chest x-ray (PA and Lateral) early the following AM, re “1 day post-embo”
6. Potential complications post-embolization:

   a) **pleuritic chest pain (30%), usually within 48 hours**
   b) **paradoxical embolization of coil (1%)**:
      - usually occurs during procedure, under visualization
      - has never been described post-procedure, but theoretically possible
      - symptoms will depend on where coil goes (brain, peripheral artery, etc.)
      - **this is an emergency**: contact Dr. Prabhudesai (interventional radiology) and Dr. Faughnan and INVESTIGATE
      - coils can usually be removed with another catheter or can be left in place if not problematic

   c) **other complications rare**:
      - DVT
      - Stroke/TIA:
      - usually due to air embolism
      - must rule out paradoxical embolization of coil, urgently
      - could also be due to thromboembolism (very rare)
      - Groin hematoma
- Massive hemoptysis: can occur during embolization and is managed with embolization

- If IV access must be maintained, please assure no introduction of IV air (risk of cerebral embolism). Use IV air filter (0.22 micron filter).
PLEURAL EFFUSIONS

Size of pleural effusion from CXR

- 75cc blunts costophrenic angle on lateral film
- 200cc blunts costophrenic angle on PA film
- 500cc obscures dome of diaphragm on PA film

Evaluation of pleural effusions

Aside from a detailed history and physical examination, the first step in evaluation of a pleural effusion is a thoracentesis followed by analysis of the fluid to determine whether it is an exudate or a transudate. Generally, if the effusion layers out to >1 cm measured on a decubitus film, it should be tapped. The usual criteria are the ones described by Light:

<table>
<thead>
<tr>
<th>Light’s Criteria</th>
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</thead>
<tbody>
<tr>
<td>Classify as an exudate if ANY of:</td>
</tr>
<tr>
<td>Pleural fluid protein / serum protein</td>
</tr>
<tr>
<td>Pleural fluid LDH/ serum LDH</td>
</tr>
<tr>
<td>LDH absolute</td>
</tr>
</tbody>
</table>

Alternative criteria using solely pleural fluid values exist and are equally valid:

<table>
<thead>
<tr>
<th>Classify as an exudate if ANY of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid protein</td>
</tr>
<tr>
<td>Pleural fluid cholesterol</td>
</tr>
<tr>
<td>Pleural fluid LDH</td>
</tr>
</tbody>
</table>
Common Transudates

These occur principally as an imbalance between oncotic and hydrostatic forces in the chest, although fluid movement from the peritoneal or retroperitoneal space may also be responsible.

CHF – most common. Usually bilateral. When unilateral, usually occur on the right side. However, even unilateral effusions due to CHF are usually found to be bilateral on CT scan. Aggressive diuresis can occasionally transform effusions due to CHF into an exudate. Effusions in the setting of CHF should be tapped if: predominantly left sided, increasing in size despite diuresis, fever.

Cirrhosis – usually occur predominantly on right side in setting of ascites.

Nephrotic Syndrome

Atelectasis and Trapped Lung – common cause in ICU and post-op. Volume loss of atelectatic lung creates negative pressure gradient, which favours fluid accumulation.

Hypoalbuminemia - usually requires another inciting cause.

Peritoneal dialysis – large right-sided effusion may be secondary to diaphragmatic defects. Testing the pleural fluid for high levels of glucose (similar to dialysate) makes the diagnosis.

Common Exudates

Inflammation of the lung pleura or parenchyma can result in exudative effusions. Impaired lymphatic drainage of the pleural space or an increase in fluid movement from the peritoneal cavity can also be seen.
Parapneumonic effusions – significant effusion (> 1 cm on lateral decubitus or loculated) in the setting of pneumonia should generally be tapped. Complicated parapneumonic effusions and empyemas are infected and require chest tube drainage. Predictors of the need for drainage include:

- Fluid pH < 7.2 (“best” predictor)
- size > ½ hemithorax
- glucose < 2.5
- +ve culture/Gram stain
- frank pus
- imaging characteristics (loculations, thickened/split pleura).

Malignant – most common causes: lung, breast. Yield of malignant cells by tap ~60%. VATS increases yield to ~95%. Note that not all effusions in the setting of malignancy are malignant (e.g. secondary to atelectasis, PE, drugs, radiation, etc.).

TB – yield of AFB or +ve culture from pleural fluid ~30%. VATS increases yield to ~90%.

Pulmonary embolus – usually exudate but may be transudate. Presence of a bloody pleural effusion secondary to PE is not a contraindication to anticoagulation.

Pancreatitis – diagnose via high amylase

Rheumatoid pleurisy – classically yellow-green with low pH and glucose.

Lupus pleuritis – patients are usually symptomatic with pleuritic chest pain and have other manifestations of lupus flare. LE cells in fluid are diagnostic.

Postcardiotomy syndrome – probably immunologically mediated.
Occurs commonly post-cardiac surgery and less commonly post myocardial infarction (Dressler’s syndrome), often with concomitant fever, high WBC, pulmonary opacities.

Chylothorax – occurs secondary to obstruction of lymphatics by tumour (esp. lymphoma), or interruption by surgical trauma. Less common causes: lymphangioleiomyomatosis (LAM), yellow nail syndrome.

Esophageal perforation – most commonly caused by iatrogenic rupture from dilatation procedure or endoscopy. Boerhaave’s syndrome of spontaneous rupture is rare.
### Summary of other useful tests in diagnosis of pleural effusions:

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormal value</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs</td>
<td>&gt;100,000 / mm³</td>
<td>Malignancy, trauma, PE</td>
</tr>
<tr>
<td>WBCs</td>
<td>&gt;10,000 / mm³</td>
<td>Infection</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>&gt;50%</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&gt;90%</td>
<td>TB, malignancy, RA</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>&gt;10%</td>
<td>Asbestos, drug rxn, pneumothorax, hemothorax,</td>
</tr>
<tr>
<td>Mesothelial cells</td>
<td>Absent or &lt;5%</td>
<td>TB</td>
</tr>
<tr>
<td>Glucose</td>
<td>&lt;2.5</td>
<td>Empyema, TB, malignancy, rheumatoid</td>
</tr>
<tr>
<td>PH</td>
<td>&lt;7.2</td>
<td>Complicated parapneumonic effusion, TB, malignancy, esophageal rupture, rheumatoid</td>
</tr>
<tr>
<td>Amylase</td>
<td>Pleural fluid &gt; serum</td>
<td>Pancreatitis, Esophageal perforation</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Any +ve</td>
<td>Infection</td>
</tr>
<tr>
<td>Cytology</td>
<td>Any +ve</td>
<td>Malignancy</td>
</tr>
</tbody>
</table>
PERFORMING A THORACENTESIS

Different hospitals use different kits. Ideally, the kit should have a needle + catheter type design. A long angiocath may be a reasonable substitute, but depending on the body habitus of the patient, may not be sufficient.

Before you begin the thoracentesis, ensure you have all the necessary equipment:
- Thoracentesis needle / angiocath
- Freezing needle (25 or 22 gauge, 1 ½ inch length)
- Syringes (1 large 50 cc, 1 small 5-10 cc)
- Lidocaine
- Cleaning supplies, swab sticks
- Gauze & bandage
- Gown & gloves
- Drapes
- Three way stopcock and tubing for connections
- Vacuum bottles or drainage bag

1. Try to aim immediately above the underlying rib of the interspace. Often the safest technique is to aim directly at the rib then guide the needle over it. This will avoid traumatic injury to the neurovascular bundle, which is located on the inferior margin of each rib.

2. Remove the metal needle from the angiocath as soon as you have entered the pleural space. This will minimize the risk of pneumothorax.

3. Do not drain more than about 1 - 1.5 L at one session, particularly if the effusion is chronic. Draining more than this amount can result in re-expansion pulmonary edema.
4. If the effusion is parapneumonic, remember to send for pH, as this is the single most useful test to determine if the effusion requires a chest tube. The pH must be sent in a blood gas syringe on ice in order to be accurate. If the lab is unwilling to analyze the pH in this manner, a pleural fluid glucose would be the next best alternative.

5. When sending pleural fluid for cytology, it is best to contact the laboratory in advance to ask how much they want and in what container. This seems to vary from one-hospital to the next. In general, send as large a quantity of fluid as possible, as this will increase the yield of the specimen for finding malignant cells.
PNEUMOTHORAX

BACKGROUND

The pressure within pleural space is negative with respect to the alveolar pressure. When a communication develops between an alveolus and pleural space, air will move into pleural space until equalization of pressures is achieved or the communication is sealed.

Classification

1. Spontaneous
   a. Primary: no clinical lung disease
   b. Secondary: a complication of clinically apparent lung disease
2. Traumatic (penetrating or blunt chest injury)
3. Iatrogenic (e.g. thoracentesis, central line placement)

Primary Spontaneous Pneumothorax (PSP):

Occurs without a precipitating event in a person who does not have known lung disease. Most individuals with PSP have unrecognized lung disease, with the pneumothorax resulting from rupture of a subpleural bleb or bullae. Virtually all patients have ipsilateral pleuritic chest pain and/or acute dyspnea.

Risk factors:

This condition typically occurs in tall, thin, young men ages 10-30. PSP is 2-7 times more likely in men than women. Cigarette smoking increases the risk proportional to amount smoked. For men who smoke 1-12 cigarettes/day, risk is increased 7 times, 13-22 cigarettes/day (21x), and >22 cigarettes/day (102x). Family history, including Birt-Hogg-Dube syndrome, Marfan syndrome and homocystinuria.
Signs and Symptoms:
Often occurs at rest. Patients typically in their 20s (rare after age 40). Usually present with sudden onset of dyspnea and pleuritic chest pain. Tachycardia is the most common physical finding. In patients with a large pneumothorax, findings may include: decreased chest excursion, a hyper-resonant percussion note, diminished fremitus, and decreased or absent breath sounds on the affected side. Subcutaneous emphysema may be present. Hypoxia is common because of V/Q mismatch. Hypercapnia is unusual. Blood gas may show increased A-a gradient and respiratory alkalosis. Tachycardia with hypotension, or cyanosis should raise the suspicion of a tension pneumothorax.

Secondary Spontaneous Pneumothorax (SSP):
This could be a potentially life-threatening event since patients with this condition have associated lung disease and limited cardiopulmonary reserve. Most commonly associated with COPD (70% - correlates with severity of disease), pneumocystis pneumonia, cystic fibrosis and tuberculosis.

Clinical Presentation:
Often have dyspnea and ipsilateral chest pain. Symptoms are often more severe than PSP due to less pulmonary reserve given underlying lung disease. Hypercapnia is common, and physical findings may be masked by the underlying disease.

Major causes of secondary pneumothorax

<table>
<thead>
<tr>
<th>Airway disease</th>
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</thead>
<tbody>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Infectious lung disease</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td>Necrotizing pneumonia</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Connective-tissue disease</td>
</tr>
<tr>
<td>RA, Scleroderma</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
</tbody>
</table>
Radiology:
Chest radiograph shows a thin, visceral pleural line (<1mm in width), which is found to be displaced from the chest wall. This may be challenging in severe emphysema.

Quantitation:
Volume of the collapsed lung can be crudely estimated with the following formula:
\[
100 - \left( \frac{\text{Diameter of collapsed lung}}{\text{D of affected hemithorax}} \right)^3
\]

Estimation of Pneumothorax Size
CHEST Definitions
- Determined by the distance of the lung apex to the ipsilateral thoracic cupola at the parietal surface as determined by an upright standard CXR
- **Small** - < 3 cm apex to cupola distance
- **Large** - ≥ 3 cm apex to cupola distance

The most accurate method is to calculate the percentage of the hemothorax occupied by the pneumothorax using CT quantitation.

**TREATMENT**

- Management of pneumothorax is based on evacuation of air from the pleural space and preventing recurrences. Available therapies include simple observation, aspiration with a catheter, or insertion of a chest tube. Occasionally pleurodesis and thoracoscopy are required. The selection of an approach depends on the size of the pneumothorax, the severity of
symptoms, whether there is a persistent air leak, and whether the pneumothorax is primary or secondary.

- The rate of resorption for a patient breathing room air is 1.25% of the volume of the hemithorax per 24 hours. Breathing 100% oxygen increases the rate of resorption by 6 times by setting up a gradient of gas concentration between the pleural space and the blood vessels found within the pleural surface.

**PSP:**

- First PSP, clinically stable and small pneumothorax (≤3 cm between lung and chest wall on anterior radiograph) → supplemental oxygen and observation (repeat CXR in 6 hours, if no progression can be discharged)
- First PSP, clinically stable and large pneumothorax (>3 cm) → needle aspiration
- Failed aspiration → chest tube and thoracoscopy
- Recurrent PSP or concomitant hemothorax → chest tube and thoracoscopy
- Any unstable patient → immediate chest tube insertion

**SPP:**

- All patients should be hospitalized
- Stable and small pneumothorax (≤2-3 cm) → supplemental oxygen and observation
- Large pneumothorax or symptomatic → chest tube
- If air leak >3 days → thoracoscopy
- As with PSP, all unstable patients → immediate chest tube

**CHANCE OF RECURRENCE**

Rate of recurrence after PSP is 25-50%. Most recurrences are within the first year. Rate of recurrence may increase with each subsequent episode.
1. **Tension pneumothorax**: When intrapleural pressure is greater than atmospheric throughout expiration and often during inspiration. The mechanism is by disruption of the visceral or parietal pleura in such a manner to cause a one-way valve. Signs include tachycardia, tachypnea, cyanosis, tracheal deviation, and distended neck veins. Patients may deteriorate due to diminished venous return, and low cardiac output, as well as increased intrapulmonary shunting.

2. **Persistent Air leaks**: More common in secondary pneumothorax, surgical intervention often required if persistent.
SLEEP-DISORDERED BREATHING

Sleep-disordered breathing (SDB) is common in the general population and is characterized by abnormal breathing patterns during sleep, which lead to a number of physiologic derangements including, episodic hypoxemia and sleep fragmentation.

The major clinical consequences of SDB:
1. Excessive daytime sleepiness.
2. Increased risk of motor vehicle accidents.
3. Possible increased risk for cardiovascular complications including hypertension, stroke, MI and congestive heart failure.

SDB consists of three clinical syndromes:
1. Obstructive sleep apnea-hypopnea syndrome (OSAHS)
2. Central sleep apnea-hypopnea syndrome (CSAHS) including Cheyne-Stokes breathing syndrome (CSBS)
3. Sleep hypoventilation syndrome (SHVS)

OSAHS

Diagnostic Criteria (Need to fulfill criteria A or B plus C)
A) Daytime sleepiness that is not better explained by other factors.
B) ≥2 of the following that are not better explained by other factors:
   1) Choking or gasping during sleep;
   2) Recurrent awakenings from sleep;
   3) Unrefreshing sleep;
   4) Daytime fatigue; and
   5) Impaired concentration
C) Sleep monitoring demonstrating ≥5 obstructive apneas/hypopneas per hour during sleep
- Characterized by repetitive collapse of the upper airway during sleep, leading to ineffective respiratory efforts.
- Obstructive apneas are commonly terminated by transient awakenings of the patient, which leads to sleep fragmentation.
- OSA is very common and is thought to be present in 2-4% of the population.
- Risk factors include male pattern obesity (collar size >17).
- Accumulation of fat under strap muscles causes lateral narrowing.
- With sleep, pharyngeal muscle tone decreases, and the threshold at which negative pressure will collapse the airway is affected.
- EtOH and Benzo’s affect the tone.

<table>
<thead>
<tr>
<th>CSAHS/CSBS</th>
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<tbody>
<tr>
<td>CSAHS: Need to fulfill A, B, C, D</td>
</tr>
<tr>
<td>A) ≥1 of the following symptoms that is not explained by other factors:</td>
</tr>
<tr>
<td>1. Excessive daytime sleepiness or fatigue; and</td>
</tr>
<tr>
<td>2. Frequent nocturnal awakenings.</td>
</tr>
<tr>
<td>B) Sleep monitoring demonstrates ≥5 central apneas/hypopneas per hour of sleep</td>
</tr>
<tr>
<td>C) Normocapnia while awake (PaCO₂ 35 to 45 mmHg)</td>
</tr>
<tr>
<td>D) Not explained by the presence of a medical disorder, medication, or substance abuse.</td>
</tr>
</tbody>
</table>

| CSBS: Need to fulfill A and B  |
| A) Presence of a serious medical illness, such as cardiac or neurological disease.  |
| B) Sleep monitoring demonstrates the following:  |
| 1. ≥5 central sleep apneas/hypopneas per hour of sleep  |
| 2. The presence of cyclical crescendo and decrescendo change in breathing amplitude that may or may not be associated with arousals from sleep.  |
Present in up to 50% of patients with severe congestive heart failure and is an independent predictor of mortality.

**SHVS**

Need to fulfill A and B

A) $\geq 1$ of the following:
   1. Right heart failure;
   2. Pulmonary hypertension;
   3. Excessive daytime sleepiness that is not explained by other factors;
   4. Erythrocytosis;
   5. Hypercapnia during wakefulness ($\text{PaCO}_2>45$ mmHg)

B) Sleep monitoring demonstrates 1 or both of the following:
   1. An increase in $\text{PaCO}_2$ during sleep $>10$ mmHg from awake supine values.
   2. Sustained hypoxemia $\text{SaO}_2<90\%$ during sleep not related to apnea or hypopnea

**Common Causes of Excessive Daytime Sleepiness**

OSA
Narcolepsy
Periodic limb movements (Restless leg syndrome)
Sleep restriction or shift work (not enough sleep)
Drugs (carryover effect from sedatives, EtOH)
Depression
The Sleep History

A simple approach is to ask questions related to the entire sleep-wake cycle and simply “go around the clock”.

1. What time do you retire to bed?
2. How long does it take to fall asleep?
3. Is there a history of snoring or witnessed apneas?
4. Once asleep, is there any waking through the night? Why? Are there ever any sensations of choking or gasping? Sensations of restless legs?
5. What time do you wake up for the day?
6. Is there a history of morning headaches?
7. How much coffee do you drink?
8. Are there any symptoms of daytime sleepiness? Have you ever fallen asleep involuntarily? In passive situations? In active situations?
9. Is there a history of cataplexy (drop attacks)?
10. Do you take naps during the day?
11. Do you take any sleeping pills or alcohol?
**Polysomnography -- Basics**

Nocturnal polysomnography is the gold standard for diagnosis of sleep-disordered breathing.

The following physiologic variables are recorded continuously as the patient sleeps:

1. EEG (to assess sleep stage)
2. EKG
3. Electro-oculogram (to identify REM)
4. Submental EMG (to assess muscle tone)
5. Chest wall and abdominal movements
6. Oximetry
7. Tibial EMG (to look for periodic limb movements)

**Polysomnographic Terms**

Apnea is defined as complete absence of ventilation for 10 seconds.

Hypopnea is defined as a tidal volume less than 50% of baseline for 10 seconds.

Obstructive apneas and hypopneas are associated with respiratory efforts. Central apneas and hypopneas are associated with an absence of respiratory efforts.

Apnea/hypopnea index (AHI) is the total number of apneas and hypopneas divided by the total sleep time. Mild: 5-15 events/hr; moderate: 15-30 events/hr; severe: ≥30 events/hr.
Management of OSAHS

1. Driving
   a. There is an increased risk of motor vehicle accidents in untreated patients with OSAHS.
   b. Physicians should advise all patients with OSAHS about the dangers of driving while sleepy, and have a duty to report to Ministry of Transportation if the patient refuses treatment.

2. Behavioural and pharmacologic treatment
   a. Weight loss should be encouraged in all obese patients with OSAHS, however attempts to lose weight should not delay the initiation of additional treatment if indicated
   b. Patients should be informed of the potential for alcohol and sedatives to exacerbate OSAHS
   c. Patients with positional OSAHS may derive significant clinical benefit from positional therapy (i.e. sleeping on side)

3. Who should be treated
   a. All patients with OSAHS should be offered a treatment trial to improve their symptoms
   b. Indications for treatment of asymptomatic patients unclear; consider in patients with significant comorbid illness, who work in a safety critical occupation, or who have AHI>30/hour

4. CPAP
   a. Primary treatment for OSAHS
   b. Acts as a pneumatic splint, keeping the upper airway open by delivering a constant pressure

5. Oral appliances
   a. Appropriate first-line therapy for patients with mild-moderate OSAHS with minimal daytime symptoms
   b. Appropriate alternative for patients unable to tolerate
CPAP
c. Should be fitted and followed by qualified dental practitioners who have undertaken special training
d. Should undergo follow-up sleep monitoring with the oral appliance to ensure effective treatment

6. Upper airway surgery
a. Large tonsils should prompt referral to ENT for consideration of tonsillectomy
b. Uvulopalatopharyngoplasty may be considered in patients who have failed CPAP and/or oral appliance treatment. One caveat is possible mouth leak if these patients go on to CPAP in the future.

7. Anesthesia
a. Increased risk for difficult intubation
b. Medications administered during anesthesia and in the post-op period may increase severity of OSAHS
c. Post-operatively, all patients at risk of respiratory complications from OSAHS should be monitored with oximetry, and cardiac monitoring as well if risk of ischemia or arrhythmia.

Management of CSAHS/CSBS

1. CSBS is associated with an increased mortality in patients with heart failure, and optimal medical management of the heart failure is the first line therapy.
2. CPAP and/or oxygen are not recommended as routine therapy for patients with CSBS and heart failure.

Management of SHVS

1. CPAP is the first-line treatment for patients with SHVS when there is associated upper airway obstruction.
2. Assisted ventilation (bilevel positive airway pressure with or without a timed backup rate, and pressure and volume-cycled ventilators) should be considered if CPAP fails to improve daytime and nocturnal gas exchange.

3. Oxygen should be considered in patients who have persistent hypoxemia despite treatment with CPAP or assisted ventilation.
NEUROMUSCULAR DISEASES

CONTROL OF BREATHING

- Spontaneous rhythmic contraction of respiratory muscles occurs without conscious initiation of inspiration or expiration.
- Impulses are generated in the brainstem and are regulated by reflexes from the lungs, cardiovascular system, arterial chemoreceptors, central chemoreceptors.
- The respiratory centre in the brainstem is located in the medulla and is made up of the dorsal respiratory group and ventral respiratory group.
- Information is sent via axons located in the ventero-lateral columns of the spinal cord to the inspiratory and expiratory muscles.
Muscles of Inspiration

- Diaphragm
- Parasternal intercostals
- Lateral external intercostals
- Sternocleidomastoids
- Scalenes

Muscles of expiration

- External and internal oblique muscles
- Rectus abdominal muscles
- Lateral intercostal muscles
- Transverse abdominis

Reduced Ventilatory Drive

CNS
- Congenital Central Hypoventilation Syndrome (CCHS or Ondine’s curse)
- Obesity Hypoventilation Syndrome
- Central sleep apnea
- Drugs (narcotics or sedatives)
- Diseases of Medulla (infarct, tumour)
- Multiple Sclerosis
- Hypothyroidism
- Metabolic Alkalosis
- Rabies

Motor Neurons
- Spinal Cord Injury (C3-C5)
- Tetanus (Clostridium tetani)
- Diseases involving anterior horn cells (AML, Poliomyelitis)
- Syringomyelia

**Peripheral Nervous System**
- Guillain-Barre Syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy
- Phrenic Nerve Injury
- Critical Illness Polyneuropathy
- Others: Diptheria, Porphyria, Tick Paralysis

**Neuromuscular Junction**
- Myasthenia Gravis
- Eaton-Lambert Syndrome
- Organophosphates
- Botulism (Clostridium botulinum)

**Causes of Muscle Weakness**
- Aging
- Malnutrition
- Denervation
- Muscular Dystrophy (Duchenne’s, Becker’s, Myotonic, Emery-Dreifuss)
- Inflammatory (Polymyositis, Dermatomyositis)
- Drug-induced (Neuromuscular blocking agents, Steroids)
- Endocrinopathy (Hyperthyroidism, Cushing syndrome)
- Electrolyte Imbalance (Hypo- or Hyper: K, Mg, Phos)
- Acidosis
- Hyperinflation

**Other Causes of hypoventilation**

**Decreased Compliance**
- Chest wall abnormalities (e.g. severe pectus excavatum)
- Pleural Disease (e.g. large pleural effusion/ calcifications)
Reduced lung compliance

**Airway Obstruction**
- COPD
- Asthma
- Obstructive sleep apnea

**Other Considerations**

Conditions that increase dead space (PE, ARDS, long ETT) or CO2 production (fever, seizure, sepsis, hyperalimentation) may also play a role in hypercapnia. Treating these conditions might help in decreasing CO2 level. However, very rarely, will these conditions cause hypercapnia on their own unless there is also a problem with the ventilatory drive. This is because one can usually compensate by increasing ventilation (tidal volume and/or respiratory rate).

**Evaluation of Respiratory Muscle Strength**

A. Volitional Tests

**Maximum static inspiratory and expiratory pressures** (Pimax, Pemax)
- Highly variable due to patient effort.
- Affected by lung volume.
- Pimax usually measured at low lung volumes since the inspiratory muscles are at their longest and can generate the most force.
- Pemax usually measured at high lung volumes.
- Pimax usually must drop to <40% of predicted before VC is decreased.
- Wide range of normal – in general if Pimax > -80 cmH2O, no disease exists.
Trans-diaphragmatic pressures
- Balloon in esophagus and stomach.
- Pressures of 100cmH20 should be generated from RV or FRC.
- Pdi < 40% of Pimax predicts fatigue.

B. Non-Volitional Tests

Phrenic nerve stimulation
- Electrical or magnetic stimulation of the diaphragm.
- Produces a twitch contraction of the diaphragm.
- Magnetic stimulation is better tolerated than electrical, but is not as specific since more than the phrenic nerve is stimulated.
- Trans-diaphragmatic pressure (Pdi) can be measured and is called “twitch Pdi”.
- Normal twitch Pdi = 25-35 cmH2O.

Fluoroscopy
- Can examine diaphragmatic movement.
- Paradoxical movement of a hemi-diaphragm may be seen on inspiration.

Treatment

Management of hypercapnia involves treating the specific causative condition. However, some of these conditions can only be managed supportively. Some of the more common supportive treatments include the following:

Respiratory Stimulants
- Theophylline
- Acetazolamide
- Progesterone

Non-invasive Positive Ventilation
- BiPAP
FLEXIBLE BRONCHOSCOPY

Flexible bronchoscopy allows for direct visualization of the airways and sampling of alveolar fluid. In addition, transbronchial biopsy (TBB) can establish a diagnosis in a limited number of diffuse lung diseases. The procedure is performed on the conscious patient under mild intravenous sedation, and with use of topical lidocaine on the oropharynx and vocal cords.

Indications

Because every clinical situation is different, bronchoscopy may be indicated in any number of circumstances, but the following are some of the more common indications:

Lung nodules or masses – The diagnostic yield is enhanced for lesions that are more central in location or associated with compression or invasion of airways on radiologic investigation. Methods to obtain specimens during bronchoscopy include forceps biopsy, bronchial brushing, bronchial wash/ lavage, and blind transbronchial needle aspiration (TBNA) of larger lymph nodes. More peripheral lesions may be better sampled with a transthoracic approach, usually with CT guidance.

Hemoptysis - Generally, patients with hemoptysis and a lesion on CXR should undergo bronchoscopy. In individuals >40 years old and with a >40 pack year smoking history, the yield is ~5% with a normal CXR.

Infections - Bronchoalveolar lavage (BAL) is sensitive for pneumocystis, tuberculosis, fungal and bacterial infections. It is of most value in the diagnosis of unusual infections not covered by routine broad-spectrum antibiotics.

Interstitial lung disease – The yield of diagnosing most ILDs on
bronchoscopy with TBB is small, but there are exceptions: the most important is **sarcoidosis**, which can be identified with 80-90% sensitivity in stage II and III disease through the demonstration of noncaseating granulomas. Lymphangitic carcinomatosis, rejection after lung transplantation, hypersensitivity pneumonitis and sometimes, mycobacterial and invasive fungal infection may also be diagnosed with BAL and TBB.

**Others** – Aside from providing a specific diagnosis, BAL results can also serve to limit the differential diagnosis:

<table>
<thead>
<tr>
<th>Predominance</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte</td>
<td>Granulomatous disease such as sarcoidosis, berylliosis, or a lymphoproliferative disorders</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>Bacterial infection, acute interstitial pneumonia, UIP, asbestosis</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Eosinophilic pneumonias, hypereosinophilic syndromes, Loffler’s syndrome, Churg-Strauss</td>
</tr>
<tr>
<td>“Milky” protein</td>
<td>Pulmonary alveolar proteinosis</td>
</tr>
</tbody>
</table>

**Contraindications**

There are few absolute contraindications to bronchoscopy. Strong **relative contraindications** would include:
- hemodynamic instability
- uncooperative patient
- uncontrolled asthma
- severe respiratory distress (bronchoscopy itself typically causes transient worsening of gas exchange)
- coagulopathy and positive pressure mechanical ventilation are contraindications to TBB, but not to bronchoscopy

**Complications**
Bronchoscopy is a safe procedure. The majority of surveys have reported mortality rates of 0.1% or less. The risk of a major complication (defined as being life-threatening) is below 0.5%. The risk of pneumonia is probably under 1%. In the absence of TBB, the risk of pneumothorax is very small.

There are a number of minor complications:

- Fever following bronchoscopy is seen in up to 50% of patients, due to local release of inflammatory mediators
- Slight worsening of gas exchange is a common occurrence after the majority of procedures. The degree of impairment may be more severe if large volumes of lavage fluid are employed or multiple lobes are lavaged
- A focal infiltrate on CXR corresponding to the lung region lavaged may be seen
- Slight hemoptysis may occur

**Transbronchial biopsy** is associated with more serious complications:

- Pneumothorax occurs in 1-5%
- Excessive bleeding (defined as greater than 50cc of blood) is seen in less than 4% of patients. The risk is increased in the presence of coagulopathy or pulmonary hypertension.

**BOOKING A BRONCHOSCOPY**

1. Informed consent should be obtained from the patient, describing the above risks.
2. The following orders should be written in the chart:
   - NPO after midnight on the preceding evening
   - Saline lock if IV access not already in place
   - Please have porter bring patient to the endoscopy suite to arrive 15 minutes prior to the booked time.
INTERVENTIONAL PULMONARY MEDICINE

Traditionally, flexible bronchoscopy is almost solely a diagnostic tool. Interventional pulmonary medicine is a relatively new term that describes a field of Respirology that includes advanced tools to increase diagnostic yield and minimally invasive techniques with a therapeutic intent. Interventional Respirologists are often trained in performing rigid bronchoscopy where general anaesthesia is almost always required.

Unfortunately, Toronto currently does not have an interventional pulmonary medicine program and Respirologists in Toronto do not employ any of these techniques.

Diagnostics

Endobronchial Biopsies (EBUS) – The earliest EBUS system used a radial probe with a 20-MHz transducer that could be inserted into a traditional flexible bronchoscope. Despite not allowing for real-time guidance the yield of TBNA, sampling of peripheral nodules and distinguishing tumour invasion vs. compression in central airway is greatly improved.

More recently, a flexible bronchoscope with dedicated convex 7.5 MHz linear array transducer and distinct working channel has been developed to provide real-time guidance for TBNA of mediastinal and hilar lymph nodes for stations 2, 4, 7, 10, 11, and sometimes 12. Because sensitivity is > 90% for nodes >1 cm and specificity is close to 100%, EBUS is now an important modality for the diagnosis and staging of lung cancer that can help many patients avoid a full mediastinoscopy.

However, a non-diagnostic result is not equivalent to a negative result as the false-negative rate can be as high as 20%. Therefore, most negative results are still followed by surgical biopsies.
**Autofluorescence** – Autofluorescence bronchoscopy can be used for early detection of cancer in central airways, primarily carcinoma in situ (CIS), and squamous cell carcinoma. Abnormal mucosal and submucosal disease is manifested by loss of green autoflorescence, causing a red-brown appearance of the airway wall. Due to the lack of evidence on how these lesions should be managed, the clinical use of this technique is presently limited and still being researched.

**Therapeutics**

Many techniques have been developed to manage both malignant and non-malignant causes of central airway stenosis:

**Bronchoplasty** – This general term refers to the dilatation of narrowed airways (used for both malignant and benign etiologies). For more severe central airway obstructions, various techniques used include sequential insertion of Jackson bougies of increasing size via rigid bronchoscopy; and balloon dilatation (which can also be done with flexible bronchoscopy usually with fluoroscopic guidance).

**Photodynamic Therapy** – This involves the IV injection of a photosensitizing agent, and then activating the drug with a non-thermal laser to produce a phototoxic reaction and cell death of tumours located in central airways.

**Brachytherapy** – Refers to endobronchial radiation, primarily used for the treatment of endobronchial malignant airway obstruction. Commonly, an agent such as 192Ir is delivered at different dose rates through a catheter inserted bronchoscopically.

**Airway Stents** – “Temporary” silicone stents can be inserted via rigid bronchoscopy for both benign and malignant endobronchial airway obstruction after bronchoplasty to maintain airway patency.
“Permanent” metal stents can be inserted by flexible or rigid bronchoscopy and are usually restricted for palliative usage of malignant lesions. Long term stent placements are often complicated by stent erosion, stent migration, and growth of granulation tissue at stent ends resulting in stent occlusion (which is why “permanent” stents are rarely used for benign diseases).

Other Debulking Modalities:

**Laser Therapy** – The Nd:YAG laser is the most widely used laser in the lower respiratory system and has been used for both benign and malignant airway obstruction. Because the depth of penetration can approach 10 mm, care must be taken to avoid airway perforation, pneumothorax, and vascular injury. This modality can be used with flexible and rigid bronchoscopes.

**Cryotherapy** – By releasing nitrous oxide or carbon dioxide stored under pressure, the tip of the cryoprobe rapidly cools to low temperatures and can be used for the removal of organic foreign bodies with high water content. When used as an intervention for either benign or malignant airway obstruction (e.g. tumour destruction), cryotherapy has a delayed effect and requires repeat bronchoscopy to remove necrotic tissue, making it less than ideal for acute severe cases.

**Argon Plasma Coagulation (APC)** – Uses ionized argon gas (plasma) to achieve tissue coagulation and hemostasis. Depth of penetration for APC is approximately 2-3 mm and so risk of complications is less compared to lasers.

**Electrocautery** – Also employed to achieve hemostasis or for cutting in cases of narrowed airways.
Future Directions

**Bronchial Thermoplasty** – Controlled thermal energy (radiofrequency energy at 65°C) is applied directly to visible airways though the bronchoscope. The goal is to ablate airway smooth muscle without causing scarring and stenosis. A preliminary study in which mild to moderate asthma patients were treated using the technique showed that mild exacerbations were reduced, daily symptoms and PEFR were improved. Larger trials are still required to validate this technique.

**Enhanced Navigation** – Electromagnetic navigation bronchoscopy, especially when used in conjunction with radial-probe EBUS, has been shown to allow accurate sampling of peripheral solitary pulmonary nodules <2 cm in diameter of yields up to 90%. A virtual bronchoscopy is generated from CT scanning followed by the marking of the target lesion and other major anatomic landmarks using specialized software. The patient lies in an electromagnetic field during bronchoscopy, and navigation is then performed using a program analogous to GPS to guide operators to the desired target. Unfortunately, this technology is still in research stages and very expensive.

**Bronchoscopic Lung Volume Reduction** – Several airway stents that act as one-way valves have been created to achieve lung volume reduction. Bronchoscopic deployment of such a stent at an airway orifice would cause subsequent collapse of the distal airway over time. This technique has potential benefits for patients with upper-lobe-predominant disease who would otherwise undergo lung volume reduction surgery. However, no such device has yet been approved by the FDA.
Pulmonary Function Testing Fundamentals

The following is borrowed with permission from the St. Michaels Hospital resident orientation package. It is not intended to be a manual of pulmonary function tests (PFT) interpretation, but to provide some general guidelines. We refer only to “routine” PFTs, leaving specialized tests such as methacholine challenge, inspiratory flow-volume curves, assessment of diaphragmatic function and measurement of lung compliance to seminars as may be applicable to specific cases.

I. First, do not be discouraged when you see a PFT report. Although it contains 14 lines, we do not perform 14 tests, rather only three tests. All of the parameters listed in the report come from these three tests, which are:

1. Spirometry, i.e., maximum expiratory flow-volume curve (if upper airway obstruction is suspected, we also perform maximum inspiratory flow-volume curve).

From this test we obtain slow vital capacity (SVC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), the ratio of the two (FEV1/FVC), flow rates after 50% and 75% of the vital capacity are exhaled (V50 and V25), and expiratory reserve volume (ERV).

Flow-volume is the most important and informative pulmonary function test!

2. Body plethysmography, also called “body box”.

From this test we obtain functional residual capacity (FRC), total lung capacity (TLC Box), residual volume (RV), the ratio of the two (RV/TLC), and airway resistance (Raw).

From this test we obtain diffusing capacity (DCO) and total lung capacity by helium dilution (TLC He).

The definition of these parameters will be covered in your lectures/seminars.

II. Second, remember that generally pulmonary function tests cannot make a specific diagnosis of disease. PFTs can only give you a pattern of physiologic abnormalities. These abnormalities are compatible with many different diseases. You, as a physician, must use all of the available information about your patient to achieve a specific diagnosis.

III. Third, when you are asked to interpret PFTs, do not recite the obvious, such as which parameter is increased and which is decreased. This is clearly marked on the test and the reader (or examiner) can see by her/himself what is increased or decreased. Interpreting PFT means synthesizing the abnormalities into a physiologic pattern. Fortunately, it is not too difficult since there are only three distinct patterns:

1. Airflow limitation (commonly called “airways obstruction”)
2. Lung restriction
3. Abnormal (generally decreased) diffusing capacity

and one additional pattern:
4. Combination of airflow limitation and lung restriction.

The table below illustrates definitions of the three major patterns of PFT abnormalities, and gives some examples of specific diseases generally (but not invariably) associated with each pattern. Note that only one specific abnormality needs to be present in order to diagnose the pattern, e.g., it is quite appropriate to diagnose “airflow limitation” when the sole specific abnormality is reduced V25.

**Interpreting PFT’s – Use the Above Patterns**

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>SPECIFIC ABNORMALITIES</th>
<th>EXAMPLES</th>
</tr>
</thead>
</table>
| Airflow limitation (commonly called airways obstruction) | 1. Reduced FEV1 and FEV1/FVC  
2. Increased RV and RV/TLC – air trapping  
3. Increased TLC and RV/TLC – hyperinflation | Asthma, bronchitis, emphysema, bronchiectasis        |
| Lung restriction               | 1. Reduced TLC  
2. Proportionate reduction in FVC and FEV1 with normal FEV1/FVC | ILD, neuromuscular diseases, musculoskeletal abnormalities, pleural effusion, cardiomegaly |
| Reduced diffusing capacity     | 1. Reduced DCO                                            | Interstitial lung diseases, emboli, anemia, PAH     |
Now let’s talk about some finer points you should keep in mind when diagnosing one of the above patterns.

**Airflow Limitation**

Severity of airflow limitation is based on FEV1

FEV1/FVC<70%

a. If FEV1 >70%pred: “mild”
b. 60%pred<=FEV1<70%: “moderate”
c. 50%pred<=FEV1<60%: “moderately severe”
d. 35%pred<= FEV1<50%: "severe"
e. FEV1<35 %pred: “very severe”

Sometimes the only abnormality that defines “airflow limitation” pattern is air trapping, i.e., increased RV and RV/TLC. Flow-volume curve can be completely normal.

**Lung Restriction**

The only way to diagnose it is when TLC (measured using body plethysmograph) is reduced. Severity of lung restriction is based on reduction in TLC.

In such cases there is also a proportionate reduction in FEV1 and FVC with a normal or high ratio. In addition, V50 and V25 will be high for the measured vital capacity.
Reduced Diffusing Capacity

This is a sensitive, but very non-specific test. It depends on the patient’s hemoglobin, and before interpreting reduced DCO as a reflection of parenchymal or vascular disease, check that the hemoglobin is normal. We can correct DCO for the hemoglobin if we know it.

Conclusion

Finally, let us list some common abnormalities (either patterns or isolated abnormalities), which are usually very specific for particular diseases.

<table>
<thead>
<tr>
<th>PFT Abnormality</th>
<th>Compatible with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airflow limitation + reduced DCO</td>
<td>Emphysema (in a smoker)</td>
</tr>
<tr>
<td>12% improvement in FEV1 after inhaling bronchodilator</td>
<td>Asthma (but baseline FEV1 must be less than 80% of predicted)</td>
</tr>
<tr>
<td>Reduced FRC</td>
<td>Overweight or obese</td>
</tr>
<tr>
<td>Lung restriction + reduced DCO</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Lung restriction + normal DCO</td>
<td>Extrapulmonary problem affecting chest wall or diaphragm</td>
</tr>
</tbody>
</table>
## APPENDIX I: INHALED MEDICATIONS

### Short-acting bronchodilators

<table>
<thead>
<tr>
<th>Trade</th>
<th>Generic</th>
<th>Class</th>
<th>Device</th>
<th>Dose</th>
<th>Usual dose</th>
<th>Price (2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrovent</td>
<td>ipratropium bromide</td>
<td>anti-cholinergic</td>
<td>MDI</td>
<td>20 mcg</td>
<td>Maint: 2 inh qid Exac: 8 inh q20min</td>
<td>18.34/200dose</td>
</tr>
<tr>
<td>Bricanyl</td>
<td>terbutaline sulfate</td>
<td>beta-agonist</td>
<td>Turbuhaler</td>
<td>0.5 mg</td>
<td>Maint: 1-2 inh q4h prn Exac: 4-8 inh q20min</td>
<td>14.70/200dose</td>
</tr>
<tr>
<td>Ventolin</td>
<td>salbutamol</td>
<td>beta-agonist</td>
<td>MDI</td>
<td>100 mcg</td>
<td>Maint: 2 inh q4h prn Exac: 4-8 inh q20min</td>
<td>6.50/200dose</td>
</tr>
</tbody>
</table>

### Long-acting bronchodilators

<table>
<thead>
<tr>
<th>Trade</th>
<th>Generic</th>
<th>Class</th>
<th>Device</th>
<th>Dose</th>
<th>Usual dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxeze</td>
<td>formoterol fumarate</td>
<td>beta-agonist</td>
<td>Turbuhaler</td>
<td>6 mcg</td>
<td>1 inh bid</td>
<td>32.70/60dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 mcg</td>
<td>1 inh bid</td>
<td>43.55/60dose</td>
</tr>
<tr>
<td>Serevent</td>
<td>salmeterol</td>
<td>beta-agonist</td>
<td>Diskus</td>
<td>50 mcg</td>
<td>1 inh bid</td>
<td>56.10/60dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diskhaler</td>
<td>50 mcg</td>
<td>1 inh bid</td>
<td>56.10/60dose</td>
</tr>
<tr>
<td>Spiriva</td>
<td>tiotropium</td>
<td>anti-cholinergic</td>
<td>Handihaler</td>
<td>18 mcg</td>
<td>1 inh daily</td>
<td>63.00/30dose</td>
</tr>
</tbody>
</table>

### Steroids

<table>
<thead>
<tr>
<th>Trade</th>
<th>Generic</th>
<th>Class</th>
<th>Device</th>
<th>Dose</th>
<th>Usual dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvesco</td>
<td>ciclesonide</td>
<td>steroid</td>
<td>MDI</td>
<td>100 mcg</td>
<td>2-2 puffs once to bid</td>
<td>42.65/120dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200 mcg</td>
<td></td>
<td>70.45/120dose</td>
</tr>
<tr>
<td>Flovent</td>
<td>fluticasone propionate</td>
<td>steroid</td>
<td>Diskus</td>
<td>250 mcg</td>
<td>1 inh bid</td>
<td>41.28/60dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MDI</td>
<td>500 mcg</td>
<td>1 inh bid</td>
<td>82.54/60dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 mcg</td>
<td>2 puffs bid</td>
<td>23.93/120dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>125 mcg</td>
<td>2 puffs bid</td>
<td>41.28/120dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>250 mcg</td>
<td>2 puffs bid</td>
<td>82.54/120dose</td>
</tr>
<tr>
<td>Pulmicort</td>
<td>budesonide</td>
<td>steroid</td>
<td>Turbuhaler</td>
<td>100 mcg</td>
<td>200-400 mcg bid</td>
<td>30.40/200dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200 mcg</td>
<td></td>
<td>60.85/200dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mcg</td>
<td></td>
<td>109.50/200dose</td>
</tr>
<tr>
<td>QVAR</td>
<td>beclomethasone dipropionate</td>
<td>steroid</td>
<td>MDI</td>
<td>50 mcg</td>
<td>50-200 mcg bid</td>
<td>29.20/200dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mcg</td>
<td></td>
<td>58.40/200dose</td>
</tr>
</tbody>
</table>

### LABA/steroid

<table>
<thead>
<tr>
<th>Trade</th>
<th>Generic</th>
<th>Class</th>
<th>Device</th>
<th>Dose</th>
<th>Usual dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advair</td>
<td>salmeterol/ fluticasone</td>
<td>LABA/ICS</td>
<td>Diskus</td>
<td>100/50 mcg</td>
<td>1 inh bid</td>
<td>80.19/60dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MDI</td>
<td>250/50 mcg</td>
<td>1 inh bid</td>
<td>95.99/60dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500/50 mcg</td>
<td>1 inh bid</td>
<td>136.27/60dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>125/25 mcg</td>
<td>2 puffs bid</td>
<td>95.99/120dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>250/25 mcg</td>
<td>2 puffs bid</td>
<td>136.27/120dose</td>
</tr>
<tr>
<td>Symbicort</td>
<td>formoterol/ budesonide</td>
<td>LABA/ICS</td>
<td>Turbuhaler</td>
<td>100/6 mcg</td>
<td>1-2 inh once to bid</td>
<td>60.00/120dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200/6 mcg</td>
<td></td>
<td>78.00/120dose</td>
</tr>
</tbody>
</table>
APPENDIX II: INHALER TECHNIQUE

Metered Dose Inhaler

- Delivery improved with use of spacer device (i.e. Aerochamber®), except Alvesco®
- Drug delivery very sensitive to technique
- Assessment of technique should be routine part of patient evaluation

How to use a metered dose inhaler (MDI) with a spacer

1. Remove the plastic cap from the MDI mouthpiece and from the spacer mouthpiece.
2. Put the inhaler mouthpiece into the large opening of the spacer.
3. Hold the spacer and inhaler together, and shake well.
4. Breathe out.
5. Put the mouthpiece of the spacer into your mouth.
6. Close your lips around the mouthpiece. (Do not cover the small slots).
7. Press the metal canister down into the inhaler.
8. Breathe in slowly and deeply through your mouth, for about 5 seconds.
9. Hold your breath for about 10 seconds.
10. If additional dose required, wait 30-60 seconds then repeat steps 3-9.

Steps to use MDI without a spacer

1. Remove the cap.
2. Shake the inhaler.
3. Breathe out normally.
4. Hold the mouthpiece about 4cm (the width of 2 or 3 fingers) away from your mouth. (If you find this method difficult, you can close your lips around the mouthpiece. Keep your mouth
open and teeth apart and your tongue flat so that the medication can flow into your lungs.)
5. Open your mouth and tilt your head back slightly.
6. Push the metal canister down about one second after breathing in slowly. Continue until your lungs are full (about 5 seconds).
7. Hold your breath for about 10 seconds.
8. If additional dose required, wait 30 to 60 seconds then repeat steps 3-8.

Dry Powder Inhaler

- Diskus® and Turbuhaler®
- Less coordination required; no spacer device required
- Dry powder inhalers are breath-actuated and some patients with very severe disease may not be able to generate a sufficient inspiratory flow rate to actuate the device

Diskus®

1. To open the inhaler, hold the outer case in one hand and put the thumb of your other hand on the grip. Push your thumb away until you hear a click.
2. Push the lever down until you hear a click.
3. Hold the Diskus inhaler away from your mouth and breathe out completely.
4. Put the mouthpiece to your lips with teeth apart.
5. Seal your lips around mouthpiece.
6. Remove the Diskus inhaler and hold your breath for about 10 seconds. Inhale quickly and deeply through the Diskus inhaler.
7. Breathe out slowly AWAY FROM THE INHALER.
8. Hold your breath for about 10 seconds.
9. To close the Diskus inhaler, slide the thumb grip back until you hear a click. The lever is then reset for the next dose.
Turbuhaler®

1. Unscrew the cover and lift it off.
2. Hold the Turbuhaler upright.
3. Turn the coloured wheel all the way to the right, and then to the left, until you hear a click. Once you have done this, do not shake or turn the Turbuhaler sideways or upside down or the medication will be lost.
4. Breathe out, away from the Turbuhaler.
5. Put the mouthpiece between your sealed lips and breathe in deeply through your mouth.
6. Remove the Turbuhaler from your mouth, while holding your breath. Continue holding your breath for about 10 seconds.
7. Breathe out slowly through your mouth, away from the Turbuhaler.
8. If additional dose required, repeat steps 2-7.
9. Replace the cover.