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GUIDELINES FOR MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN INDIA

These guidelines were developed to help in the management of COPD, especially at the Primary Care Level with standard criteria for management and referral strategies. These Guidelines were developed under the WHO-GOI Biennium (2002-2003) at the consensus Workshop organized by the Department of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research Chandigarh, in December 2002. The Workshop was attended by experts/consultants from National Institutes, Medical Colleges, and representatives from Government and private health services. The Indian Council of Medical Research, Indian Chest Society, National College of Chest Physicians, and the American College of Chest Physicians were also involved in the preparation of these guidelines.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common problem encountered in medical practice. A review of studies available from India reveal the median prevalence of COPD is about 5% in men and 2.7% in women of over 30 years of age.

Definition

COPD, which includes two distinct pathophysiological processes as (chronic bronchitis and emphysema) is a condition characterized by airflow obstruction/limitation that is not fully reversible. It is associated with an abnormal inflammatory response of the lungs to noxious particles or gases especially tobacco smoke and air pollution - both indoor and outdoor. Chronic bronchitis manifests as chronic cough and sputum production for more than 3 months of a year for at least 2 consecutive years on most days. Emphysema presents with dyspnoea of insidious onset. The disease is gradually progressive leading to respiratory disability and death.

Risk Factors

1. Tobacco smoking - most important
2. Exposure to environmental tobacco smoke (passive smoking)
3. Use of solid fuel (dried dung, wood , etc.) for combustion
4. Outdoor air pollution (vehicular, industrial & occupational exhausts, dusts & fumes)

Symptoms

1. Chronic cough with sputum production; present on most days for at least 3 months/year for 2 or more consecutive years; cough is rarely nocturnal.
2. Dyspnoea persistent and progressive, worsening on exertion

Physical Examination

A. Findings supportive of COPD :

1. Features of hyperinflation: barrel shaped chest, increased antero-posterior diameter, low placed diaphragm, i.e. downward displaced upper border of liver dullness and absence of cardiac dullness on percussion.
2. Diminished intensity of breath sounds with prolonged expiration
3. Prolonged forced expiratory time; pursed lip breathing

B. Exclusion of alternate diagnoses especially asthma; it is also important to exclude tuberculosis in all patients with sputum production. Look for:

1. Presence of localized physical findings
2. Evidence of fibrocavitary disease/malignancy

C. Complications of COPD :

Look for evidence of (i) chronic cor pulmonale with or without right heart failure (raised jugular venous pressure, pedal oedema, loud P2) and (ii) respiratory failure (cyanosis, flaps, altered sensorium)

Investigations

1. Sputum for acid fast bacilli (AFB) (thrice): recommended for all patients presenting with chronic cough and expectoration.
2. Chest radiograph: as far as possible, should be obtained at primary care level to exclude and/or recognize alternate diagnoses and problems. It should always be done at the secondary care level.

Spirometry: if available, should be offered. Patients should also be referred for spirometry if the diagnosis is in doubt. Spirometry should be made available at least at the secondary care (district hospital) level.

Diagnosis

I. Provisional

The diagnosis of COPD should be considered in any patient with (1) history of exposure to risk factors (esp. tobacco smoking) and (2) suggestive symptoms.

II. Confirmatory

Spirometry is essential for confirmation of diagnosis of COPD. The presence of a post-bronchodilator forced expiratory volume₁ (FEV₁) <80% of the predicted value in combination with an FEV₁/FVC < 70% confirms the presence of airflow limitation that is not fully reversible. Where necessary, reversibility of airflow obstruction should be excluded (defined as > 200 ml and 12% increase in FEV₁ or FVC (forced vital capacity) after bronchodilator). FEV₁ value should be used for grading of severity of COPD. Other diseases, especially tuberculosis should be excluded. *If sputum is positive for (AFB), patient should be referred to the nearest Centre under Revised National Tuberculosis Control Programme. If no Centre is available, anti-tubercular treatment should be started as per standard guidelines.*

Management

A. Assess the disease severity and start treatment depending upon the stage. **Refer to Tables 1 and 2 for details.**

Table 1. Staging and management principles

	0 - At risk	I - Mild	II - Moderate	III - Severe
Risk Factors	Tobacco Smokers			
Symptoms ^a	No dyspnoea Mucoid expectoration	Dyspnoea on unaccustomed activity or climbing two flights of stairs	Dyspnoea on accustomed activity	Dyspnoea at rest
Signs		Nil or minimal	Chest hyperinflation Use of accessory muscles (mild) Wheezing	Moderate to severe use of accessory muscles Near absence of breath sounds Respiratory failure Evidence of right heart failure
Six minute walk test ^b		>200 m	100-200 m	<100 m
Peak expiratory flow (PEF)	Normal	50-70%	30-50%	<30%
Spirometry ^c	Normal	FEV ₁ /FVC <70% FEV ₁ >80% predicted	FEV ₁ /FVC <70% FEV ₁ 30-80% predicted	FEV ₁ /FVC <70% FEV ₁ <30% predicted
Treatment ^d	Tobacco cessation	Short acting bronchodilators, when needed	Regular treatment with one/more bronchodilators (Table 2) Pulmonary rehabilitation	As in II, plus Inhaled corticosteroids ^e Treatment of complications

a Cough and expectoration are present at all stages.

^b Performed by measuring distance covered in 6 minutes when patient walks at his/her own speed (under physician supervision).
^c Important for good staging and definitive diagnosis. PEF (peak expiratory flow) is a good and cheap substitute for spirometry.
^d Smoking cessation, patient education and other components of respiratory rehabilitation at all stages.

B. Assess the risk factors and other complications. Advise and help to quit smoking. Smoking cessation is the most important and effective step. Standard guidelines for this purpose are summarized in Table 3.

Table 2. Commonly used bronchodilator drugs in India

Drugs	Metered dose / dry powder inhalers (μ g)	Oral
Beta agonists		
<i>Salbutamol</i>	100 - 200 SOS/tid/qid	2 - 4 mg tid/qid
<i>Terbutaline</i>	250 - 500 SOS/tid/qid	2.5 - 5 mg tid
<i>Salmeterol</i>	25 - 50 bid	-
<i>Formoterol</i>	6 - 12 bid	-
<i>Bambuterol</i>	-	10 - 20 mg/day
Anticholinergics		
<i>Ipratropium</i>	40 - 80 tid/qid	-
<i>Tiotropium</i>	18 - 36 od	-
Methylxanthines		
<i>Aminophylline</i>	-	225 - 450 mg/day
<i>Theophyllins</i>	-	200 - 600 mg/day

C. Manage acute exacerbation if any.

- Increase the dose and/or frequency of the existing bronchodilator therapy. Add new

bronchodilators, drugs that are not being taken by the patient.

- Administer bronchodilators by metered dose inhalers with spacers or by nebulization in severe cases. If not available, use intravenous aminophylline with due attention to its toxicity modify the dose for the elderly, patients with cirrhosis, congestive cardiac failure and those already taking oral methyl-xanthines, cimetidine, ciprofloxacin or erythromycin.
- Use of systemic glucocorticoids e.g. oral prednisolone (40 mg/day) for 5-10 days with rapid tapering thereafter. Carefully look for tuberculosis by sputum examination and chest radiograph before starting corticosteroids
- Antibiotic administration in case of suspected infection.
- Refer the patient to a secondary/tertiary care center (as per following guidelines).

D. Assess response to treatment

Good response is based mostly on clinical assessment which includes improvement in symptoms of cough and breathlessness; reduction in sputum production, and increased exercise tolerance (e.g. six-minute walking)

When to refer the patient to Secondary/Tertiary Care Level?

- Any patient with symptoms of cardiac or respiratory failure
- Those patients not responding to treatment at primary level
- The patients in whom alternate diagnoses are strongly suspected
- Patients requiring assistance in tobacco cessation and/or respiratory rehabilitation.

The patient should be referred to a center where diagnostic and other facilities, including spirometry and inpatient services, are available

Add if significant response of symptoms and lung function to a six week trial, or if repeated exacerbations. Inhaled corticosteroids are administered in a daily dose of 400-800 ug (or even more) of Beclomethasone propionate or equivalent.

Fig 1. Algorithm for diagnosis and management of COPD at different levels of health care



Table 3. Guidelines for doctors on smoking cessation

Follow the 5A strategy

ASK about tobacco use

ASSESS the status and degree of use

ADVISE to stop

ASSIST in smoking cessation

ARRANGE follow-up programme

EVIDENCE BASED CLINICAL PRACTICE

Evidence based medicine is a term coined at McMaster University (Canada) in the 1980s. It is defined as a process of turning clinical problems into questions, then systematically locating, appraising and using clinical research findings as the basis for clinical decisions. Medical practice based on conclusions thus derived can be called as evidence based clinical practice.

Evidence based medicine involves harnessing information for everyday clinical practice. Clinicians in the practice of every day medicine come across several problems which require discrete decisions. In today's world of rapidly changing science, it is essential to make all clinical decisions in the light of the available evidence. However, it is important to develop the ability to discern what the available evidence is and its applicability in the given clinical situation. A large number of clinical observations and experiments are published every year. Information today is available not only in books but it is hovering all over in cyber space.

More than two million articles are published annually in the biomedical literature. One generally gets about 100-500 articles per year about every relevant topic. One has to decide which ones to read. Dr. Stern Lock, an ex-editor of medical journal - Lancet laments: "It is generally surprising to the lay that upto 99% of published articles belong to the bin and certainly not be used to inform practice."

A large amount of money is spent globally to study the effect of therapies. To develop a clinical approach in the light of the published observations and to carry out research efforts which have not already been carried out one requires :

1. An access to all available literature needing state of the art library support. This job has been made partly simpler by the available electronic data bases like Medline, Index Medicus, Embase, Excerpta Medica and Current Contents.
2. An education in interpreting the findings of the previous research in light of its applicability in

the given context. This involves systematic review of the available literature. Recently, application of the technique of meta-analyses has been able to provide answers in several clinical problems where limitless research had been going on.

3. After an evidence has been produced and interpreted, it is important to disseminate it to the user i.e. the clinician. This requires an active group of individuals in a centralized facility who are able to supply this information to the doctors at the bedside. This dissemination of information from bench to bed side has been made easy again with the help of electronic communication where on-line access may be provided to the users of the electronic media. Several professional bodies are developing evidence based guidelines to improve the clinical practice.

Medical literature however is vast. It is a stupendous task to review all the available evidence before making a decision in each and every clinical problem. However this exercise has become essential in this age of specialized medicine and increased consumer awareness. Today, a patient has an access to available medical literature on his or her computer through internet or other agencies and a doctor may find it increasingly difficult to convince such a person unless he himself is well informed and knows the value of the available information. Such situations may not be very common in India at present but with ongoing revolution in the communication technology which is moving at a fast pace one can foresee such in implosion before it is too long.

Evidence based medicine has been practised in many countries in different guises. There has been evidence to its clinical effectiveness. Short term trails have shown better and more informed clinical decisions following even brief training in clinical

appraisal(1). However this approach is very difficult to evaluate. It is a process for solving problems, and monitoring all possible outcomes is a formidable task. However it has been found that the graduates of a medical school that teaches lifelong, self directed evidence based medicine are still up to date as long as 15 years after medical graduation(2). Systematic reviews of computer based clinical decision support systems and implementing clinical practice guidelines have shown that, at least some of the time and in certain circumstances, it is possible to change what the clinicians do(3,4).

One of the international agencies which has taken up the task of building up evidence based medicine as a scientific discipline is the Cochrane Collaboration. This collaboration came into existence nine years ago and has grown at a very rapid pace. It is an international network named after the physician epidemiologist, Archie Cochrane. The collaboration was founded at a meeting of about 80 people from several countries in Oxford, England in the fall of 1993. The goals of the collaboration are to produce high quality systematic reviews (where possible meta-analyses) of trials of every sort of health interventions, to ensure that these are subjected to very high quality peer reviews, and when necessary, updating, and to disseminate these systematic reviews electronically both on CD-ROM and internet. The collaboration has already brought out Cochrane library which contains systematic information on research in a number of research topics. The review groups undertaking a Cochrane are called Cochrane review groups and have a lifelong commitment to carry out and update these systematic reviews and meta-analyses. This is in contrast to the reviews published in print journals which become outdated very soon. This collaboration has the sort of promise that led David Naylor to write "the Cochrane Collaboration is an enterprise that rivals the Human Genome Project in its potential for the modern medicine"(5). At present there are Cochrane Centres in 14 different countries.

Evidence based medicine and guideline formulation

Clinical guidelines are needed in order to have uniform standardized clinical practice. Table 1 gives the hierarchy of evidence. Randomized controlled trials and systematic reviews of randomized controlled trials are classified as Grade 1 evidence. Cohort studies, uncontrolled studies, cross sectional surveys come in the Grade 2 evidence Case reports and the so called expert opinions come lower down as Grade 3 evidence. Only grade 1 evidence should be included in the recommendations for clinical practice.

Table 1. Hierarchy of Evidence

- ◆ Systematic review
- ◆ Randomized controlled trial with definite results
- ◆ Randomized controlled trial with non-definite results
- ◆ Cohort Studies
- ◆ Case Control Studies
- ◆ Cross sectional surveys
- ◆ Case Reports
- ◆ Expert opinion

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PULMONARY THROMBOEMBOLISM: NEWER DIAGNOSTIC MODALITIES

Venous thromboembolism represents a spectrum of diseases that include both deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE). Pulmonary embolism most commonly occurs from deep vein thrombosis, occurring in deep veins of lower extremities proximal to and involving the popliteal vein.

Pulmonary thromboembolism is a common disease particularly in the hospitalized and debilitated patients, those with cancer or patients undergoing major abdominal, pelvic or orthopedic surgeries. PTE is frequently unsuspected and more than half of the cases are never diagnosed. Acute PTE is found in as many as 25-30% of routine autopsies. The importance of a correct and prompt diagnosis lies in the fact that untreated PTE carries a mortality of 30% which can be reduced to 8% with anticoagulant treatment. However, the hazards of over-treatment are also significant as 15% of patients on anticoagulation therapy incur complications.

I. **Role of Ventilation-perfusion (\dot{V}/\dot{Q}) scan** in the diagnosis of pulmonary thromboembolism - \dot{V}/\dot{Q} scan has been traditionally used as the initial screening test for pulmonary thromboembolism. The prospective investigation of pulmonary embolism diagnosis (PIOPED) study published in 1990 defined the usefulness of \dot{V}/\dot{Q} scan :

1. \dot{V}/\dot{Q} scan is more useful if read along with the clinical probability of PTE.
2. A high probability \dot{V}/\dot{Q} scan is highly predictive of pulmonary thromboembolism, particularly in those patients who have a high clinical probability.
3. A normal or near normal \dot{V}/\dot{Q} scan virtually rules out the diagnosis of PTE.
4. Majority of the \dot{V}/\dot{Q} scans, done in patients with suspected pulmonary thromboembolism are of low, indeterminate or intermediate probability and about 30% of these patients will have pulmonary

thromboembolism. These groups of patients need further work up.

II. **Newer screening tests:** In view of the above limitations of \dot{V}/\dot{Q} scan, other diagnostic modalities have been tested for screening of pulmonary thromboembolism.

A. **D-Dimer assay:** D-Dimer is an epitope present only after stabilization (cross linking) of the fibrin network in a clot and subsequent lysis by plasmin.

D-dimers have a circulating half life of 4-6 hours. It may rise as early as 1 hour after thromboembolism. Continued fibrinolysis of pulmonary thromboembolism increases the plasma D-dimer level for at least 1 week. However D-dimer levels may normalize in those patients who are symptomatic for 7-days.

1. **Methods of determination:** Standard ELISA technique is most well established and gives most accurate and quantitative measurement but takes 2-4 hours. Latex particle agglutination test is rapid, less expensive, but gives only semiquantitative results and lesser sensitivity than standard ELISA technique.

Several second generation proprietary assays have been developed for D-dimer test such as the erythrocyte agglutination assay, immunofiltration assay, automated ELISA technique and turbidimetric assay. Some of these methods are rapid, simple and can be performed at bedside but need more extensive evaluation before they can be routinely recommended.

2. **Diagnostic value of D-dimer in DVT and PTE:** The standard ELISA technique of D-dimer assay has > 90% sensitivity and > 95% negative predictive value in cases of symptomatic DVT and PTE. However, the specificity of this test is only 30-50% in these clinical situations. The performance of latex particle agglutination assay is usually lower than the standard ELISA technique.

3. **Uses and limitations of D-dimer assays:**

a. The test is nonspecific; high d-dimer values are common in the presence of a

postoperative state, infection or neoplasm.

- b. The test has very high negative predictive value (90-99%) in different studies. A cut off value of 500 ug/L is generally accepted and a value lower than this reasonably rules out venous thromboembolism.
- c. Normal values vary with age and age adjusted values are not available.
- d. There are too many assays and there are no standardization or calibration. There are considerable intra-assay and inter assay variations and the normal values in a reference healthy population differ considerably in between the assays.

Thus, D-dimer assay is a promising screening technique. However, the techniques need urgent standardization and calibration. When used along with clinical profile, investigations for deep vein thrombosis and \dot{V}/\dot{Q} scan, pulmonary angiography can be avoided in a significant proportion of patients.

B. Airways dead space determination : In pulmonary thromboembolism, the alveoli in the affected region are normally ventilated but not perfused. Thus the physiological dead space and total airway dead space increase. Airway dead space can be calculated from mixed expired CO_2 tension and arterial CO_2 tension with the help of volume capnography. This test has a sensitivity of >90% and specificity of about 85% in the diagnosis of pulmonary thromboembolism. This test appears to compare favourably to \dot{V}/\dot{Q} scan as a screening test for PTE. It also provides an estimate of the clot size. But, no standard method or protocol are available for the test and it needs further evaluation before it is universally accepted as the screening method of choice for pulmonary thromboembolism.

C. Alveolar arterial oxygen gradient (A-a DO_2) : This test has been evaluated as a screening test but shows very poor specificity and overall test performance. This test currently cannot be recommended as an acceptable screening test.

III. Newer confirmatory tests : Spiral CT scan and MRI have been evaluated as noninvasive means of confirmation of PTE and both of them hold promise for the future.

A. Conventional pulmonary angiography : Pulmonary angiography is considered as the gold standard for definite diagnosis of pulmonary thromboembolism. But pulmonary angiography is an invasive procedure with risk of severe complications such as the contrast reactions, cardiac arrhythmias, cardio-respiratory compromise, groin hematoma and renal failure (total 3-4%). Death rate of 0.2-0.4% is quoted. Thus a noninvasive confirmatory test for PTE is highly desirable.

B. Spiral CT scan : It involves continuous movement of the patient through the CT scanner and concurrent scanning by a rotating gantry and detector system. It has a short scanning time of 20-30 sec and continuous volume acquisition, making multiplanar 2D and 3D reconstruction, possible. The high speed of spiral CT enables imaging of dyspnoeic patients; resolution improves if the patient can hold breath.

Acute embolism is seen as central luminal thrombosis or as occlusion of a vessel. Chronic emboli are seen as eccentric emboli in contiguity with the vessel wall as evidence of recanalisation within an area of arterial hypoattenuation, as arterial webs or as reduction of arterial diameter by >50%.

1. Advantages of spiral CT scan :

- High sensitivity and specificity in case of emboli in the main, lobar and segmental bronchi
- Relative safety and rapidity of the procedure
- The required amount of contrast is about half of that required in pulmonary angiography
- Multiplanar 2D reformation may enable precise analysis of the extent of PE
- Diagnosis of other disease entities which can masquerade as PTE is possible.

2. Disadvantages and limitations :

- Peripheral areas of the upper and lower lobes are poorly visualized and horizontally oriented vessels in right middle lobe and left lingula are inadequately scanned

- The ability of spiral CT to pick up subsegmental emboli is limited
- Tortuosity or oblique orientation of certain segmental arteries can attenuate the vessel image and give a false appearance of pulmonary embolism. Kinetic artefacts from breathing or cardiac motion can also cause false positive results.
- High specificity of spiral CT requires reader's expertise.
- Intersegmental and hilar LN, surrounding areas of atelectasis and perivascular oedema in case of congestive heart failure may be potential sources of error in interpretation

The overall test accuracy of spiral CT is slightly better than \dot{V}/\dot{Q} scan. Also it enables direct visualization of the clot as against indirect evidence on \dot{V}/\dot{Q} scan. These points make spiral CT also an attractive option as a screening test. However, the need for patient transport, radiation exposure, the need for high skill and expertise, absence of studies in outpatients and lack of cost benefit analyses do not permit it to be recommended as a screening test at the present moment.

C. Magnetic Resonance Imagine :

Various image acquisition protocols like spin echo, MR imaging, cine gradient recalled MR imaging, velocity encoded cine MR imaging, conventional MR angiography and ultra fast contrast enhanced MR angiography have been used for diagnostic imaging of pulmonary thromboembolism.

1. **Advantages** : The procedure is rapid and allows imaging of other thoracic structures. It does not use ionizing radiation and is therefore a safe method of imaging in pregnant patients. It has excellent sensitivity and specificity for diagnosis of DVT.
2. **Disadvantages** : MRI is expensive and not uniformly available. Requires the patient to lie still in a narrow tube which may be difficult for a dyspnoeic patient. There is a wide variability in the methodology and of results among different studies. While central emboli are well visualized, it is difficult to properly evaluate the peripheral vessels.

The role of MRI vis a vis spiral CT remains unidentified. The slightly higher ability of spiral CT to detect clot, the examination speed and the ease of patient monitoring during spiral CT makes it a superior choice.

D. Echocardiography :

The utility of echocardiography in the diagnosis of PTE is limited. Transthoracic echocardiography rarely visualizes thrombi in the main pulmonary artery. Transesophageal echocardiography can visualise thrombi in the main pulmonary artery, right pulmonary artery and unusually in left pulmonary artery. The evidence of PTE on echocardiography is more commonly indirect - by showing features of pulmonary arterial hypertension (PAH). The features of PAH come when 30-40% of circulation is blocked. This echocardiography may be useful in the diagnosis of very ill patients with a high embolic burden.

Echocardiography also has an important role in evaluating the hemodynamic impact of PTE. It picks up evidence of RV dysfunction in the form of diminished right ventricle free wall contractility or diminished tricuspid annular plane septal excursion. Echocardiography, therefore, selects the patients who will be candidates for surgical or catheter embolectomy or thrombolysis. In overall, echocardiography has a central role in evaluating an ill and hemodynamically unstable patient with suspected PTE.

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