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**THE INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES**


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## Allergic Bronchopulmonary Aspergillosis: Indian Perspective

Over 150 species of the ubiquitous fungus, *Aspergillus*, have been identified; of which *Aspergillus fumigatus* (Af) is responsible for about 95% of *Aspergillus*-related illnesses in humans. Broadly, the *Aspergillus*-associated respiratory disorders may be classified into three clinical categories, viz allergic-bronchopulmonary aspergillosis (ABPA), aspergilloma and invasive aspergillosis.<sup>1</sup> The ABPA is world-wide in distribution and is being increasingly recognised in our country too.

From India, first three cases of ABPA were reported in 1971.<sup>2</sup> Early sporadic case reports were followed by large series of ABPA cases from different parts of the country<sup>3</sup> including the largest one of 126 cases from north India.<sup>4</sup> All these reports indicate that ABPA is a common entity in India too.

Majority of ABPA cases occur in patients with bronchial asthma or cystic fibrosis. Type I *Aspergillus* cutaneous hypersensitivity has been reported in 16% to 50% patients of bronchial asthma by the workers from other countries.<sup>3</sup> From India, Chakrabarti *et al*,<sup>5</sup> Maurya *et al*<sup>6</sup> and Agarwal *et al*<sup>4</sup> reported *Aspergillus* cutaneous type I sensitisation in 50%, 28.5% and 39.5% of their asthma patients, respectively.

It is rather difficult to estimate the prevalence of ABPA because of lack of uniform diagnostic criteria and standardised tests. From India, Kumar and Gaur,<sup>7</sup> Maurya *et al*<sup>6</sup> and Agarwal *et al*<sup>4</sup> reported ABPA prevalence of 16%, 7.5% and 27.2% among their asthmatic patients, respectively. However, such high figures do not reflect the prevalence of ABPA in general community, but only represent the referral bias as there are hospital-based figures from tertiary care institutes.

Despite such a high prevalence of ABPA reported in hospital studies from India, ABPA is still under-recognised and under-diagnosed in our country. A number of factors may be responsible for this situation. There is high prevalence of tuberculosis (TB) in our country and due to ignorance and lack of suspicion, a large number of ABPA cases may be mis-diagnosed as TB and go on receiving prescribed anti-tuberculosis treatment. In some Indian studies, ABPA was mis-diagnosed as TB in as high as 17% to 50% cases.<sup>3</sup> Corticosteroids are grossly misused in asthmatics, in our country and this may mask the presentation of ABPA. Chest radiographs are often not routinely done in asthmatics, and hence, ABPA may be missed. By and large, there is a lack of awareness about ABPA among general practitioners and even medical specialists and many chest specialists. The mycoserological tests and investigations, like computed tomographic (CT) scan required for diagnosing ABPA are not widely available

and are rather expensive.

There is no simple test that can establish the diagnosis of ABPA and a set of criteria is required for this purpose.<sup>6,8</sup> Greenberger<sup>9</sup> laid down eight diagnostic criteria in 1997. However, there is still no consensus on the number of criteria used to diagnose ABPA. Lung biopsy is not required for diagnosing ABPA, as it can be established on the basis of clinical, radiological and serological features only.

A number of radiological features, subdivided into transient and permanent shadows have been described in ABPA, though none are pathognomonic of ABPA.<sup>10,11</sup> Till a few years ago, bronchography was the "gold standard" investigation for detecting bronchiectasis in ABPA, but in recent years, high resolution CT (HRCT) scan has emerged as the investigation of choice for this purpose. An Indian study compared HRCT with bronchography in ABPA cases and found that HRCT had a sensitivity of 83% and a specificity of 92.5% when compared to bronchography.<sup>12</sup> A few Indian studies<sup>4,12,13</sup> have also reported HRCT findings in ABPA. Tuberculosis is widely prevalent in India, but its co-existence with ABPA is rare. It has been suggested that the fungus *Aspergillus* and mycobacteria are unable to grow simultaneously in the human lung, which may partly explain their uncommon co-existence.<sup>14</sup>

Patterson *et al*<sup>15</sup> and Greenberger and Patterson<sup>16</sup> have described five stages of ABPA, i.e. acute stage, stage of remission, stage of exacerbation, stage of steroid-dependent asthma and fibrotic stage. Fibrotic lung stage in ABPA may, at times, be difficult to differentiate from the fibrocavitary lesions of tuberculosis. As the diagnosis of ABPA is often delayed in our country due to reasons mentioned above, a fairly large number of ABPA cases may be diagnosed in advanced stage, i.e., stages IV or V only.

Patterson *et al*<sup>17</sup> described two stages of ABPA, i.e. ABPA-S (serological positive) and ABPA-CB (with central bronchiectasis). The ABPA-S cases are only sero-positive and probably represent the earliest stages of ABPA. Based on radiological, serological and clinical severity, Kumar<sup>18</sup> categorised ABPA into three stages, such as ABPA-S, ABPA-CB and ABPA-CB-ORF (with central bronchiectasis and other radiological features), and labelled them as mild, moderate and severe forms of ABPA. Patients with ABPA-CB or ABPA-CB-ORF had more signs and symptoms and higher serological values as compared to ABPA-S patients.

A high index of suspicion is required to establish the diagnosis of ABPA. In the Indian context, all asthmatics who have a type I cutaneous reaction positive to Af antigen should be investigated for ABPA. Bronchial

asthma patients having systemic complaints and/or a history of expectorating golden brownish plugs should also be investigated for ABPA. Allergic bronchopulmonary aspergillosis should also be excluded in asthmatics having radiological infiltrates or central bronchiectasis and peripheral blood eosinophilia. Patients with a history of having received repeated anti-tuberculosis therapy without confirmation or improvement and having associated symptoms of dyspnoea and wheezing should also be evaluated to exclude ABPA.

The goals of treatment of ABPA are: (a) to detect and treat exacerbations promptly so as to prevent or minimise the occurrence of bronchiectasis that may develop at the site of infiltrates; (b) to manage associated asthma or irreversible lung disease; (c) to exclude ABPA in family members, and (d) to identify a potential fungal source in the environment.<sup>3</sup>

Oral glucocorticoids are currently the treatment of choice, as they suppress both the immune response and inflammation. Different studies and reviews have recommended different dosages and duration of therapy.<sup>19,20</sup> In these dose schedules, high relapse rate and steroid-dependence was observed. Recently, Agarwal *et al*<sup>4</sup> treated their ABPA cases with higher dosage of prednisolone given for longer duration. In this study, 0.75mg/kg prednisolone was given for six weeks and then reduced to 0.5mg/kg for next six weeks. This dose was then tapered by 5mg every six weeks and the therapy was continued for a total duration of at least 6 to 12 months. In this study, higher remission rates and lower prevalence of steroid dependent ABPA was reported. In view of these varying results of different studies, further trials are needed to optimise the dose and duration of steroid therapy for the treatment of ABPA. The role of various antifungal agents is being explored. It has been suggested that antifungal agents may decrease the fungal load, and thus, reduce the antigenic stimulation and inflammatory response. A recent Cochrane review<sup>21</sup> has concluded that azole antifungal drugs may be of some benefit in treating ABPA, if added to the standard therapy of high dose or oral corticosteroids.<sup>5</sup> However, long-term trials are needed before a final recommendation can be made.

To conclude, ABPA is quite common in our country too, but a high index of suspicion is required to diagnose it early as this along with aggressive treatment may prevent further lung damage and end-state fibrosis.

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# Computed Tomography in Blunt Chest Trauma

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## ABSTRACT

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**Objective.** To assess the role of multidetector spiral CT in patients with blunt chest trauma.

**Methods.** Forty-two patients (38 males and four females), age range from 6 to 80 years, of blunt chest trauma were evaluated with multidetector computed tomogram (MDCT) after initial radiographs and the results were tabulated.

**Results.** The most common mode of injury was motor vehicle accidents (64%). On computed tomography (CT), major injuries were haemothorax (83.33%), consolidation (66.6%), rib fractures (61.90%), pneumothorax (54.76%), diaphragmatic injury (30.95%), lung contusions (28.57%), spinal injury (16.66%), lacerations (9.52%), tracheo-bronchial injury (4.76%), mediastinal haematoma (4.76%), thoracic-aortic injury (4.76%) and oesophageal injury (2.38%). Operative intervention was performed in 11 (26.19%) patients. Of these, diaphragmatic rent repair was done in seven patients (63.63%), exploratory laparotomy alone was done in two (18.18%) and resection and anastomosis and polytetrafluoroethylene graft in one patient each. Three patients each with chest wall injury, thoracic vascular injury and diaphragmatic injury died; while only one patient with lung injury died.

**Conclusion.** Multidetector computed tomogram is the modality of choice for rapid assessment of emergency chest trauma patients. [Indian J Chest Dis Allied Sci 2009;51:75-81]

**Key words:** CT, Chest, Blunt trauma, Diaphragmatic injury, Tracheo-bronchial injury.

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## INTRODUCTION

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Trauma causes an estimated 10% of deaths worldwide and is the third common cause of death after malignancy and vascular disease.<sup>1</sup> Blunt thoracic trauma causes 20% of trauma related deaths. Blunt thoracic injuries are caused by motor vehicle crashes in 63% to 78%, while only 10% to 17% are related to fall from a height.<sup>2</sup> Blunt thoracic trauma is almost exclusively the result of rapid deceleration, or crushing in road traffic accidents. Severity of thoracic injury can be predicted from the type of impact, speed of impact and the adequacy of restraint.<sup>3</sup>

The supine chest radiograph remains the initial assessment-screening tool for victims of chest trauma who are stable enough to undergo diagnostic studies. Most immediate life threatening thoracic injuries can be detected using a chest radiograph.<sup>4</sup> In recent years, multidetector computed tomogram (MDCT) has begun to change the imaging approach in patient sustaining blunt or penetrating thoracic injury. The ability to directly detect some injuries that are often occult on chest radiography, such as pericardial haemorrhage, major thoracic vascular injury, small pneumothorax and diaphragm tears, as well as the ability to better define the extent of other

injuries, such as lung contusion and laceration account for this transition.<sup>5</sup>

Many patients with multi-trauma require scanning of several body sections. The advent of multislice CT provides the potential for essentially whole-body CT scanning in 1-2 minutes. Sixteen-channel MDCT images the entire thorax in less than 10 seconds. This has the immediate advantage that patients spend less time in CT and more time receiving appropriate care.<sup>6</sup> The speed and accuracy of CT in detecting multisystem injury has proven to be invaluable in the prompt diagnosis and triage of trauma patients. With the advent of MDCT, scanning times have progressively decreased while the image resolution has increased owing to thinner collimation and reduced partial volume and motion artifacts. This high quality image data can be processed further into multiplanar reformatted (MPR) or maximum intensity projection (MIP) images and three-dimensional volumetric (3-D) images, which often aid in the diagnosis of complex injuries in the trauma patients.<sup>7</sup>

Magnetic resonance imaging (MRI) has limited role in the initial evaluation of the trauma patients, but may be of use for the evaluation of the spine and diaphragm in patients who are haemodynamically stable.<sup>8</sup> The present study was conducted to assess the role of MDCT in patients with blunt chest trauma.

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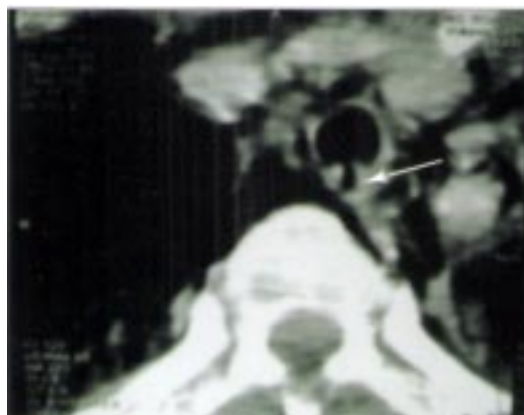
**Table 2. Location of pneumomediastinum and associated injuries detected on CT in six patients**

Patient No.	Location of Pneumomediastinum	Associated Injuries				
		Lung Parenchymal Injury	Tracheal Tear	Oesophageal Rupture	Chest Wall Injury	Neck Structures Injury
1	Central pulmonary arteries and aorta	-	+	+	-	-
2	Arch of aorta	-	-	-	+	-
3	Ascending aorta central pulmonary arteries	-	-	-	+	-
4	Arch of aorta	+	-	-	+	-
5	Arch of aorta	+	+	-	-	-
6	Central pulmonary arteries	+	-	-	-	-

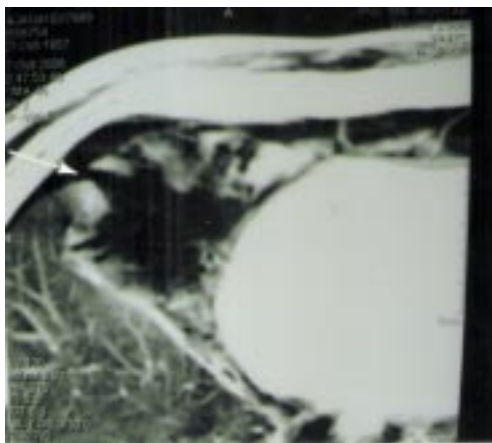
+ = Present, - = Absent.



**Figure 1a.** Chest radiograph in a 46-year-old male patient with chest tenderness and increasing dyspnoea after blunt injury with a stone during an assault. It reveals extensive subcutaneous emphysema in neck and chest wall with chest tube *in situ*.



**Figure 2a.** Axial CT section at the level of the aortic arch in a 28-year-old male who sustained blunt force trauma in a fist fight. It shows discontinuity of posterior tracheal wall (arrow) with communication with oesophagus and air tracking into mediastinum-tracheal tear with tracheo-oesophageal fistula.



**Figure 1b.** Axial CT section showing linear tear through lung parenchyma seen as air containing line (arrow)-laceration Type 1 in the medial segment of the right middle lobe.

two patients and were within 2.5cm of carina, and these were associated with pneumomediastinum and cervical emphysema (Figures 2a and 2b).

Thoracic aortic injury (Figures 3a and 3b) was suspected on chest radiograph in three patients. Computed tomography was performed in all. On radiographs, superior mediastinal widening, right-



**Figure 2b.** Sagittal MPR showing tracheal tear with tracheo-oesophageal fistula (arrow) in the same patient.

sided pleural effusion and fullness of the right paratracheal stripe were seen in two patients each, while bilateral pleural effusion and widening of the right paraspinal stripe were seen in one each. On CT, mediastinal/periaortic haematoma was seen in two patients, while indistinctness of mediastinal fat planes, fracture clavicle with fluid



Table 3. CT findings in 13 patients with rupture of diaphragm

Patient No.	Age (years)	Sex	Mode of Injury	Side of Rupture	CT Findings					
					Diaphragm Discontinuity	Collar Sign	Thickened Diaphragm	Visceral Herniation	Dependent Viscera Sign	Others
1	40	M	RSA	Left	+	+	-	Present (stomach and omentum)	+	B/L haemothorax, fracture ribs
2	8	M/C	History of fall into pond	Left	+	+	-	Present (stomach and gut loops)	-	-
3	18	M	RSA	Left	+	+	-	Present (stomach and colon)	+	Left haemothorax, haemoperitoneum
4	48	M	RSA	Right	-	-	+	-	-	B/L haemothorax
5	20	M	RSA	Left	+	+	+	Present (stomach and colon)	-	Left haemothorax
6	25	M	RSA	Right	+	-	+	Present (liver)	-	B/L haemothorax, fracture ribs, haemoperitoneum
7	35	M	RSA	Right	-	-	+	-	-	Right haemothorax, fracture multiple ribs, haemoperitoneum
8	18	M	RSA	Right	-	-	+	-	-	Right haemothorax, fracture ribs, haemoperitoneum
9	20	M	RSA	Right	-	-	+	-	-	-
10	31	M	History of assault (2 years back)	Left	+	+	-	Present (splenic flexure, stomach and omentum)	+	Left haemothorax, fracture left side ribs
11	45	M	RSA	Left	-	-	-	-	-	Left haemothorax, fracture left side ribs
12	50	F	RSA	Left	+	-	-	Stomach and bowel loops	+	Right haemothorax,
13	55	M	History of fall of heavy object	Right	+	+	+	Liver, gall bladder and gut loops	+	B/L haemothorax, fracture ribs

M=Male; C=Child; F=Female; RSA=Roade side accident; B/L=Bilateral.

with tracheal injury with tracheo-oesophageal fistula. Computed tomography findings in blunt thoracic trauma patients are shown in table 4.

Associated abdominal visceral injuries were seen in 17 patients. The frequency of injuries was as follows: liver: 14, right kidney injury: 4, left kidney injury: 2, splenic injury: 4, adrenal injury: 3,

mesenteric injury: 2 and pancreatic injury: 1. Right-sided rib fractures were associated with liver, right kidney and right-adrenal injuries.

Injuries were graded 1 to 3. The frequency in each grade, respectively, was as follows: (a) chest wall: 14 (2 expired), 18 (1 expired) and 9; (b) lung: 0, 19, and 7 (1 expired); (c) thoracic vascular: 24 (1 expired), 12 (two

**Table 4. CT findings in chest injury patients (n=42)**

Abnormality	Number of Abnormalities Seen on CT
Contusion	12 (28.57%)
Laceration	4 (9.52%)
Pneumothorax	23 (54.76%)
Haemothorax	35 (83.33%)
Subcutaneous air	13 (30.95%)
Subcutaneous (air including mediastinal air)	6 (14.28%)
Consolidation	28 (66.66%)
Pneumopericardium	0
Air in pulmonary ligament	0
Fractured sternum	7 (16.66%)
Fractured rib	26 (61.90%)
Fractured scapula	7 (16.66%)
Fractured clavicle	4 (9.52%)
Extraplural haematoma	3 (7.14%)
Tracheobronchial injury	2 (4.76%)
Mediastinal widening	2 (4.76%)
Mediastinal haematoma	2 (4.76%)
Spinal injury	7 (16.66%)
Diaphragmatic injury	13 (30.95%)
Thoracic aortic injury	2 (4.76%)
Oesophageal injury	1 (2.38%)

expired), and 1; (d) aorta: 2, 0 and 0; (e) diaphragm: 4 (1 expired), 1, and 8 (2 expired). Operative intervention was done in 11 out of 42 patients. Mortality occurred in three patients in whom operative intervention was performed. No mortality was seen in conservatively managed patients.

## DISCUSSION

Chest injuries directly cause 25% of trauma related deaths and contribute markedly to another 25 percent.<sup>9</sup> Trauma is the leading cause of death in the first four decades of life.<sup>1</sup> Admission chest radiographs will probably remain the "first look" at the traumatised chest. While MDCT serves as the definitive screening study in major trauma patients,<sup>5</sup> bedside sonography can be used to assess the pericardium and the pleural spaces. However, it falls well short of CT when detection of full spectrum of major thoracic injuries must be excluded.<sup>5</sup> Application of MRI in acute trauma patients is limited technically.<sup>8</sup>

Rib fracture occur in 56% of patients with major blunt chest trauma but many of these fractures are missed on chest radiographs possibly due to difficulties in obtaining good radiographic views.<sup>10</sup> Fractures of the lower ribs should increase the suspicion for spleen, liver and renal injury.<sup>4</sup>

Scapular fractures are overlooked or obscured on chest radiograph in as many as 35% of patients.<sup>10</sup> Crestanello *et al*<sup>11</sup> found that fractures of sternum are frequent, occurring in 1.5% to 4% of blunt chest trauma. Clavicular fractures from blunt chest trauma accounts for 3% of all dislocations. Anterior

dislocations are most common and usually without clinical significance.<sup>4</sup> Fractures involving the thoracic outlet, upper ribs, sternum, scapula and clavicle are significant because they are accompanied by brachial plexus/vascular injury in 3% to 15% of patients.<sup>4,5</sup>

Fractures of the thoracic spine occur in 3% of blunt trauma cases.<sup>6</sup> The most common site is the thoracoabdominal junction involving the T9-T12 vertebral bodies.<sup>12</sup> Pleural effusion is the result of many different injuries such as intercostal vessels, pulmonary laceration, diaphragmatic/mediastinal tears, and traumatic insertion of vascular lines. Gavelli *et al*<sup>13</sup> pointed out that a pleural effusion below 200-300ml is usually not detected in the supine chest radiograph. It is difficult to make a differential between an exudative effusion and a haemothorax using only the ultrasound and for which CT is useful. Small pneumothoraces are not initially recognised by clinical examination or by admission chest radiography in 30% to 50% of trauma patients.<sup>8</sup>

Pneumomediastinum represents extra alveolar air in the mediastinum, a consequence of both blunt and penetrating trauma.<sup>4</sup> Computed tomography imaging is much more sensitive than chest radiography for detection of pneumomediastinum particularly adjacent to the central pulmonary arteries, and aorta.<sup>6</sup> Pulmonary contusion is seen in 30% to 70% of patients.<sup>4,6,13</sup> In civilian trauma, rapid deceleration after motor vehicular accident and falls are the predominant mechanisms of injury.<sup>14</sup> These are generally found near solid structures, such as vertebra, sternum, ribs, liver and the heart usually within 1-2 hours.<sup>6</sup> Cohn<sup>14</sup> found that chest CT is highly sensitive in identifying pulmonary contusion and may help in predicting the need for mechanical ventilation. Airspace consolidation when greater than 28%, will require mechanical ventilation.<sup>15</sup> Contusions begin to resolve after 48-72 hours and tend to disappear completely after 1-2 weeks. Failure of lung density to resolve leads to superimposed pathological process.<sup>4</sup> Pulmonary laceration frequently accompanies pulmonary contusion.<sup>5</sup>

Pulmonary lacerations were considered an uncommon injury before the widespread use of CT in trauma patients as these were not frequently identified on chest radiographs.<sup>4-6,12</sup> Wagner *et al*<sup>12</sup> classified the lacerations into four types. They confirmed the lesion to be laceration when an air-filled radiolucency surrounded by lung parenchyma was seen on CT. Tracheobronchial injuries are relatively uncommon and often go unrecognised because of lack of visible external signs of injury. They have been reported in 2.8 to 5.4% of autopsy series and in 0.4% to 1.5% of clinical series of patients following major blunt thoracic trauma.<sup>4,5,16,17</sup>

More than 80% of injuries are anatomically located within 2.5cm of the carina, and right sided bronchial injuries occur more frequently than the left side.<sup>4,6,13</sup> The clinical signs and symptoms of acute airway injury after blunt chest trauma may initially be undetected with as many as 10% of patients.<sup>18</sup> The presence of persistent pneumothorax and increasing subcutaneous emphysema despite adequate chest tube insertion should be a clue to a possible airway injury.<sup>6</sup>

The incidence of thoracic aortic injury diagnosed by CT in two large patients series varied from 1.1 to 2.2%.<sup>6</sup> Even under the best of circumstances, findings on the plain chest radiographs can only suggest the diagnosis of aortic rupture. Demetriades *et al*<sup>19</sup> suggested that aortography can be replaced by helical CT and angiography should be reserved only for patients whose CT scan is indeterminate. Direct signs of thoracic aortic injury (TAI) on CT include active extravasation, pseudoaneurysm, abrupt changes in the caliber of aorta, aortic dissection, intimal flap or filling defects and irregularity of the aortic wall. Indirect signs of TAI include indistinctness of mediastinal fat planes, mediastinal hematoma, and periaortic haematoma.

Diaphragmatic injury occurs in 0.8% to 8% of patients following blunt trauma.<sup>4,6,20</sup> with left hemidiaphragm more often involved right.<sup>4,21</sup> The mechanism of injury is thought to be a lateral impact distorting and shearing the chest wall or a direct frontal impact causing a sudden increase in intraabdominal pressure.<sup>22</sup> The initial radiographs are diagnostic in 27% to 60% of cases with left-sided injury, but only 17% in right-sided injury.<sup>4</sup> Helical CT is valuable in the preoperative detection of diaphragmatic ruptures.<sup>22,23</sup> Nchimi *et al*<sup>24</sup> found that helical CT has a 100% sensitivity and a 94.6% specificity for blunt traumatic rupture. Larici *et al*<sup>20</sup> found that the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of helical CT as 84%, 77%, 81%, 81% and 83%, respectively, which in our series was 100%, 96%, 88%, 100% and 97%, respectively. Esophageal disruption is largely the result of penetrating trauma and with blunt trauma accounting for only 10%.<sup>4-6,13</sup> Cardiac injury has been reported in 10% to 16% of patients admitted following blunt thoracic trauma.<sup>4,13</sup>

## CONCLUSIONS

Multidetector computed tomogram is the modality of choice for rapid assessment of emergency chest trauma patients where associated abdominal injuries can be scanned in one sitting with high sensitivity and specificity, though chest radiograph remains the initial screening modality.

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# Effect of Tripod Position on Objective Parameters of Respiratory Function in Stable Chronic Obstructive Pulmonary Disease

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## ABSTRACT

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**Objective.** To examine changes in respiratory dynamics in patients with chronic obstructive pulmonary disease (COPD) sitting leaning forward with hands supported on the knees (tripod position), a posture frequently assumed by patients in respiratory distress.

**Methods.** Spirometry, maximal inspiratory and expiratory pressures (MIP and MEP) generated at the mouth, and diaphragmatic excursion during tidal and vital capacity maneuver breathing measured by B-mode ultrasonography were studied in 13 patients with stable COPD in sitting, supine and tripod positions.

**Results.** Mean±SD age of patients was 52.2±6.8 years. Median disease duration was three years. There was no statistically significant difference in spirometry for sitting, supine and tripod positions (FEV<sub>1</sub>: 1.11±0.4L, 1.14±0.5L and 1.11±0.4L; p=0.99), respectively, (FEV<sub>1</sub>/FVC: 49.2±11.0, 53.7±8.5 and 48.5±11.3, p=0.37), mouth pressures (MIP: 102.9±28.9, 90.6±29.1 and 99.2±32.9 cm H<sub>2</sub>O, p=0.61 and MEP: 100.8±29.9, 100.4±34.4 and 90.6±32.6 cmH<sub>2</sub>O, p=0.74) and diaphragmatic movements during tidal (16.1±5.9, 20.1±6.8 and 16.6±6.2 mm, p=0.22) and forced breathing (33.9±11.0, 43.1±19.6 and 37.4±17.1 mm, p=0.35).

**Conclusion.** Commonly measured indices of respiratory function were not different in the tripod compared to sitting and supine positions. [Indian J Chest Dis Allied Sci 2009;51:83-85]

**Key words:** COPD, Posture, Respiratory dynamics, Tripod, Diaphragm.

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## INTRODUCTION

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Patients with chronic obstructive pulmonary disease (COPD) in respiratory distress often various maneuvers such as pursed lips breathing, sighing and sitting with leaning forward supporting hands on their knees. The latter is called the tripod position because of the characteristic use of three points of support. Several authors have hypothesised that the forward leaning posture probably helps by optimising recruitment of accessory muscles,<sup>1</sup> or conversely by promoting relaxation of accessory muscle consequent upon fixation of arms and hence reducing the use of upper chest muscles.<sup>2</sup> Alternatively, cephalad displacement of a short flattened diaphragms could lead to stretching and greater tension generation,<sup>3</sup> and hence improve diaphragmatic function. The evidence has however been in consistent and conflicting. Only one of these studies actually involved fixing the upper limbs on the knees, the classic tripod position.<sup>4</sup> We hypothesised that fixed arms would

probably splint the upper chest wall and that improved diaphragmatic function would explain the benefit observed in tripod position. We used spirometry, measurement of pressures generated at the mouth during maximal inspiration and expiration, and ultrasonography for direct visualisation and measurement of diaphragmatic function in three primary postures to elucidate the effect of posture on respiratory dynamics.

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## MATERIAL AND METHODS

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We enrolled 13 patients with stable COPD ( defined as no exacerbations in the preceding four weeks) after obtaining informed consent. The diagnosis of COPD was based on the characteristic features on history and examination with typical radiographic abnormalities and confirmed by pulmonary function tests (PFTs). An exacerbation was defined as the occurrence of two of the following: worsening dyspnoea, increased expectoration and increased purulence of sputum.<sup>5</sup> Baseline demographic

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variables were obtained in all the patients. Active smoking was defined as smoking within the past six months. Patients with co-morbidities such as hypertension, diabetes mellitus, congestive heart failure, tuberculosis, bronchiectasis and intercurrent respiratory illness were excluded. Ethical clearance was obtained from the Institute's Internal Review Board.

Measurements were carried out in three primary postures in three settings. First, the patients were subjected to spirometry using a rolling seal electronic spirometer (PK Morgan, UK, model S232)<sup>6</sup> in sitting, supine and tripod positions in a random order with sufficient rest in between the tests. Tripod position was defined as sitting with leaning forward on a firm stool with hands supported on knees. Each test was carried out after the patient had been in that posture for five minutes. The best of three readings was taken. Next, MIP and MEP measured at the mouth were recorded in the three primary postures in random order<sup>7</sup> using a Pmax mouth pressure monitor (Morgan Medical Limited, UK). The best of three readings was recorded. Finally, diaphragmatic excursion during normal tidal and forced vital capacity maneuver breathing was measured by B-mode ultrasonography by a qualified sinologist using a

**Table 1. Baseline anthropometric, demographic and lung function characteristics of the study population**

Variable	Values (n=13)
Age (years)	52.2 ± 6.8 (Range 45 to 70)
No. of males (%)	10 (77%)
Height (m)	1.61 ± 0.09
Body mass index (m/kg <sup>2</sup> )	19.5 ± 3.7
Median disease duration (years)	3 (Range 1 to 8)
Smoker	
Current	5
Ex	5
No	3
Pack-years	20 (0 to 72)
FEV <sub>1</sub> (L)	1.11 ± 0.4
FEV <sub>1</sub> %	39.4 ± 13.0
FEV <sub>1</sub> /FVC	49.2 ± 11.0
Six-minute walk distance (m)	417.9 ± 88.5

Values expressed as Mean±SD or in absolute numbers. M=Meter, kg=Kilogram, L=Litre, FEV<sub>1</sub>=Forced expiratory volume in one second, in sitting posture, FVC=Forced vital capacity in sitting posture.

**Table 2. Variation of lung function parameters between the three positions in the study patients**

Variable	Sitting	Supine	Tripod	P*
FEV <sub>1</sub> (L)	1.11±0.4	1.14±0.5	1.11±0.4	0.99
FEV <sub>1</sub> %	39.4±13.0	39.9±2.8	39.0±11.4	0.98
FVC (L)	2.3±0.7	2.1±0.8	2.3±0.7	0.73
FEV <sub>1</sub> /FVC	49.2±11.0	53.7±8.5	48.5±11.3	0.37
MMFR (L)	0.6±0.3	0.7±0.3	0.6±0.3	0.95
MIP (cmH <sub>2</sub> O)	102.9±28.9	90.6±29.1	99.2±32.9	0.61
MEP (cmH <sub>2</sub> O)	100.8±29.9	100.4±34.4	90.6±32.6	0.74
Tidal excursion of diaphragm (mm)	16.1±5.9	20.1±6.8	16.6±6.2	0.22
Forced excursion of diaphragm (mm)	33.9±11.0	43.1±19.6	37.4±17.1	0.35

\*p value calculated using nonparametric Kruskal-Wallis test. All values expressed as Mean±SD, FEV<sub>1</sub>=Forced expiratory volume in one second, FVC=Forced vital capacity, MMFR=Mid maximal flow rate, MIP=Maximal inspiratory pressure, MEP=Maximal expiratory pressure.

3.5MHz sector transducer (Model ATL, HDI 3000, Philips Bothel, USA). A fixed point on the right lateral chest wall was chosen on the anterior axillary line to obtain a longitudinal plane of the right hemidiaphragm which included the maximal renal bipolar length. The adjacent posterior aspect of the hemidiaphragm was identified. A craniocaudal displacement line was marked with a cursor at the midpoint of the kidney and the excursion of the hemidiaphragm was measured along this line with another cursor at the same depth from the transducer. Diaphragmatic excursion was measured during both tidal breathing and during a vital capacity maneuver. For each maneuver, at least three satisfactory readings were taken. The higher of two values which agreed most closely were taken for tidal breathing and the best of three efforts was taken for forced breathing. All measurements were repeated in the three primary postures. All patients underwent a six-minute walk distance test to determine the baseline functional exercise tolerance.

### Statistical Analysis

Descriptive data was recorded for all patients. The mean values of parameters measured in three postures were compared using the non-parametric Kruskal-Wallis test. A p value of ≤0.05 was considered significant for all analyses.

## RESULTS

The anthropometric, demographic and baseline sitting pulmonary function test variables of the study population are presented in table 1. The three non-smokers had a history of significant exposure to biomass fuel. Nine (69%) had stage 3 or 4 COPD by GOLD criteria<sup>8</sup>. Table 2 shows the effect of change in posture on lung function test parameters. There was no difference in the spirometric variables and in pressures generated at the mouth during maximal inspiratory and expiratory maneuvers in the three different postures. Though there was no statistical significance between the three postures in the degree of excursion of the diaphragm, it tended to be higher in the supine posture as compared to the other postures.

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## DISCUSSION

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Postures and maneuvers adopted by patients in acute respiratory distress have always been fascinating but yet not fully explained scientifically. The tripod position has been historically described as a clinical sign of patient in respiratory distress. Few studies have been carried out to assess the effect of posture and position on respiratory dynamics. Most studies have assessed erect and supine postures and found that assuming supine posture from sitting or erect posture results in an increase in indices of airflow resistance and a greater excursion of the diaphragm.<sup>9,10</sup> Very few studies have looked at the effect of forward leaning position. These could not demonstrate any improvement in airway obstruction, minute ventilation or oxygenation.<sup>2,4</sup> Forward leaning was found to cause a reduction in the activity of the scalene and sternocleidomastoid muscles measured by electromyography.<sup>4</sup> It also caused an increase in MIP,<sup>11</sup> and an improvement in thoracoabdominal movements.<sup>4-11</sup> Though inconsistent and sometimes conflicting, these studies suggested that the improvement of dyspnoea in patients with COPD was due to a more optimal position of the diaphragm on its length-tension curve. This was thought to be due to reduction in tension imposed by abdominal muscles and a decrease in downward pressure of the viscera attached to the diaphragm, facilitating excursion of the diaphragm.

We conducted this quasi-physiological experiment in stable COPD patients who would be able to perform the tests in different postures. We hypothesised that leaning forward in a seated position with upper limbs fixed on the knees would splint the upper chest diverting the energy demands toward the main muscle of inspiration, and that leaning forward would reduce the abdominal visceral pressure on the diaphragm. Any improvement in ventilation and gas exchange would have to occur in the lower lung zones. We failed to demonstrate any change in spirometric parameters on changing posture from sitting or lying down to tripod position. Neither was there any change in the maximal pressure generated at the mouth during inspiration or expiration. Though the diaphragm excursion was higher in the supine posture as compared to sitting, a fact documented in previous studies, it was not significantly different in the tripod position.<sup>12</sup> The FVC was lesser in the supine position, a finding seen in a previous study,<sup>13</sup> but there was no significant difference between the three postures. Failure to demonstrate any change in respiratory mechanics by change of posture may suggest that there might be other factors at play than just change in the former. However, it would be prudent to note that respiratory mechanics are a dynamic process, more so in patients in acute respiratory distress. Bronchoconstriction and dynamic hyperinflation in a sick patient with COPD would place the diaphragm at a progressively increasing disadvantage, a process we could not reproduce in this cohort of stable COPD patients. Further, the study was

limited by small numbers. The very small change induced by posture suggests that there may be factors other than the ones measured, such as altered ventilation perfusion balance. This needs to be investigated. The observation that only some patients adopt this posture seems to suggest that there may not be universal benefit. Whether this is due to variations in strengths of abdominal and accessory muscles that are brought into play during forceful expiration remains to be investigated.

In summary, it is clinically difficult to reproduce the respiratory dynamics of a sick patient and other mechanisms might be able to explain the perceived benefits of assuming tripod position in some patients. The commonly measured indices of respiratory function were not different in tripod position compared to sitting and supine in patients with stable COPD.

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# Assessment of Pulmonary Function in Amyotrophic Lateral Sclerosis

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## ABSTRACT

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**Background.** Amyotrophic lateral sclerosis (ALS) is characterised by diffuse and progressive death of motor neurons and deteriorating pulmonary functions. At diagnosis most patients with ALS usually do not have any respiratory complaints. However, sub-clinical pulmonary dysfunction is known.

**Objective.** To study pulmonary dysfunction in patients who clinically and electro-physiologically fulfil El escorial criteria of probable and definite ALS.

**Methods.** We performed a standard battery of pulmonary function tests (PFTs) including spirometry, maximum voluntary ventilation (MVV) and maximum inspiratory and expiratory pressure (MEP, MIP) on 63 patients fulfilling the El escorial criteria for probable and definite ALS. Results were compared between the El escorial groups, bulbar- and limb-onset ALS and with age- and sex-matched healthy volunteers, taken as controls.

**Results.** Only 11% of the patients had respiratory complaints at diagnosis. There was no statistical difference in pulmonary parameters between bulbar- and limb-onset ALS. The pulmonary dysfunction was restrictive. Both definite and probable ALS patients had significant reduction in all the measured pulmonary function parameters. The reduction in definite ALS patients was greater in forced vital capacity percent (FVC%) predicted, peak expiratory flow rate (PEFR) percent predicted and MIP. The proportion of patients with severe and very severe dysfunction was higher in the definite ALS group as compared to probable ALS group.

**Conclusions.** Significant pulmonary dysfunction of restrictive type was noted in ALS patients. Both types of ALS, bulbar- and limb-onset, had similar levels of dysfunction. [Indian J Chest Dis Allied Sci 2009;51:87-91]

**Key words:** Pulmonary function, Amyotrophic lateral sclerosis, Muscle.

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## INTRODUCTION

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Amyotrophic lateral sclerosis is a disorder characterised by degeneration of motor neurons in the motor cortex, cranial nerve nuclei and anterior horn cells. This leads to muscle atrophy, spasticity and weakness, resulting in paralysis and death, invariably due to respiratory failure, usually within five years of the diagnosis.<sup>1</sup> Though the rate of progression of symptoms varies widely among patients, those with respiratory muscle weakness as their main complaint have a median survival period of only two months from the time of the diagnosis.<sup>2,3</sup>

The diagnosis of ALS is by the El escorial criteria, that is based on clinical and electro-physiological demonstration of upper motor neuron (UMN) and lower motor neuron (LMN) involvement in the upper extremities, lower extremities, bulbar or thoracic

regions. The ALS is broadly classified as “definite, probable and possible”, depending on the involvement of three, two or one of the four mentioned areas, respectively along with electro-physiological and neuro-imaging data.<sup>4</sup>

Patients may not have any respiratory complaints until their forced vital capacity (FVC) falls to as low as 38% of the predicted due to physiological compensation.<sup>5</sup> Bulbar symptoms, like dysphagia and dysarthria, may not be accompanied by respiratory symptoms. Respiratory involvement in ALS is known to be of progressive restrictive type. Respiratory muscle strength is also significantly lower in patients with ALS and is a good predictor of the disease progress.

The aim of the present study was to quantify the degree of pulmonary dysfunction in patients with ALS, attending the out-patient Department of

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Neurology, National Institute of Mental Health and Neuro Sciences, Bengaluru, and to study the relationship between pulmonary dysfunction and the different El escorial sub-groups (probable ALS and definite ALS). Further, the bulbar-onset and limb-onset ALS were compared for pulmonary dysfunction.

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## MATERIAL AND METHODS

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This study was conducted at the National Institute of Mental Health and Neuro Sciences, a university teaching hospital in South India between 2006 and 2007. The protocol of the study was approved by the Institute's ethics committee. Written informed consent was obtained from each patient. Volunteering, patients who fulfilled the inclusion criteria and attending the Out-patient Department of Neurology were included.

The diagnosis was based on meticulous clinical examination, electroneuromyography and, when required imaging. All patients underwent routine biochemical tests including thyroid functions, Collagen vascular work-up and serum protein electrophoresis.

The patients were categorised as per El escorial criteria into definite ALS, probable ALS or possible ALS. Equal number of healthy age- and gender-matched, non-smoker volunteers were included as controls from a data pool consisting of hospital staff, volunteers and relatives of the ALS patients. The patients were also grouped as limb-onset and bulbar-onset ALS, based on their complaints and clinical and electroneuromyography examination at presentation.

Spirometry was performed using the spirometry kit Micro, Cosmed Italy. Forced vital capacity, forced expiratory volume in one second ( $FEV_1$ ), and peak expiratory flow rate (PEFR) were measured. Results were expressed as a percentage of the predicted values. The ratio of forced expiratory volume in the first second to forced vital capacity ( $FEV_1/FVC$ ) was calculated. Inspiratory capacity (IC) and expiratory reserve volume (ERV) were also determined and expressed as liters BTPS (at body temperature and ambient pressure, and saturated with water). Maximal inspiratory pressure and maximal expiratory pressure were measured by a fabricated digital peak pressure monitor, designed on the Black and Hyatt principle<sup>7</sup> and expressed in centimeters of water. For inspiratory efforts, the subject was asked to attempt to inspire as forcefully as possible at the end of a normal expiration and for expiratory efforts, to expire as forcefully as possible after a full inspiration. Maximum voluntary ventilation was performed with instructions to breathe out and in as rapidly as possible. This was performed for twelve seconds and expressed per one minute. Lip seal was augmented either by the patient or the technician holding the lips

closed whenever necessary.

All patients had to repeat each maneuver three times at an interval of two minutes between tests in the sitting position. The best of three technically acceptable tests was selected. Percentage predicted values were calculated using the Knudson<sup>8</sup> equation for flow volume parameters and Lindall<sup>9</sup> and Kory<sup>10</sup> equations for MVV. Based on the severity of reduction in the FVC, the parameters were classified into mild (70% to 79% of predicted), moderate (60% to 69% of predicted), moderately severe (50% to 59% of predicted), severe (35% to 49% of predicted) and very severe (less than 35% of predicted).<sup>11,12</sup>

## Statistical Analysis

All continuous variables were expressed as mean  $\pm$  standard deviation. Duration of illness at diagnosis was expressed as median. Comparison of PFT parameters between patients with ALS and controls, between definite ALS group and probable ALS group, and between the limb-onset ALS and bulbar-onset ALS was done using the 't' test.

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## RESULTS

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Of the 72 cases who fulfilled the inclusion criteria, three cases of possible ALS were excluded due to their low numbers that precluded statistical analysis. Six patients had associated Parkinson's disease, pulmonary tuberculosis, bronchial asthma, rheumatoid arthritis, lower respiratory tract infection or malignancy and were also excluded. The remaining 63 patients were grouped into either the definite ALS group (n=40) or the probable ALS group (n=23), based on the El escorial criteria. Clinically two patients in the probable ALS group and five in the definite ALS group had complaints of respiratory distress. This did not correlate with the degree of reduction in the FVC% predicted.

The demographic data of the controls and ALS groups were comparable for mean age at diagnosis, duration of illness and sex ratio (Table 1).

Bulbar-onset of symptoms was seen in 24 patients, while 39 patients presented with limb-onset symptoms. In the bulbar-onset group, 20 patients had definite ALS and four had probable ALS, while in the limb-onset group, 20 patients had definite ALS and 19 had probable ALS. The mean age at presentation of bulbar-onset ALS was later than that within limb-onset ALS. There was no statistical difference in the PFT parameters of patients with bulbar-onset and limb-onset ALS (Table 2). Pulmonary dysfunction was of restrictive type in both the groups.

The break-up of the patients based on decrease in the FVC% predicted values is presented in the figure.

**Table 1. Demographic data of amyotrophic lateral sclerosis (ALS) patients and controls**

Parameters	Controls (n=63)	ALS Definite (n=40)	ALS Probable (n=23)
Age (years)	53.1±10.3	53.9±12.8	50.5±11.9
Sex (M:F)	2:1	2.6:1	1.3:1
Mean duration of illness (in months)		22.3±29.5	13.5±8.9
Median duration of illness (in months)*		12 (1.5-30)	12 (1.5-144)
Proportion with respiratory distress present		12.5%	8.7%
Height (cm)	161.9±7.69	162.6±8.87	161.5±9.5
Weight (kg)	65.1±11.5	58.3±10.5	58.6±6.74

Data is presented as mean±SD, \*=represents median values with range in parenthesis.

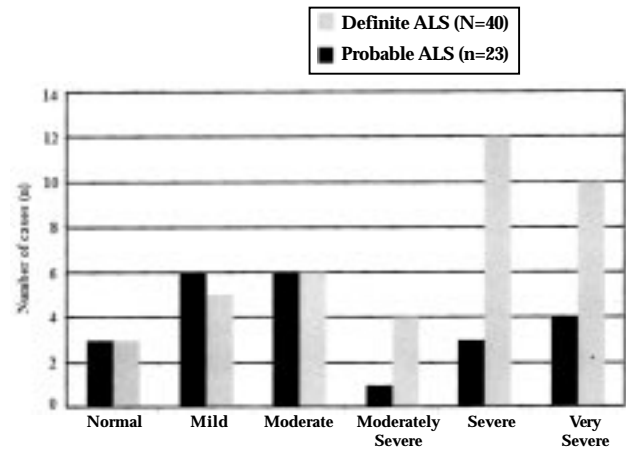
**Table 2. Demographic data and pulmonary function tests (bulbar-onset and limb-onset ALS)**

Parameters	Bulbar-onset ALS (N=24) (Mean±SD)	Limb-onset ALS (N=39) (Mean±SD)
Definite : Probable ALS	5:1	1.05:1
Age (years)	58.2±9.8	49.2±14.1
Duration of illness (years)	15.10±28.4	21.6±25.1 <sup>NS</sup>
FVC%	52.1±20.3	54.8±20.8 <sup>NS</sup>
FEV <sub>1</sub> %	58.6±23.2	59.0±22.7 <sup>NS</sup>
FEV <sub>1</sub> /FVC	91.9±10.6	93.8±24.6 <sup>NS</sup>
PEFR%	40.4±20.0	50.1±21.6 <sup>NS</sup>
ERV(1 BTPS)	0.65±0.42	0.8±0.51 <sup>NS</sup>
IC(1 BTPS)	1.03±0.47	1.06±0.57 <sup>NS</sup>
MVV%	47.0±25.8	55.6±26.8 <sup>NS</sup>
MIP (cmH <sub>2</sub> O)	17.1±9.0	20.1±9.6 <sup>NS</sup>
MEP (cmH <sub>2</sub> O)	23.3±13.2	29.0±12.5 <sup>NS</sup>

NS=not significant; p>0.05

Proportion of patients in the definite ALS group having severe and very severe reduction of the predicted FVC% was 55% while in the probable ALS group it was only 30 percent. In the probable ALS group, 52% had only mild or moderate decrease in the predicted FVC% values.

The PFT parameters revealed a characteristic restrictive type of dysfunction with statistically significant reduction in both the groups (Table 3) when compared to age- and sex-matched controls. The reduction was significant for all the parameters in the definite ALS group while in the probable ALS group the reduction in the ERV did not reach statistical significance when compared to age- and



**Figure. Frequency of patients with normal and different degrees of reduction in FVC in patients with definite and probable ALS.**

sex-matched controls.

Comparison between the definite ALS group and the probable ALS group (Table 3) showed that the quantum of dysfunction was greater in the former group for MIP, FVC% predicted and PEFR% predicted.

## DISCUSSION

Amyotrophic lateral sclerosis is a diffuse process with loss of motor neurons occurring simultaneously in patchy areas and manifests clinically when the

**Table 3. Comparison of pulmonary function test data of patients with ALS and controls**

Parameters	Controls (n=63)	ALS Total (n=63)	ALS Definite (n=40)	ALS Probable (n=23)
FVC% predicted	84.6±14.8	53.8±20.9*	49.6±18.9*	61.0±22.8*.a
FEV <sub>1</sub> % predicted	85.9±16.8	58.9±22.7*	55.6±20.8*	64.5±25.0*.b
FEV <sub>1</sub> /FVC	84.9±10.8	93.1±21.3**	92.6±9.2*	93.9±33.6 <sup>NS</sup> .b
PEFR% predicted	67.2±23.2	46.4±21.2*	41.7±18.4*	54.3±23.7+.a
ERV (1 BTPS)	0.98±0.40	0.75±0.52**	0.71±0.44+	0.79±0.63 <sup>NS</sup> .b
IC (1 BTPS)	1.77±0.67	1.05±0.57*	0.99±0.48*	1.14±0.72+.b
MVV % predicted	92.3±16.9	52.4±26.3*	48.1±24*	59.9±28.8*.b
MIP (cmH <sub>2</sub> O)	50.2±20.4	18.9±9.44*	16.7±8.87*	22.9±9.4*.a
MEP (cmH <sub>2</sub> O)	64.8±20.7	26.7±12.4*	25.7±12.4*	28.7±12.6*.b

Data is presented as mean±SD;

ALS definite and ALS probable versus controls: \*p<0.001; \*\*p<0.01; +p<0.05 and NS=not significant, p>0.05

ALS probable versus ALS definite : a=p<0.05, b=not significant, p>0.05

dysfunction crosses a threshold which is beyond the capacity of the body to compensate.<sup>1</sup> The progress of ALS to paralysis and death, invariably due to respiratory failure occurs usually within five years of the diagnosis.<sup>13</sup>

Studies have found that bulbar-onset occurs in 20% of ALS patients and is associated with female sex and older age groups.<sup>1,14</sup> Most of our patients presented with limb-onset symptoms (62%) and patients with bulbar-onset comprised 38% of ALS patients. We also found that patients in the bulbar-onset ALS group were significantly older than the limb-onset ALS group. It appears that motor neurons supplying bulbar musculature are more resistant to the disease process when compared to other motor neurons. We did not find any female sex predilection for bulbar-onset ALS.

Bulbar symptoms cause greater functional impairment and our study revealed that they had a shorter duration of illness at diagnosis. Patients with bulbar involvement often had additional limb weakness and were more likely to satisfy the definite ALS criteria. Earlier studies<sup>1,2,15</sup> showed that there was no relationship between upper limb-onset ALS and early respiratory failure though bulbar-onset ALS is known to present with earlier and greater dysfunction.

We found that the mean duration of illness was greater in the definite ALS group compared to the probable group. This is expected in a progressive disease, like ALS, as the El Escorial criteria classifies illness according to the number of muscle groups involved which increase with time.

Another study<sup>16</sup> have shown that the FVC% predicted is an excellent and simple test for quantifying diaphragmatic function and can replace more invasive and labour intensive procedures, like oesophageal pressure and trans-diaphragmatic pressure; the latter being the gold standard. Respiratory muscle weakness is assessed by FVC, MIP and MEP, and strongly correlates with the clinical outcome.<sup>17-19</sup> In most patients with ALS, respiratory complaints occur only at the end of the disease course.

Sub-clinical pulmonary dysfunction can be demonstrated from the onset of the illness and in 8.2% of the patients respiratory symptoms are known to appear before limb weakness.<sup>20</sup> In the present study, respiratory distress was seen in only 8.7% of patients in the probable ALS group and 12.4% in the definite ALS group.

Fallat *et al*<sup>21</sup> found that 93% of the ALS patients at diagnosis have abnormal PFT parameters. In our study, we found a mean FVC% of 53.8 percent. The values of the PFT parameters in our series were comparable to previous reports.<sup>16,22,23</sup>

The PFT parameters revealed a characteristic

restrictive type of respiratory involvement with a significant reduction in most pulmonary functions in both the groups with a reduced FVC but normal or elevated FEV<sub>1</sub>/FVC ratio, corroborating other studies.<sup>17,21</sup> There was no difference in the PFT parameters between patients with bulbar-onset and limb-onset ALS. Inspiratory and expiratory muscle weakness can exist and progress together or independently of each other due to the patchy involvement of motor neurons in ALS.<sup>24,25</sup> In the present study, parameters measuring active and forceful use of both inspiratory and expiratory muscles were affected in patients with ALS similarly.

The rate of decline of FVC has been estimated to be about 2.5% to 8.3% of the predicted values per month.<sup>17</sup> Another study<sup>26</sup> have reported a linear decrease in muscle strength with progression of the disease. The definite ALS group had lower pulmonary parameters (FVC, PEFr and MIP) than the probable ALS group at diagnosis. In the present study as follow-up measurement of respiratory parameters was not done, we cannot comment on the linear temporal decline. However, we found larger absolute reduction in FVC in the definite ALS group who had a longer duration of illness.

To conclude, amyotrophic lateral sclerosis is characterised by restrictive type of pulmonary dysfunction. The ALS of both bulbar- and limb-onset had comparable levels of pulmonary dysfunction. Clinical pulmonary complaints were seen in about 10.6% of the patients. The proportion of the patients with severe and very severe pulmonary dysfunction was higher in the definite ALS group as compared to the probable ALS group.

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# Pulmonary Manifestations of Primary Sjögren's Syndrome

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## ABSTRACT

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Sjögren's syndrome (SS) is a complex autoimmune exocrinopathy with multifactorial pathogenesis and multisystem manifestation. It is called primary Sjögren's syndrome (PSS) when the manifestations are seen without any other co-existent rheumatic diseases. The incidence of respiratory system involvement varies widely in the reported medical literature, partly due to lack of a universal agreement over the diagnostic criteria of the disease and the type of study methods employed. Respiratory system manifestations are protean; upper airway symptoms are very common and so is the complaint of dry cough. The PSS patients may develop interstitial lung diseases (ILDs) such as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), bronchiolitis obliterans and organising pneumonia (BOOP), etc. They may also develop the whole spectrum of lymphoproliferative disorders of the lung ranging from LIP to follicular bronchiolitis, nodular lymphoid hyperplasia and low-grade lymphomas. Therapeutic options include symptomatic and supportive measures and corticosteroids as the mainstay of the treatment for ILDs occurring in these patients. In recent years, rituximab (anti-CD20) has emerged as a promising treatment for this disease, though data from controlled trials are still lacking. Pulmonary involvement may be a source of significant morbidity in these patients, though only rarely, it is the cause of death. [Indian J Chest Dis Allied Sci 2009;51:93-101]

**Key words:** Primary Sjögren's syndrome, Non-specific interstitial pneumonia, Lymphoid interstitial pneumonia, Marginal zone B-cell lymphoma, Rituximab.

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## INTRODUCTION

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Sjögren's syndrome (SS) is an autoimmune exocrinopathy with clinical hallmarks of keratoconjunctivitis sicca and xerostomia. The SS may be classified as primary Sjögren's syndrome (PSS) or secondary Sjögren's syndrome (SSS) depending on the co-existence of another rheumatic disease. At least six sets of criteria have been suggested for the diagnosis of SS; however, none are universally accepted and the controversy and disagreement seem to center around whether or not inflammation and auto-immunity should be included in the definition.<sup>1</sup> A revised version of the European criteria proposed by the American-European consensus group in 2002 is shown in table 1; a revised rule for classification (table 2) was also proposed by the same group.<sup>2</sup>

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## PATHOGENESIS AND PATHOLOGY

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Sjögren's syndrome appear to be a complex autoimmune disease with multifactorial pathogenesis. A genetic predisposition to Sjögren's, syndrome has been suggested on the basis of familial aggregation, animal

models and candidate gene association studies.<sup>3</sup> Genetic polymorphism of some minor histocompatibility antigens, transforming growth factor- $\beta$  gene, apolipoprotein E or tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) have been associated with susceptibility, age of onset or some of the systemic involvement of the disease. It has been postulated that in a patient with distinct genetic and hormonal milieu, an environmental trigger factor most likely leads to initial glandular inflammation, disturbed cytokine expression and failed antigen clearance or neoantigen presentation; these in turn, lead to T-cell activation, aberrant B-cell activation with disturbed differentiation, migration and homing, cytokine dysregulation with enhanced proinflammatory cytokines, local and systemic autoimmunity.<sup>4</sup> Triantafyllopoulou *et al*<sup>5</sup> recently presented a strong line of evidence implicating A13 and B4 strains of Coxsackie viruses in the induction and maintenance of autoimmunity in PSS. The B-lymphocytes have a pivotal role in the pathogenesis of PSS and B-cell activating factor (BAFF), a member of the TNF superfamily that regulates B-lymphocyte proliferation, maturation and survival has a key role in the B-cell disturbances and malignant complications in PSS.<sup>6,7</sup>

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**Table 1. Revised International Classification Criteria for Sjögren's Syndrome<sup>2</sup>**

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- I. Ocular symptoms: a positive response to at least one of the following questions:
- Have you had daily, persistent, troublesome dry eyes for more than three months?
  - Do you have a recurrent sensation of sand or gravel in the eyes?
  - Do you use tear substitute more than three times a day?
- II. Oral symptoms: a positive response to at least one of the following questions:
- Have you had a daily feeling of dry mouth for more than three months?
  - Have you had recurrently or persistently swollen salivary glands as an adult?
  - Do you frequently drink liquids to aid in swallowing dry food?
- III. Ocular signs, that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
- Schirmer's I test, performed without anaesthesia (5mm in 5 minutes)
  - Rose Bengal score or other ocular dye score (4 according to van Bijsterveld's scoring system)
- IV. Histopathology: In minor salivary gland (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes ) per 4mm<sup>2</sup> of glandular tissue.
- V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
- Unstimulated whole salivary flow (1.5mL in 15 minutes)
  - Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts<sup>19</sup>
  - Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer<sup>20</sup>
- VI. Autoantibodies: presence in the serum of the following autoantibodies:
- Antibodies to Ro (SSA) or La (SSB) antigens, or both
- 

Pathologically characteristic changes in salivary glands in Sjögren's syndrome include focal periductal mononuclear cell infiltrate composed of T- and B-lymphocytes, a loss of acinar cells and relative preservation of ductal cells.<sup>8</sup> Similar autoimmune inflammation of other mucosal surfaces is also seen. Involvement of extra glandular tissues, like kidneys, biliary tree, is predominated by lymphocytic infiltration. Vasculitis may also develop in some patients. Polyclonal B-lymphocyte activation is a key feature and this B-cell hyperactivity in PSS is reflected by circulating hypergammaglobulinemia as well as by a host of antibodies against both ubiquitous autoantigens (Ro/SS-A, La/SS-B, a-fordin) and organ specific

**Table 2. Revised Rules for Classification of Sjögren's Syndrome****For Primary Sjögren's Syndrome (PSS)**

In patients without any potentially associated disease, primary SS may be defined as follows:

- A. The presence of any four of the six items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive.
- B. The presence of any three of the four objective criteria items (that is, items III, IV, V, VI).
- C. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey.

**For Secondary Sjögren's Syndrome (SSS)**

In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or item II plus any two from among items III, IV, and V may be considered as indicative of secondary SS.

**Exclusion Criteria**

- Past head and neck radiation treatment
  - Hepatitis C infection
  - Acquired immunodeficiency disease (AIDS)
  - Pre-existing lymphoma
  - Sarcoidosis
  - Graft versus host disease
  - Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug)
- 

Source: Ref. 2

autoantigens (islet cell antigen 69, muscarinic receptor M3).

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**PULMONARY INVOLVEMENT IN  
PRIMARY SJÖGREN'S SYNDROME:  
EVIDENCE IN THE LITERATURE (TABLE 3)**

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The reported prevalence of pulmonary involvement in SS varies widely in the literature, owing, in part, to a lack of uniform diagnostic criteria. Long-term observational studies evaluating symptomatic pulmonary disease in SS are scant. Coupled with the challenge of distinguish whether existing pulmonary disease stems from SS or a co-existing rheumatic disease, data concerning pulmonary involvement in SS are deficient. In a retrospective study of a community-based cohort of 201 consecutive SS patients from Israel, pulmonary involvement was reported to be present in 15 percent.<sup>9</sup> In a study of 80 Spanish SS patients, pulmonary involvement was more common in those with greater than 10 years of disease.<sup>10</sup> In radiological studies of patients with PSS, pulmonary involvement has been more frequently observed. In an early high resolution computed tomographic (HRCT) study of 50 non-smoking PSS patients, Franquet *et al*<sup>11</sup> reported abnormalities in 34% of the patients. It was emphasised that 74% of

this cohort did not have any respiratory symptoms at the time of the radiological studies. The most commonly observed HRCT abnormalities were small airway disease and linear parenchymal opacities. The strength of this study lies in the fact that the study population was recruited from an ambulatory non-smoking population and excluded patients with a history of bronchopulmonary abnormalities unrelated to SS. Subsequently, other radiological studies have shown higher rates of lung involvement in PSS. In a study of 37 PSS patients with normal chest radiographs, Uffmann *et al*<sup>12</sup> reported abnormalities on HRCT in 24 (65%) patients. A retrospective review of HRCT in 24 patients with PSS yielded abnormal scans in 79.2% of patients.<sup>13</sup>

Correlations between radiological findings and pulmonary function test (PFT) abnormalities have been variable. Uffmann *et al*<sup>12</sup> obtained PFTs in 34 of 37 patients in their study, but observed no correlation between HRCT and PFT results.<sup>12</sup> In a study of 35 patients who met the European criteria of diagnosis of PSS including positive accessory salivary gland biopsy and had respiratory symptoms, Tauli *et al*<sup>14</sup> described thin-section lung computed tomography (CT) findings and correlated them to an individual's PFT values. In patients with large and/or small airways disease on CT, obstructive pattern were predominantly found on PFT. A significant correlation was found between scores of air trapping and forced expiratory volume in one second (FEV<sub>1</sub>). Patients with interstitial lung fibrosis and lymphocytic interstitial pneumonitis (LIP) generally had restrictive profile and/or decreased diffusing capacities (DLCO); significant correlation (p<0.01) found between the source of ground-glass attenuation and total lung capacity (TLC) and DLCO.

Sjögren's syndrome has only rarely been reported from India and from the available literature, it is difficult to ascertain the prevalence of PSS.<sup>15,16</sup> One possible reason for this rarity may be the lack of awareness of this entity among non rheumatologists, like dentists, ophthalmologists and internists, who often encounter these patients first, due to the nature of the clinical presentation in this disease.<sup>17</sup> Lung involvement in Indian patients with PSS has been described in isolated case reports.<sup>18</sup> Misra *et al*<sup>17</sup> reported a series of 26 PSS patients, diagnosed in the Rheumatology Clinic of a tertiary care hospital over more than 10 years period, out of which 15 patients had definite PSS employing rigorous immunological and histological criteria. None of their patients was reported to have clinical lung disease; however, in the absence of results of PFTs and lung imaging, it is difficult to rule out subclinical pulmonary involvement.

### Upper Airway Manifestation

Symptoms of upper airway involvement are far more

**Table 3. Respiratory manifestations in primary Sjögren's syndrome**

#### Upper Airways Disease

Rhinitis sicca  
Xerostomia

#### Lower airways disease

Xerotrachea-sicca cough  
Lymphocytic bronchitis/bronchiolitis  
Bronchial hyperresponsiveness

#### Lymphoproliferative Disorders

Diffuse lymphoid hyperplasia of the lungs: Follicular bronchiolitis, Lymphoid interstitial pneumonia  
Nodular lymphoid hyperplasia (also known as Pseudo-lymphoma)  
B-cell non-Hodgkin's lymphoma (commonly extranodal marginal zone B-cell lymphomas of the bronchus-associated lymphoid tissue)  
High-grade malignant B-cell non-Hodgkin's lymphoma

#### Other Diffuse Interstitial Pneumonias

Non-specific interstitial pneumonia  
Usual interstitial pneumonia  
Bronchiolitis obliterans organising pneumonia (BOOP)

#### Pulmonary Hypertension

#### Miscellaneous Pulmonary Manifestations

Multiple lung cysts or bullae  
Pulmonary haemorrhage  
Pulmonary amyloidosis

Source: Ref. 19

common than objective findings in patients with SS. In a retrospective analysis, up to 50% of patients with PSS complained of nasal symptoms, although only 20% had abnormal findings on rhinoscopy.<sup>20</sup> Epistaxis and sinusitis can occasionally occur as complications. Approximately 60% of patients complained of throat symptoms, although only 20% had abnormal findings on indirect laryngoscopy. Thirty-eight percent of PSS patients had parotid gland symptoms, and 25% had abnormally swollen glands. Parotid gland infection is also a potential complication in these patients.

### Lower Airway Disease

A dry cough of variable intensity may be reported in as many as 50% of patients with SS. As was described in the original report by Henrik Sjögren in 1933, cough is usually attributed to xerotrachea secondary to destruction of bronchial glands by the disease process. However, histological studies often do not support these observations and suggest that the cough may be related to other processes, including lymphocytic infiltration of the bronchial mucosa and submucosa.<sup>21</sup> About half of the patients with PSS have been shown to have bronchial hyperreactivity (BHR) and intermittent airway narrowing may manifest itself as episodes of cough, dyspnoea and wheezing that might

mimic xerotrachea symptoms.<sup>22</sup> The BHR has been attributed to the inflammatory infiltrate in the bronchial submucosa with large number of neutrophils, mast cells and lymphocytes and observation of associated increased bronchial epithelial damage and structural change of subepithelium.<sup>23</sup> Like many other airway inflammatory diseases, increased amount of nitric oxide has been shown in the exhaled air of PSS patients; the airway epithelial cells or the inflammatory cells in the epithelium may be the source of the increased amount of nitric oxide.<sup>24</sup>

### Diffuse Parenchymal Lung Diseases

A wide variety of diffuse proliferative lung diseases have been described in PSS, including the idiopathic interstitial pneumonias and the whole spectrum of pulmonary lymphoproliferative disorders. Since the recognition of non-specific interstitial pneumonitis (NSIP) as a distinct histological category of idiopathic interstitial pneumonias (IIP), two recent histopathological studies<sup>25,26</sup> have evaluated the pulmonary pathology of PSS patients presenting with interstitial lung disease (ILD). Ito *et al*<sup>25</sup> retrospectively studied 33 biopsies from multiple centers and found NSIP as the most common histological pattern (20 of 33 cases, 61%). Malignant lymphoma and bronchiolitis were the next most common histological patterns, respectively. In another study<sup>25</sup> of 18 patients with PSS and suspected ILD, non-specific interstitial pneumonia (5 patients), organising pneumonia (4 patients), usual interstitial pneumonia (3 patients), and lymphocytic interstitial pneumonia (3 patients) were the four most common histological patterns.

#### *Non-specific Interstitial Pneumonia (NSIP)*

First proposed by Kitaichi<sup>27</sup> in 1990 as “unclassified interstitial pneumonia”, the definition of NSIP has evolved. It is now recognised as a distinct clinicopathological entity and has been shown to differ from idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP) with regards to treatment and prognosis.<sup>27</sup> In recent histological studies, it has also been recognised as the most common histological pattern in patients with PSS.<sup>25,28</sup> Onset of symptoms, which may include breathlessness, cough and fatigue, is insidious. Pulmonary function tests in the majority of cases show a restrictive pattern along with gas transfer abnormalities. The NSIP typically causes bilateral lower zone infiltrates on the chest radiograph. Ground-glass opacity is the predominant finding on HRCT. Irregular reticular or linear opacities may also be observed, but, in general, honey-combing and consolidation are infrequently encountered. Key histological features include mild to moderate chronic interstitial inflammation, type II pneumocyte hyperplasia in areas of inflammation and dense or

loose interstitial fibrosis. Lack of any temporal heterogeneity pattern, uniformity of the pathological features and relatively preserved lung architecture as seen with elastic stains, helps to histologically differentiate NSIP from UIP. Ninety-four percent of patients with histological evidence of NSIP had HRCT abnormalities in one study<sup>28</sup>, however, such a correlation has not been uniformly observed.

#### *Usual Interstitial Pneumonia*

Early reports found UIP to be a common histological pattern in patients with PSS.<sup>29,30</sup> However, more recent reports have challenged the frequency with which UIP complicates PSS perhaps, in part, because of the recent change in the definition and classification of interstitial pneumonias. When occurring in PSS patients symptoms, physical findings, lung imaging, pulmonary function tests and clinical course of UIP are often similar to that in patients with idiopathic pulmonary fibrosis (IPF). The key histological features of the UIP pattern are architectural destruction, fibrosis often with honey-combing scattered fibroblastic foci, patchy distribution, and involvement of the periphery of the acinus or lobule.

#### *Bronchiolitis Obliterans Organising Pneumonia*

Bronchiolitis obliterans organising pneumonia (BOOP) was described as the second most frequent pathological pattern after NSIP in a recent case series of PSS patients fulfilling the European-American diagnostic classification. As none of the patients in this series received corticosteroids prior to lung biopsy, this might be one reason for the high prevalence of BOOP.<sup>25</sup> There are also several case reports of BOOP in PSS, some being complicated by acute respiratory distress syndrome (ARDS) and alveolar haemorrhage.<sup>31,32</sup>

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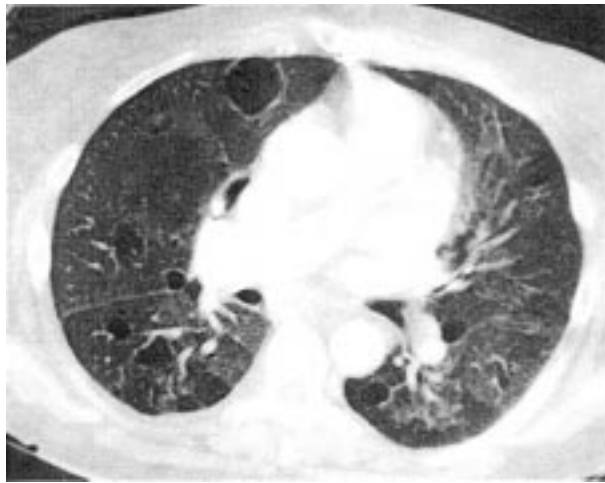
## PULMONARY LYMPHOPROLIFERATIVE DISORDERS

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#### *Lymphocytic Interstitial Pneumonia*

Lymphocytic interstitial pneumonia (LIP), a component of a spectrum of pulmonary lymphoid proliferative disorders, is the morphological entity that has most consistently been associated with SS. The LIP is an uncommon disease, and SS is the single most common disease entity that has been associated with it. Approximately 0.9% of adults with SS have LIP, and up to 50% of adults with LIP have SS.<sup>33-35</sup> The clinical presentation is no different than that observed in patients with diffuse interstitial lung disease; in that most patients have cough, dyspnoea or a combination of both. Weight loss, fever, pleuritic chest pain and arthralgia may also be seen. Basilar rales are the most common physical findings.<sup>35</sup> Ground-glass haziness and

centrilobular nodules are almost universally observed on HRCT.<sup>36</sup> Septal thickening, bronchovascular thickening and subpleural nodules, cystic spaces (see Figure) and mediastinal lymphadenopathy are less commonly



**Figure.** Multiple cysts and ground-glass haziness in the high resolution CT scan of a patient with lymphocytic interstitial pneumonia.

visualised. The LIP is characterised histologically by a prominent interstitial lymphoid infiltrate that diffusely spreads into alveolar septae. The interstitial infiltrate is rich in lymphocytes with variable numbers of plasma cells. Germinal centers may be seen and scattered multinucleated giant cells or ill-formed granulomas are seen in the lymphoid infiltrates in about half of the cases.<sup>37</sup> The infiltrate is a mixture of B- and T-cells. The B-cells are polyclonal as determined by immunostaining for immunoglobulin light chain. In late stages, LIP can produce advanced interstitial fibrosis and honey-combing. Progression of LIP to pulmonary lymphoma is known but is distinctly rare.

#### *Follicular Bronchiolitis*

Follicular bronchiolitis (FB) is another pattern of diffuse lymphoid hyperplasia affecting the lung of the patients with SS. The histological difference between FB and LIP is that former is associated with lymphocytic infiltrates that are peribronchial and include coalescent reactive germinal centers adjacent to airways in the absence of clinical or pathologic evidence of chronic obstructive pulmonary disease or bronchiectasis.<sup>38</sup> It is a disease process resulting from hyperplasia of bronchus-associated lymphoid tissue (BALT), which consists of small lymphoid aggregates along the bronchial tree, especially around the division points and respiratory bronchioles. In patients with PSS follicular bronchiolitis usually co-exists with lymphocytic bronchitis, lymphocytic bronchiolitis, or LIP.<sup>19</sup>

#### *Nodular Lymphoid Hyperplasia*

Nodular lymphoid hyperplasia, also known as pseudolymphoma, refers to the presence of reactive lymphoid cells in one or more pulmonary nodules or infiltrates. Controversy has surrounded the existence of this condition as some cases of low-grade lymphoid proliferation in lungs have been recognised by others as extra-nodal marginal zone B-cell lymphoma. However, a recent study,<sup>39</sup> employing sophisticated immunohistochemical and molecular biology techniques, has confirmed the existence of pulmonary nodular lymphoid hyperplasia. It is infrequently encountered, and the exact relationship with SS is not known. It might be discovered because of an incidental radiological finding in asymptomatic patients, or the patients may be symptomatic with shortness of breath or pleuritic chest pain. The most common radiological finding is a solitary pulmonary nodule or mass. Alternatively, an area of parenchymal consolidation with an air bronchogram may be present. However, multifocal lesions have also been described. In the presence of mediastinal lymphadenopathy or a pleural effusion, a diagnosis of malignant lymphoma should be suspected. Histological evaluation of the lesions reveals numerous reactive germinal centers and a preserved mantle zone.

#### *Pulmonary Lymphomas*

Non-Hodgkins lymphoma is an important cause of mortality in patients with SS. In a long-term (greater than 10 years) observational study of patients with PSS, nearly 25% died of malignant lymphomas.<sup>40</sup> Polyclonal B-cell activation, which is seen in the early part of the disease, may transform to a monoclonal B-cell population in some patients. This process may result in mucosa-associated lymphoid tissue (MALT) lymphoma or more uncommonly in high-grade malignant lymphoma.<sup>41,42</sup> It is a multi-step process in which antigenic stimulation of B-cells and oncogenic events may be important factors. Of those patients who develop lymphoma, nearly half develop it in an extra-nodal site,<sup>40</sup> and the lung is one such extra-nodal site. In some of these cases, it appears that lymphoma represented a progression from LIP. These primary pulmonary lymphomas are usually low-grade extra-nodal marginal zone B-cell lymphomas (MZCL) of the MALT type.<sup>43-45</sup>

Clinical presentations of MZCL of the lung are non-specific and may consist of cough, shortness of breath, weight loss, and fatigue; therefore, these symptoms are not helpful in distinguishing lymphoma from other types of lung involvement in patients with SS. Analysis of lung CT scans has revealed the lesions to be randomly distributed with a trend towards a more extensive involvement of the

lower lobes. Radiological findings can include: confluent alveolar opacification with peribronchial distribution and air bronchograms; peripheral (usually bilateral) alveolar opacification with or without air bronchograms; micronodules and masses; ground-glass opacities; thin wall cystic spaces.

In histopathological specimen, the predominant pattern of growth is interstitial with prominent involvement of peribronchial-peribronchiolar and perivascular interstitium; in some cases, the lymphocytic infiltrate can spill into the alveolar space and alveolar septa.<sup>45</sup> Histological criteria have been proposed for differentiating malignant infiltration from LIP and pseudolymphoma. These include: invasion of bronchial mucosa and erosion of bronchial cartilage, seeding of parietal pleura, involvement of hilar and mediastinal lymph nodes; absence of lymphoid germinal centers; and the presence of mitotic figures.<sup>46</sup> However, other criteria have also been proposed, which incorporate the fact that nodal involvement is uncommon even in MZCL. Immunohistochemical studies show that the majority of lymphocytes are of a B-cell phenotype. Lymphoepithelial lesions, which are epimyoeplithelial islands with surrounding halo-like monocytoïd cells, have been thought to be the origin of lymphomas in patients with SS, and in case of salivary glands, the epithelial component of these histological lesions originate from the ductal cells. In the MALT lymphoma of lungs in patients with SS, the existence of a similar epithelial component is proven by a positive staining with cytokeratin antibodies.<sup>41</sup> Monoclonal immunoglobulin light chain can also be demonstrated in these lesions signifying a transition of polyclonal B-cell activation to monoclonal B-cell proliferation during the process of development of lymphoma.<sup>41</sup> The MALT lymphoma can occasionally progress to a high-grade malignant lymphoma.

### **Pulmonary Artery Hypertension**

Pulmonary arterial hypertension (PAH) in the absence of any other significant lung disease in PSS patients has been reported in a few cases.<sup>48</sup> There is a paucity of literature regarding pulmonary vascular pathology in this condition given the rarity of PAH, the relative lack of importance that pathology contributes to management and the reported hazards of VATS lung biopsies in patients with pulmonary hypertension.<sup>47</sup> The histopathology of PAH in association with rheumatic diseases is generally indistinguishable from that found in idiopathic PAH. The pathogenic mechanisms involved in PAH associated with PSS remain unclear. The development of PAH may be mediated by prolonged vasospasm and structural vessel remodelling which lead to irreversible and fixed narrowing of pulmonary arterioles and thrombotic obstruction.<sup>48</sup>

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## **OTHER PULMONARY MANIFESTATIONS**

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Several other manifestations have occasionally been reported in PSS. Cases have been described where HRCT has revealed multiple bullae and pathology has revealed thickening of alveolar septae as well as mononuclear cell infiltrates.<sup>49</sup> The authors suggested that the development of bullae might be related to small airway obstruction secondary to follicular bronchiolitis or LIP. Acute pulmonary haemorrhage as part of a pulmonary-renal syndrome related to cryoglobulinemic vasculitis has been described as a rare manifestation in PSS.<sup>50</sup> Pulmonary amyloidosis, with or without pulmonary lymphoproliferative disease, has also been described in patients with PSS.<sup>25,51,52</sup>

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## **TREATMENT AND PROGNOSIS**

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Primary Sjögren's syndrome usually runs a slow course but sometimes can progress at faster rates, especially if complicated by extra glandular involvement or the development of lymphoma. Treatment of SS has focused on control of sicca symptoms. Therefore, simple steps to minimise loss and/or to replace moisture are often employed. Sinusitis should be treated with antibiotics and if indicated with surgical drainage. Dry cough due to large airway involvement is treated with normal saline nebulisations; high doses of bromhexine might be tried, although its efficacy is questionable. Corticosteroids and other immunosuppressive agents are not typically used for the more common manifestation of SS given their toxicity and inability to reverse sicca symptoms. However, corticosteroids are the most widely used treatment for follicular bronchiolitis, LIP and BOOP. In patients with UIP and NSIP low-dose corticosteroids and azathioprine are usually recommended. The optimal treatment of extra-nodal MZCL of lung remains unclear in the absence of prospective studies. In localised disease, surgery alone or with chemotherapy can be used. In extensive unilateral or bilateral disease, single or multiple drug chemotherapeutic regimens have been used. Oxaliplatin as monotherapy or fludarabine-containing chemotherapy are promising therapeutic regimens for these patients.<sup>45,53,54</sup> The treatment of PAH in patients with PSS or other rheumatic diseases may follow a similar algorithm as in idiopathic PAH patients.<sup>55</sup>

In recent years, the development of agents that target cells, molecules and receptors implicated in the aetiopathogenesis of PSS have created opportunities to test these therapies in SS.<sup>56</sup> Some potential future therapies are shown in table 4.

Experience with biological agents in PSS has been gained from open-label studies, Phase I/II studies, or off-label use. Therefore, reports of efficacy of these agents in lung disease associated with PSS have been anecdotal. Optimism regarding the possible efficacy of biologics also

**Table 4. Potential biological agents in the treatment of primary SS****B-cell-targeted Therapies**

Anti CD20: Rituximab, Ocrelizumab, Ofatumumab  
 Anti CD22: Epratuzumab  
 Anti BAFF: Belimumab

**T-cell-targeted Therapies**

Anti CD 11 a: Efalizumab  
 Anti CD2: Alefacept  
 CTLA-4 Ig: Abatacept

**Cytokine-targeted Therapies**

Infliximab (chimeric anti-TNF)  
 Etanercept (soluble TNF receptor)  
 Adalimumab (human anti-TNF)  
 Golimumab (human anti-TNF)  
 Certolizumab (human anti-TNF)  
 Tocilizumab (anti-IL6 receptor)  
 Anti-IL10  
 Anti-IL17  
 Anti-IFN

Source: Ref. 56

emanates from the experiences in other rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and psoriasis. Of the approved biologic therapies, rituximab (anti-CD20) has emerged as a promising treatment for PSS. Since B-cells are believed to play a role in the pathogenesis of PSS, investigation of the use of a B-cell depleting therapy is warranted. Three recent studies<sup>56-58</sup> with an open-label design as well as several case reports have shown promising results with rituximab in PSS patients with various extra glandular manifestations. Secor *et al*<sup>57</sup> included a couple of patients with refractory pulmonary disease in their series of 18 PSS patients with various systemic manifestations, most of whom received prior immunosuppression without a satisfactory response. One patient with pleural effusion and pulmonary infiltrates responded to rituximab with complete resolution; in the second patient, dyspnea and cough due to LIP disappeared. Both the patients received four infusions of rituximab without any concomitant immunosuppressive therapy. Satisfactory responses were maintained at 17-month follow-up with the first patient and at 12-month follow-up with the second patient. Encouraging response was also seen in treating refractory polysynovitis, peripheral neuropathy and renal involvement. Majority of the patients tolerated rituximab well without any serious adverse effects. Rituximab has been successfully used in PSS patients with B-cell lymphomas with or without chemotherapy and may emerge as a first therapeutic choice for some PSS patients with indolent B-cell lymphomas. Among the anti-cytokine agents, infliximab was studied in a double-blind, placebo-controlled multi-center trial that included 103 PSS patients.<sup>58</sup> Infliximab was no more effective than placebo in improving joint pain, fatigue

and dryness symptoms. It was also not effective in improving the number of swollen and tender joints, basal salivary flow, Schirmer's test results, focal score in labial salivary gland biopsy and levels of various inflammatory markers and presence of autoantibodies. This study<sup>58</sup> did not report specifically about the efficacy or lack of efficacy of infliximab in pulmonary manifestations of PSS. Results with etanercept in PSS have also been disappointing. Thus, the general opinion is that TNF inhibitors have no role in the treatment of patients with PSS. The T-cell targeted therapies (efalizumab, abatacept, alefacept) might be considered for clinical trials in patients with PSS.

The overall prognosis of PSS patients with or without lung involvement remains favourable. A recent prospective study<sup>59</sup> did not find an increased all-cause mortality in patients with PSS compared with the general population. Lung disease in SS progresses slowly, and death from respiratory failure is distinctly rare. There is a unique subgroup of patients with PSS who over time sustain further lymphocytic organ damage or develop cancer.<sup>40</sup> Presence of hypo-complementemia and/or cryoglobulins at diagnosis has been associated with poorer prognosis and lymphoma development.<sup>60</sup> Treatment typically consists of agents that provide symptomatic relief of sicca symptoms, but in cases with severe organ involvement or lymphoma, corticosteroids, immunosuppressants, chemotherapy, or biologic therapies might be utilised.

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# Radiation Dose Escalation by Percutaneous Interstitial Brachytherapy in Locally Advanced Non-small Cell Lung Cancer

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## ABSTRACT

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Management of locally advanced non-small cell lung cancer is associated with a poor overall survival using concurrent chemoradiotherapy. Therefore, newer approaches to treatment which enable dose escalation are warranted. Interstitial brachytherapy in lung is a new emerging concept with many distinct advantages. We report here a case of locally advanced non-small cell lung cancer with residual disease after conventional treatment. The patient was successfully treated using percutaneous interstitial brachytherapy and is disease-free at 18-month follow-up. [Indian J Chest Dis Allied Sci 2009;51:103-106]

**Key words:** Carcinoma, Lung, Brachytherapy.

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## INTRODUCTION

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Locally advanced lung cancer continues to be major challenge to the thoracic oncologist worldwide. Lung cancer is the most common cancer worldwide accounting for 17.6% of all cancer deaths.<sup>1</sup> Despite aggressive concurrent chemoradiotherapy, the 5-year survival of locally advanced lung cancer is a dismal 15 percent to 20 percent.<sup>2</sup> External beam radiotherapy traditionally employs a dose of 60Gray in conventional fractionation for treating advanced non-small cell lung cancer. Dose escalation with conventional external beam is limited by unacceptable normal tissue toxicity. Recent dose escalation trials using highly conformal radiotherapy techniques have suggested that dose escalation upto 77.4 to 83.8Gy results in satisfactory outcome.<sup>3</sup> Organ motion is another vexing issue to be taken into account and even sophisticated treatment techniques, like image-guided radiotherapy are still evolving. One way of radiation dose escalation in lung cancer is by using brachytherapy. In lung cancer, brachytherapy can be bronchoscopy guided or by interstitial application. Percutaneous interstitial catheter brachytherapy involves placement of special catheters or needles within the tumour tissue. Since the implanted catheters move with the lung during respiration, the effects of organ motion are practically done away with. We report here a case with locally advanced lung cancer treated with interstitial brachytherapy treatment.

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## CASE REPORT

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A 54-year-old male presented to us with complaints of breathlessness of two-month duration. Chest radiograph showed a right-sided pleural effusion. The patient underwent tube thoracostomy and pleural fluid cytology was positive for an adenocarcinoma. A contrast enhanced computed tomography (CECT) of the chest revealed a 6cm×4cm mass in the right lower lobe. Multiple mediastinal lymph nodes were seen, the largest measuring 2cm×1cm. A bronchoscopic guided biopsy from the right lower lung mass confirmed a well-differentiated adenocarcinoma. Metastatic work up was normal. The patient was staged as carcinoma right lung cT4N2M0 (Stage IIIB).

The patient received three cycles of neoadjuvant chemotherapy with parenteral paclitaxel 175 mg/m<sup>2</sup> (day 1) and carboplatin (AUC 5) on day 2. Repeat computed tomography (CT) revealed a partial response to the chemotherapy with residual tumour measuring 4cm×4cm. The patient was then planned for radical radiotherapy with external beam radiotherapy to a dose of 60Gy in conventional fractions using 6MV photons on Clinac 2300CD linear accelerator (Varian Medical Systems Inc., USA). A dose of 45Gy over 25 fractions was delivered initially to the primary lesion and the draining nodes. This was followed by a boost of 15Gy over eight fractions to the primary.

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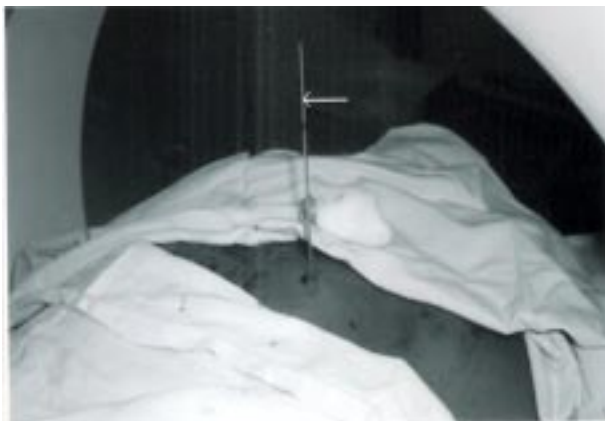
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Radiological evaluation done two months later revealed a residual lesion of the size 1.5cmx2cm in size. The patient was then planned for treatment with percutaneous interstitial brachytherapy.

### Technique of Brachytherapy

The patient underwent percutaneous interstitial brachytherapy of the residual lung lesion using remote after loading microSelectron high dose rate (HDR) machine having a 10 Ci Ir<sup>192</sup> source (Nucletron BV, Veenendaal, The Netherlands). A CT of the patient was acquired with the patient in prone position. The laser light of the CT gantry was used to determine the plane of needle entry on the patient's skin. Local anaesthesia was administered using 2% lignocaine (5mL) at the site of needle entry. An interstitial brachytherapy needle (17 gauge, 15cm long) was inserted gradually under CT guidance. The needle position was checked repeatedly and needle advanced only during suspended respiration. The tip of the needle was placed in the centre of the tumour (Figures 1 and 2). The needle was firmly secured in place using a needle stopper. A lung window image was used to rule out presence of pneumothorax at the end of the procedure. The CT images were acquired with a slice thickness of 2.5mm (2.5mm increments). The images were transferred to treatment planning system (Plato Treatment Planning System, Nucletron) and isodose distribution was analysed. A single fraction of 12Gy was prescribed at 1cm from the center of the brachytherapy needle using three-dimensional CT planning. The patient received the treatment in prone position (Figure 3). After completion of treatment, the needle was removed and puncture site sealed. The patient tolerated the procedure well and there were procedure related complications. Repeat CT at two months later showed near complete regression of the residual disease. The patient received further chemotherapy for three cycles.



**Figure 1.** Photograph showing interstitial brachytherapy needle (arrow) inserted percutaneously into the right lung under CT guidance.



**Figure 2.** CT image showing percutaneous interstitial brachytherapy needle (arrow) within the residual tumour mass.



**Figure 3.** Brachytherapy needle connected to high dose rate machine through a transfer tube.

At 18-month follow-up, radiological evaluation showed the patient to be in complete remission. There was no evidence of residual mass lesion seen earlier (Figure 4). Collapse of the right lower lobe with pleural effusion was documented. Positron-emission tomography showed no evidence of disease at local or distant sites.

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### DISCUSSION

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Indications for brachytherapy in lung cancer include debulking of endobronchial disease, palliation of intraluminal obstruction and rarely as a curative treatment. These procedures are limited by



**Figure 4. Follow-up CT at 18 months showing no evidence of residual mass lesion.**

complications, such as haemoptysis, which can occur in upto 50% of cases and by patient discomfort during the procedure. Interstitial brachytherapy is another means of treating these tumours. The American Brachytherapy Society<sup>4</sup> recommends interstitial brachytherapy in situations where endobronchial brachytherapy would inadequately encompass the tumour.

Interstitial brachytherapy applications in lung involve catheter based treatment, I-125 seed implants and mesh implants (Table 1).<sup>5,6</sup> As early as 1933, Graham and Singer<sup>7</sup> attempted the first interstitial brachytherapy in lung cancer. However, much of the brachytherapy practice in lung cancer still involves endobronchial applications with interstitial technique confined mainly to I-125 seed implants. Percutaneous catheters implants are confined to anecdotal reports.<sup>8-10</sup> High dose rate brachytherapy in lung cancer has been shown to increase both the local control and median survival. In a Phase-I study<sup>8</sup> involving 30 lung tumours, encouraging results were

seen with single session interstitial catheter application. The mean tumour diameter treated was 2cm with (range 0.6cm-11cm). A maximum dose of 20Gy was used. No major procedure related complications were reported, except for focal haemorrhage in one patient. At 5-month follow-up, a local control of 97% was seen.<sup>8</sup> In catheter-based brachytherapy, dosage ranging from 16Gy to 20Gy have been used. In our patient we chose to prescribe 12Gy since the patient had already received an external beam dose of 60Gy.

Advantages of high dose rate interstitial catheter-based brachytherapy include its minimally invasive nature with the ability to conform dose to a small tumour bearing area. Delivery of brachytherapy using interstitial catheters or needles can also help overcome the problem of seed displacement with I-125. Moreover, these procedures are performed under local anaesthesia and excellent tumour localisation can be achieved under CT-guidance. Peripherally situated lung lesions may be more suitable for this kind of treatment. However, help of a trained interventional radiologist is mandatory in such procedures as precise tumour localisation and needle placement under CT-guidance is a technically demanding procedure. A fatal haemoptysis rate of 5% to 8 % has been reported in high dose rate brachytherapy.

Pneumothorax, radiation bronchitis or fistula formation can be other complications. Facilities to carry out tube thoracostomy should be available and it is preferable to have the support of a thoracic surgeon.

Interstitial brachytherapy can be easily combined with external beam radiotherapy, chemotherapy or novel targeted therapy to improve tumour response rates. Using interstitial brachytherapy as a salvage modality is a viable option in patients presenting with residual disease after conventional chemoradiotherapy treatment.

**Table 1. Studies of interstitial brachytherapy in non-small cell lung cancer**

Study	No. of Patients	Stage	Treatment	Brachytherapy Technique	Brachytherapy Dose	Results
Rickie <i>et al</i> <sup>5</sup>	15	Two patients with T2N0M0, T3N0M0 and 13 with lung metastases	Interstitial brachytherapy	Percutaneous interstitial catheter brachytherapy	20Gy single fraction	Local control (97%)
Jain <i>et al</i> <sup>6</sup>	3	T4N0M0, metastatic lesions in two patients	RFA and brachytherapy	Percutaneous interstitial and catheter and I-125	16Gy single fraction 120Gy HDR and 144Gy LDR	-
Imamura <i>et al</i> <sup>9</sup>	12	T1-2N0M0	Interstitial or endobronchial brachytherapy	Percutaneous interstitial catheter brachytherapy and endobronchial brachytherapy	Interstitial-20Gy single fraction Endobronchial - 5×5Gy, 2×12.5Gy	Local control (88.9%)
Voynov <i>et al</i> <sup>8</sup>	118	T1-2N0M0	Sublobar resection and brachytherapy	I-125 Vicryl Mesh	85-129Gy	Local control (97%)

RFA=Radiofrequency ablation; HDR=High dose rate; LDR=Low dose rate.

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# Endobronchial Non-Hodgkin's Lymphoma Presenting as Mass Lesion

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## ABSTRACT

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A 40-year-old male presented with clinical and radiological manifestations of right lung atelectasis and post-obstructive pneumonia. Flexible bronchoscopy revealed gross narrowing of the right upper lobe bronchus and a smooth, white endobronchial mass completely occluding the right lower lobe bronchus. Endobronchial biopsy from the mass lesion yielded low grade B-cell non-Hodgkin's lymphoma. This is one of the rarest presentation of non-Hodgkin's lymphoma. [Indian J Chest Dis Allied Sci 2009;51:107-109]

**Key words:** Non-Hodgkin's lymphoma, Endobronchial lymphoma, Endobronchial mass.

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## INTRODUCTION

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Lymphomatous involvement of airways has been recognised infrequently. The clinical importance of endobronchial lymphoma lies in the capacity of these lesions to produce airways obstruction that is clinically and radiologically indistinguishable from bronchogenic carcinoma. Non-Hodgkin's lymphoma (NHL) involves thoracic structures in about 43% of cases, especially the mediastinum and pulmonary parenchyma at any time in the course of the disease.<sup>1</sup> However, endobronchial involvement is very rare even in the presence of advanced disease.

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## CASE REPORT

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A 40-year-old male presented with progressively increasing shortness of breath for four months, irregular high-grade fever, cough with purulent, foul smelling expectoration (around 25-30mL/day), weight loss (about 6kg) and loss of appetite for the last three months. He was a chronic smoker (20 *bidis*/day for the preceding 25 years) but had stopped smoking for the last five years.

At admission, on general physical examination, the patient was febrile, with a heart rate 100/min, respiratory rate 26/min and oxygen saturation of 89 percent. There was no pallor, icterus, cyanosis, clubbing, peripheral lymphadenopathy or pedal oedema. The respiratory system examination revealed findings of shift of both upper and lower mediastinum to the right,

dull percussion note and diminished vesicular breath sounds over the right hemithorax, which were consistent with collapse of the right lung. Rest of the systemic examination was unremarkable.

On investigations, haemoglobin was 9.9g/dL, blood count showed leukocytosis with neutrophils having toxic granulations, the metabolic parameters were within normal limits and sputum smears examination did not reveal acid-fast bacilli. Chest radiograph (Figure 1) showed homogeneous opacification of the right hemithorax with shifting of both trachea and heart to the right and increased translucency over left hemithorax suggesting collapse of the right lung with compensatory hyperinflation of the left lung. Computed tomography of thorax with IV contrast showed complete cut off of the

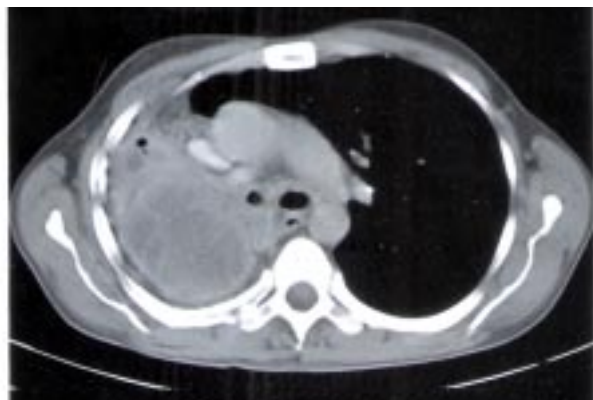


Figure 1. Chest radiograph showing homogeneous opacification of the right hemithorax with collapse of the right lung.

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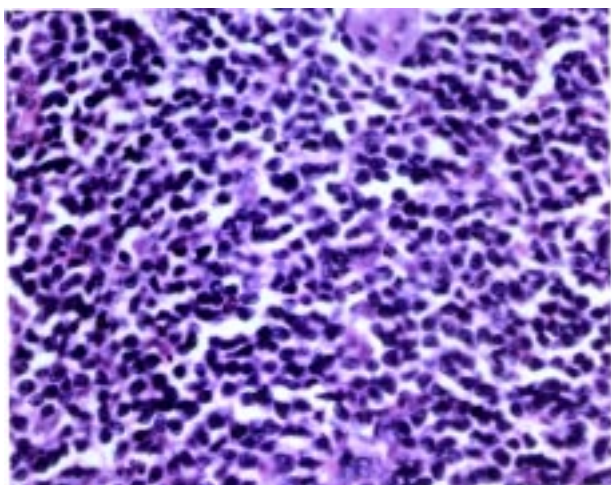
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right main bronchus by a heterogeneous mass lesion, thereby, causing complete collapse of the right lung (Figure 2). Flexible fiberoptic bronchoscopy (FOB) revealed a grossly narrowed right upper lobe bronchus with purulent secretions oozing from it and a glossy endobronchial growth at the distal end of the truncus intermedius which was completely occluding the right lower lobe bronchus.



**Figure 2.** Computed tomography of thorax showing narrowing of the right main bronchus by a heterogeneous mass lesion and collapse of the right lung.

Bronchial biopsies from the endobronchial lesion were consistent with NHL (Figure 3). Further typing with immunological staining confirmed it as B-cell type, low-grade lymphoma. The bone marrow aspirate did not reveal any infiltration by the lymphoma. Chemotherapy with cyclophosphamide, vincristine, adriamycin and prednisolone (CHOP regimen) was initiated and total of six cycles were given. The patient improved remarkably by the sixth cycle of chemotherapy.



**Figure 3.** Photomicrograph showing presence of diffuse sheets and clusters of monomorphic lymphoid cells with high nuclear-cytoplasmic ratio, coarse chromatin and scanty cytoplasm (H&E×20).

## DISCUSSION

The NHL rarely involves the endobronchial tree. Our case is probably the second case reported from India; following the report by Barthwal *et al.*<sup>2</sup> Endobronchial lesions in NHL are most frequently seen in the main bronchi, followed by lobar bronchi and trachea. The various mechanisms suggested for development of endobronchial lesions in patients with lymphoma include: direct invasion from an adjacent mediastinal or parenchymal lesion, lymphatic dissemination to the peribronchial tissues, haematogenous dissemination and transbronchial aspiration of tumour emboli. The most common mechanisms are direct bronchial invasion and haematogenous dissemination.<sup>3</sup> In patients with endobronchial involvement, chest radiographs reveal atelectasis in 50% of cases, features of obstructive pneumonia and hilar mass in 20 percent.<sup>4-7</sup> Diagnosis is established by FOB followed by biopsy of the lesion. Treatment depends on the extent of the involvement of the tumour and the general condition of the patient. Chemotherapy, either alone or in combination with radiotherapy, is the treatment of choice.

Our case suggests that lymphoid malignancies should always be kept in mind in all cases of suspected lung cancer and histopathological diagnosis is a must to differentiate between the two. Smoking may have been a risk factor in our case. Though a definite causal relationship between smoking and NHL has not been established, there are some studies in support of this association, especially in heavy smokers and middle aged men.<sup>8-9</sup>

The clinical severity of endobronchial malignant lesions is correlated with the possibility of bronchial obstruction and subsequent pulmonary collapse. Bronchoscopic examination with biopsy is essential to distinguish from bronchogenic carcinoma, since both the treatment approach and the prognosis are significantly different.<sup>10</sup>

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# Giant Cystic Thymoma with Haemorrhage and Necrosis: An Unusual Case

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## ABSTRACT

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Extreme degree of cystic, haemorrhagic and necrotic changes in a thymoma is rare. A 22-year-old male presented with cough, grade 2 dyspnoea, and occasional chest pain for the past six months. Radiological investigations revealed a large cystic lesion in the anterior mediastinum. A benign cystic tumour was suspected. Surgical resection of the tumour was done. Grossly, the almost entirely cystic and haemorrhagic dumb-bell shaped encapsulated tumour showed a subcapsular residual nodule. Histopathological examination was suggestive diagnosis of benign thymoma (World Health Organization [WHO] Type A, medullary type) associated with the rare features of cells with dendritic processes containing melanin pigment seen singly scattered throughout the tumour. [Indian J Chest Dis Allied Sci 2009;51:111-113]

**Key words:** Thymoma, Mediastinum, Cystic, Haemorrhage, Necrosis.

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## INTRODUCTION

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Cystic degeneration in a thymoma is relatively common but a focal feature.<sup>1</sup> Rarely, it can be of extreme degree that most or all of the lesion becomes cystic, posing a diagnostic problem. It has to be differentiated from congenital or acquired thymic cysts, and other thymic neoplasms with cystic change. In a neoplastic process necrosis and haemorrhage indicate an aggressive malignant tumour. However, in the context of a medullary thymoma, WHO type A, these features are not suggestive of a malignant behaviour suggesting that, a proper diagnosis is important in the management of these patients.<sup>2</sup>

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## CASE REPORT

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A 22-year-old male presented with cough and breathlessness (grade 2) of six months duration. He gave history of occasional retrosternal chest pain. He also complained of expectoration of scanty sputum with occasional blood streaking. There was no history of fever, change of voice, difficulty in swallowing or orthopnoea. General physical examination was unremarkable. Respiratory system examination revealed a dull note on percussion in the sternal region. There were no crepitations or rhonchi. Cardiovascular system and abdominal examination were within normal limits. The chest radiograph showed a large mediastinal mass. On ultrasonography, a large well-defined cystic lesion measuring 15cm×7.5cm was seen

in the anterior mediastinum. On computed tomography (CT) of the chest, the large non-enhancing cystic lesion showed hypodense and hyperdense areas (Figure 1); there were no obvious septations. There was no evidence of mediastinal extension or calcification. A diagnosis of benign cystic mediastinal tumour, either a thymoma or a mature cystic teratoma was made. Surgical resection of the tumour was done. During surgery, a large, well encapsulated bilobed tumour was seen arising from the lower lobes of the thymus. The tumour was not adherent to the surrounding structures and was easily resectable. The postoperative period was uneventful. On 18 months follow-up, the patient

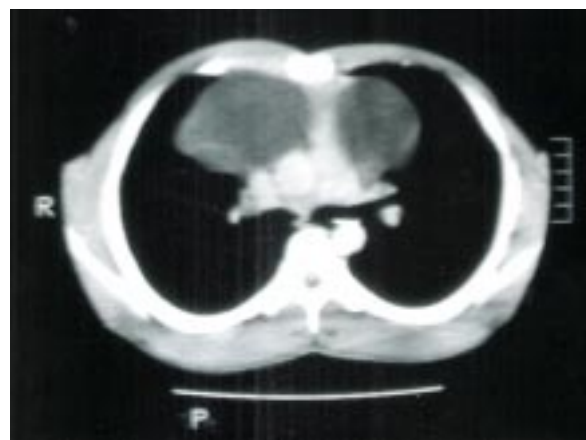


Figure 1. CT chest showing a large nonenhancing cystic lesion in the anterior mediastinum with hypodense and hyperdense areas.

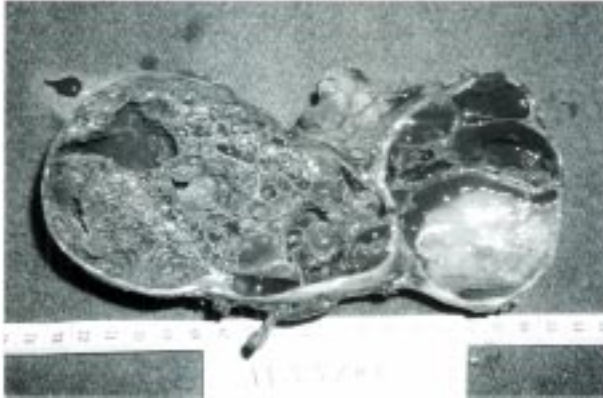
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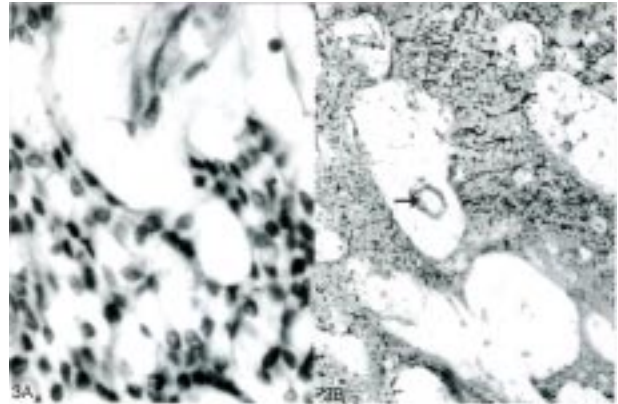
is asymptomatic and the chest radiograph was normal.

Grossly, a dumb-bell shaped encapsulated mass was received weighing 610g and measuring 15cm×8cm×8cm in size with attached fibrofatty tissue. Cut-section showed an almost entirely cystic tumour containing haemorrhagic material (Figure 2). A subcapsular yellowish nodule was seen measuring 4cm in diameter. The nodule and the cyst wall with haemorrhagic areas and the attached fibrofatty tissue were studied histopathologically.



**Figure 2.** Cut-section of the resected specimen showing a dumb-bell shaped, well-encapsulated cystic tumour filled with haemorrhagic material with a subcapsular nodule.

Microscopically, sections from the nodule showed a tumour composed of small polyhedral to ovoid to spindle shaped bland cells with minimal pleomorphism arranged in a microcystic and gland-like pattern containing pink proteinaceous material resembling a thyroid follicular tumour on low-power examination. Also seen were large cystic spaces lined by tumour cells, and containing pink fluid and few lymphocytes mimicking a lymphangioma. A complex sinuous arrangement was seen reminiscent of a carcinoid tumour. On high power, some of the cystic spaces contained a small capillary sized blood vessel indicating that cystic change represented greatly dilated perivascular spaces (Figure 3A). Reticulin stain delineated the blood vessels in these spaces (Figure 3B). Mitosis was absent. Few lymphoid cells were seen admixing with the tumour cells. A few spindly cells with dendritic processes containing melanin pigment were also seen scattered throughout the tumour. Rest of the tumour was haemorrhagic, necrotic and revealed areas of infarction. The thick fibrous cyst wall was free of tumour infiltration and was devoid of any lining epithelium. There were no fibrous bands or lobulations. Compressed thymic gland was seen in the cyst wall. The attached fibrofatty tissue showed involuted thymic tissue with mild cystic dilatation of the Hassall's corpuscles. A diagnosis of benign thymoma (WHO Type A medullary type) with marked cystic, haemorrhagic and necrotic changes was made.



**Figure 3.** Photomicrograph showing cuboidal to spindly bland cells arranged in a gland-like fashion which represents dilated perivascular spaces (3A) (H&E×400) and blood vessels (arrows) in the perivascular spaces (3B) (Reticulin stain ×100).

## DISCUSSION

Cystic change in thymoma is described in 40% of the cases and is mostly focal.<sup>1</sup> Rarely, it can be extensive and present as a unilocular or multilocular cystic mass containing blood or yellow-brown grumose material. The tumour may be seen either as a mural nodule or as randomly scattered solid areas. Sometimes tumor may be seen only on microscopic examination. It is important to extensively sample cystic lesions of the thymus as tumours like thymoma, germ cell tumours and Hodgkin's disease can develop extensive cystic change.<sup>3</sup> Among the thymic carcinomas, basaloid carcinoma and mucoepidermoid carcinoma are frequently associated with prominent a cystic change.<sup>2</sup> In tumours, cystic change may be due to degeneration. Sometimes, obstructive and inflammatory cystic change in the surrounding non-neoplastic thymic tissue can lead to firm adhesions and apparent infiltration of adjacent mediastinal structures.<sup>3</sup> Cystic change in a thymoma must be differentiated from a thymic cyst. Thymic cysts can be unilocular or multilocular and have a lining epithelium, a feature which is absent in cystic thymomas.<sup>1,3</sup> Haemorrhage commonly occurs in thymic cysts resulting in the accumulation of old blood and necrotic material in the cyst cavity. Infarction-like necrosis in thymomas is due to thrombosis of the blood vessels.<sup>2</sup> However, thrombotic blood vessels were not evident in the present case. When a thymoma becomes markedly cystic, the characteristic fibrous bands and lobulations are lost as was observed in the present case.<sup>3</sup>

Histopathologically the tumour mimicked a thyroid neoplasm and a carcinoid tumour. However, the characteristic occurrence of perivascular spaces enabled the diagnosis of a thymoma. Though thyroid lesions are described in the anterior mediastinum, an intrathymic thyroid neoplasms are extremely rare.<sup>4</sup> Carcinoid tumours in the mediastinum can grow very

large, but the cystic change which is so common in thymoma, is not a feature of this neoplasm and it is a circumscribed, unencapsulated tumour. Carcinoid tumour can show entirely a spindle cell pattern resembling medullary thymoma. The absence of granular nuclear chromatin, granular cytoplasm and the fibrovascular stroma of an endocrine tumour helped to distinguish thymoma from carcinoid tumour. Lymphocytes are generally few or absent in carcinoid tumours.<sup>3</sup> Focally there was an admixture of tumour cells with lymphocytes in this tumour. Melanocytes are described in thymic carcinoids but are also seen rarely in thymomas.<sup>5</sup> Thymic carcinoid tumours arise from the Kultschitzky cells that are normally present in the thymus.<sup>3</sup> However, rarely carcinoid tumours are described in mature thymic teratomas along with all other teratomatous components.<sup>6,7</sup> There were no teratomatous components in this tumour.

Cystic change in thymomas can be the result of extreme dilatation and confluence of perivascular spaces as was apparent in the present case. The presence of such extensive necrosis would have favoured a malignant tumour. The clue to the correct diagnosis was the bland nuclear features of the

tumour cells and the absence of mitosis. Also, the easy resectability and absence of infiltration supported the diagnosis of a benign tumour.

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4. The chest radiograph is accompanied by brief clinical account, not exceeding two page typescript (with sub-head: Clinical Summary, Investigations, Diagnosis, Discussion and References)

All the material received for publication under the Radiology Forum section will be evaluated to judge the suitability for publication by our peer-review experts panel.

*Editor-in-Chief*

# Use of Non-invasive Ventilation in a Pregnant Woman with Acute Respiratory Distress Syndrome due to Pneumonia

Amit Banga and G.C. Khilnani

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## ABSTRACT

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Utility of non-invasive ventilation (NIV) in patients with acute respiratory distress syndrome (ARDS) is not proven. We report a case of a 28-year-old primigravida female with ARDS due to community-acquired severe pneumonia in whom non-invasive ventilation was instituted in an attempt to improve oxygenation and avoid intubation. This led to an improvement in arterial oxygenation and reduction in respiratory rate of the patient and gradual disappearance of fetal distress. [Indian J Chest Dis Allied Sci 2009;51:115-117]

**Key words:** Assisted ventilation, Community acquired pneumonia, Fetal distress, Pregnancy.

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## INTRODUCTION

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Although use of non-invasive ventilation (NIV) in patients with hypercapnic respiratory failure is well established,<sup>1-5</sup> data supporting its utility in hypoxemic respiratory failure is sparse. Likewise, the utility of NIV in the setting of severe acute lung injury or ARDS is not proven. A case of ARDS due to community acquired pneumonia (CAP) in a primigravida woman is described, where timely use of NIV was associated with a favourable outcome.

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## CASE REPORT

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A 28-year-old non-smoker 34 weeks primigravida woman, presented with a 10-day-history of high-grade fever. She had associated dry cough and worsening dyspnoea but no chest pain or haemoptysis. Her antenatal course had been unremarkable. On examination, she had marked tachypnea (50/min) and tachycardia (115/min) with a maintained blood pressure. There was mild central cyanosis. Chest examination revealed bilateral coarse crepitations but no bronchial breath sounds. Uterine height was corresponding to 34 weeks pregnancy and fetal heart sounds were audible.

Blood gas analysis revealed hypoxemia with hypocapnia PaO<sub>2</sub>/FiO<sub>2</sub> (partial pressure of oxygen to fraction of oxygen in inspired air) ratio was 155. Chest radiograph showed bilateral alveolar shadows with air space consolidation in the mid and lower zones (Figure 1). An echocardiogram revealed normal left

ventricular function and atrial pressures. There was leukocytosis with shift to left (16,200 per cumm, 80% neutrophils). Renal functions were normal but hepatic enzymes were elevated (aspartate aminotransferase/alanine aminotransferase: 180/210).



**Figure 1.** Chest radiograph at admission, showing bilateral alveolar shadows with areas of air space consolidation, predominantly in the mid and lower zones.

Patient was admitted to the intensive care unit (ICU) with a diagnosis of bilateral CAP with ARDS. High flow oxygen via venturi mask and broad-spectrum antibiotics (ceftriaxone and azithromycin) were administered. Over the next few hours, the FiO<sub>2</sub>

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was gradually stepped up in an attempt to augment PaO<sub>2</sub>, but was largely unsuccessful (Figure 2). Because of persistent hypoxemia, fetal distress began to occur. At six hours post admission, Manning score was 2/8. Elective intubation and termination of pregnancy were considered, but deferred because of high maternal risk for anaesthesia and unwillingness

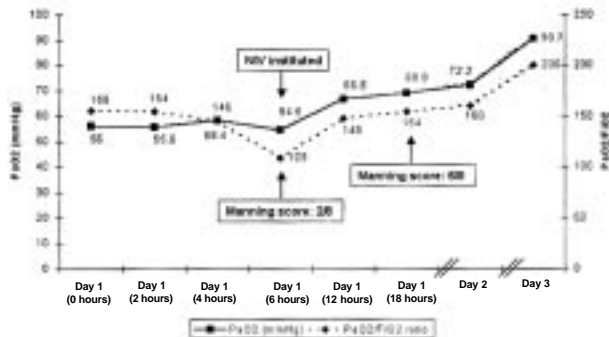


Figure 2. The trends in the arterial PaO<sub>2</sub> levels and PaO<sub>2</sub>/FiO<sub>2</sub> ratio during the initial three days of admission.

of the patient and family. After discussing various options, a trial of NIV was initiated. A bilevel NIV machine with nasal mask was used and oxygen was provided through a nasal canula @ 10 L/min. Initial settings were an inspiratory pressure (IPAH) of 8cm and an expiratory pressure (EPAP) of 4cm with gradual augmentation to 16cm and 10cm of water respectively. The patient showed a good clinical response with improvement in PaO<sub>2</sub> to above 65 mmHg (Figure 2). Gradually, the respiratory rate decreased down and a repeat Manning score at 12 hours after NIV initiation was 6/8. Over the next 36 hours, the patient continued to improve and gradual reduction of pressures was initiated. She was weaned off NIV in the next 48 hours and shifted out to the ward on day seven of the ICU admission.

## DISCUSSION

Use of NIV in the setting of severe hypoxemia but absence of hypercapnia is controversial.<sup>6</sup> It is feared that the possible benefits of NIV in such situations are likely to be offset by the drawbacks such as unnecessary delay in endotracheal intubation and mechanical ventilation. Therefore, a prospective randomised trial studying the role of NIV in such a setting would also have significant ethical implications. Nonetheless, evidence supporting the role of NIV in hypoxemic respiratory failure is slowly emerging. Non-invasive ventilation has been found to be useful in improving hypoxemia in patients with community acquired pneumonia<sup>7,8</sup> and human immunodeficiency virus infected patients with *Pneumocystis jiroveci* pneumonia (PCP).<sup>9-11</sup> In a pilot study by Rocker *et al*<sup>12</sup>, use of NIV lead to consistent improvement in hypoxemia and avoidance of intubation in 6 out of 12 episodes of ARDS among 10 patients. None of the patients in this series had

ARDS secondary to pneumonia, which is generally believed to be different from that secondary to extra-pulmonary causes.<sup>13</sup> Additional anecdotal evidence is there on the useful role of NIV in patients with ARDS secondary to tuberculosis.<sup>14</sup> However, role of NIV in patients with ARDS continues to remain controversial.<sup>15,16</sup>

The case described in the present report posed many therapeutic dilemmas. First, there was a lack of evidence to support the utility of NIV in the setting of ARDS secondary to severe pneumonia. Presence of the underlying pregnancy posed an additional challenge. Corresponding to the gestational age of 32 weeks, the uterine height was at its maximum causing elevation of the diaphragm (Figure 1). This further increased the workload of breathing. Relative laxity of the lower esophageal sphincter that occurs late pregnancy meant that high inspiratory pressures had to be avoided to prevent gastric distension. Appearance of fetal distress, likely due to hypoxemia, was another concern. Termination of pregnancy carried risks as the mother was not in a position to undergo vaginal delivery and was a high-risk case for caesarian section under general anesthesia. Finally, the patient and the family did not give consent for mechanical ventilation.

Under these circumstances, a careful trial of NIV appeared to be the best option. Absence of non-pulmonary major organ dysfunction and intact sensorium were favorable factors in this patient. After explaining the risks, NIV was instituted and administered successfully. With augmentation of pressures, a favourable response was observed. The beneficial effects of NIV possibly occurred due to unloading of respiratory muscles by IPAP with significant reduction in work of breathing, improving the balance between oxygen demand and supply. In addition, EPAP appeared to have helped in recruitment of under ventilated and atelectatic areas of the lung leading to improvement of oxygenation.

A timely decision to initiate NIV appears to be critical to its success. Patients with major organ dysfunction and obtunded sensorium would obviously be unsuitable candidates for NIV. Although additional evidence needs to be gathered before use of NIV becomes the standard of care use of NIV in carefully selected patients with ARDS may be appropriate and should be considered as an option for ventilatory support.

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# Recurrent Haemoptysis Following Sildenafil Administration

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## ABSTRACT

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Sildenafil is widely used in the treatment of male erectile disorder and is generally well-tolerated. Its adverse effects are reported to be mild and include flushing, headache, dyspepsia and visual disturbances. We document a case of recurrent haemoptysis observed soon after self administration of sildenafil in a 38-year-old male with no other causative factors. The episodes of haemoptysis stopped following stoppage of sildenafil. [Indian J Chest Dis Allied Sci 2009;51:119-120]

**Key words:** Haemoptysis, Sildenafil, Drug-induced respiratory disorders.

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## INTRODUCTION

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The sildenafil citrate, the first phosphodiesterase type-5 (PDE5) inhibitor is an effective and generally well-tolerated oral agent for the treatment of erectile dysfunction (ED) in males.<sup>1</sup> The treatment-related adverse effects of this drug are mild and include flushing, headache, dyspepsia, visual disturbances, myalgia, nasal congestion and stuffiness.<sup>2</sup> Haemoptysis following sildenafil administration is rare and so far reported only once.<sup>3</sup>

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## CASE REPORT

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A 38-year-old male presented with a history of recurrent haemoptysis for the past two months. The haemoptysis was sudden in onset, followed mild cough, was small in quantity (about 5-7mL) and stopped spontaneously each time in one to two hours. There was no history of fever, breathlessness, wheezing, cough with purulent expectoration, chest pain, a change in voice. He denied any history of nasal, oral or dental symptoms, bleeding from other body sites, chest trauma or instrumentation of gastrointestinal or respiratory tracts. He had otherwise been generally healthy with no previous medical history of note. He was a non-smoker and had never consumed alcohol. The patient initially consulted a general practitioner and received oral amoxicillin, ethamsylate and codein preparation for one week. There was no response from this treatment and the case was referred to our hospital for investigation.

His physical examination and laboratory evaluation, including chest radiograph, and pulmonary function tests were normal. The bleeding

profile revealed a platelet count of 3.5lac/mm<sup>3</sup>, bleeding time of 1.5 minutes, clotting time of 4 minutes, prothombin time of 15 seconds (INR 1.00) control of 13 seconds, and activated partial thromboplastin time (PPT) of 24 seconds. The induced-sputum was negative for acid-fast bacilli, other organisms and fungi. There was no abnormal finding on computed tomograph of thorax and bronchoscopic examination. Electrocardiogram and echocardiogram were unremarkable.

No site for bleeding was detected on careful examination of nose, oral cavity and throat. As no cause for haemoptysis was found at this stage, the patient was reassured. However, haemoptysis continued to recur. The patient also showed the coughed out specimen, ruling out possibility of malingering. Although he denied having taken any drugs during that period, his wife incidentally observed that he used sildenafil blister. On detailed questioning, the patient disclosed self-use of sildenafil 50mg without any prescription, to enhance his sexual performance in the last two months. He also reported that the episodes of haemoptysis occurred only during or soon after the sexual intercourse and had started after the first use of sildenafil. The patient was advised to stop the drug. During the 18-month follow-up, the patient denied recurrence of haemoptysis or pulmonary complaints. Cessation of haemoptysis following stoppage of the drug suggestion a cause-effect relationship.

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## DISCUSSION

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In this case report it is reasonable to assume that the cause for recurrent haemoptysis was the use of

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sildenafil as no other explanation was there after a detailed examination and investigation. As haemoptysis did not recur after withdrawal, use of sildenafil was the likely cause.

Sildenafil and the newer drug tadalafil selectively inhibits PDE5, which is found in most vascular and visceral smooth muscle cells in addition to the corpus cavernosum. Consistent with this, the reported side effects are related to the distribution of PDE5 within the body, the common adverse events reported being headache and dyspepsia followed by back pain, nasal congestion myalgia and flushing.<sup>4</sup> Venous engorgement due to sildenafil has been considered as a factor for severe episodes of epistaxis after sexual activity.<sup>5</sup> Variceal bleeding, cerebrovascular haemorrhage and bleeding from haemorrhoids have also been reported after the use of sildenafil.<sup>6,7</sup> Haemoptysis after use of sildenafil has been reported only once.<sup>3</sup>

It has been suggested that sildenafil, by inhibiting PDE5 in pulmonary tissue, leads to increase nitric oxide production causing vasodilatation of the pulmonary vascular system including pulmonary capillaries.<sup>8</sup> *In vitro* studies have also suggested that sildenafil can inhibit PDE-5 induced platelet aggregation.<sup>6</sup> Either or both of the above mechanisms may be responsible for haemoptysis in our case.

To conclude, use of sildenafil may be associated with haemoptysis and should be considered in patients with recurrent haemoptysis where no other cause is found.

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**Abstracts' Service**

## **WHO's Budgetary Allocations and Burden of Disease: A Comparative Analysis**

**David Stuckler, Lawrence King, Helen Robinson, Martin McKee**

*Lancet 2008;372:1563-69*

**Background.** Ministers of health, donor agencies, philanthropists, and international agencies will meet at Bamako, Mali, in November, 2008, to review global priorities for health research. These individuals and organisations previously set health priorities for WHO, either through its regular budget or extra-budgetary funds. We asked what insights can be gained as to their priorities from previous decisions within the context of WHO.

**Methods.** We compared the WHO biennial budgetary allocations with the burden of disease from 1994–95 to 2008–09. We obtained data from publicly available WHO sources and examined whether WHO allocations varied with the burden of disease (defined by death and disability-adjusted life years) by comparing two WHO regions—Western Pacific and Africa—that are at differing stages of epidemiological transition. We further assessed whether the allocations differed on the basis of the source of funds (assessed and voluntary contributions) and the mechanism for deciding how funds were spent.

**Findings.** We noted that WHO budget allocations were heavily skewed toward infectious diseases. In 2006–07,

WHO allocated 87% of its total budget to infectious diseases, 12% to non-communicable diseases, and less than 1% to injuries and violence. We recorded a similar distribution of funding in Africa, where nearly three-quarters of mortality is from infectious disease, and in Western Pacific, where three-quarters of mortality is from non-communicable disease. In both regions, injuries received only 1% of total resources. The skew towards infectious diseases was substantially greater for the WHO extra-budget, which is allocated by donors and has risen greatly in recent years, than for the WHO regular budget, which is decided on by member states through democratic mechanisms and has been held at zero nominal growth.

**Interpretation.** Decision makers at Bamako should consider the implications of the present misalignment of global health priorities and disease burden for health research worldwide. Funds allocated by external donors substantially differ from those allocated by WHO member states. The meeting at Bamako provides an opportunity to consider how this disparity might be addressed.

## **Health Systems and the Right to Health: An Assessment of 194 Countries**

**Gunilla Backman, Paul Hunt, Rajat Khosla, Camila Jaramillo-Strauss, Belachew Mekuria Fikre, Caroline Rumble, David Pevalin, David Acurio Paez, Monica Armijos Pineda, Ariel Frisancho, Duniska Tarco, Mitra Motlagh, Dana Farcasanu, Cristian Vladescu**

*Lancet 2008;372:2047-85*

**Background.** Sixty years ago, the Universal Declaration of Human Rights laid the foundations for the right to the highest attainable standard of health. This right is central to the creation of equitable health systems. We identify some of the right-to-health features of health systems, such as a comprehensive national health plan, and propose 72 indicators that reflect some of these features. We collect globally processed data on these indicators for 194 countries and national data for Ecuador, Mozambique, Peru, Romania, and Sweden. Globally processed data were not available for 18 indicators for any country, suggesting that organisations that

obtain such data give insufficient attention to the right-to-health features of health systems. Where they are available, the indicators show where health systems need to be improved to better realise the right-to-health. We provide recommendations for governments, international bodies, civil-society organisations, and other institutions and suggest that these indicators and data, although not perfect, provide a basis for the monitoring of health systems and the progressive realisation of the right to health. Right-to-health features are not just good management, justice, or humanitarianism, they are obligations under human-rights law.

## Food Allergy is Associated with Potentially Fatal Childhood Asthma

Nicola M. Vogel, Hary T. Katz, Rocio Lopez, and David M. Lang

*Journal of Asthma 2008;45:862-866*

**Background.** Risk factors for potentially fatal childhood asthma are incompletely understood.

**Objective.** To determine whether self-reported food allergy is significantly associated with potentially fatal childhood asthma.

**Study design.** Medical records from 72 patients admitted to a pediatric intensive care unit (PICU) for asthmatic exacerbation were reviewed and compared in a case-control design with 2 randomly selected groups of 108 patients admitted to a regular nursing floor for asthma and 108 ambulatory patients with asthma. Factors evaluated included self-reported food allergy, gender, age, poverty area residence, race/ethnicity, inhaled steroid exposure, tobacco exposure, length of hospital stay, psychologic comorbidity, and season of admission.

**Results.** At least one food allergy was documented for 13% (38/288) of the patients. Egg, peanut, fish/

shellfish, milk, and tree nut accounted for 78.6% of all food allergies. Children admitted to the PICU were significantly more likely to report food allergy ( $p = 0.004$ ) and 3.3 times more likely to report at least one food allergy compared with children admitted to a regular nursing floor, and significantly more likely to report food allergy ( $p < 0.001$ ) and 7.4 times more likely to report at least one food allergy compared with children seen in the ambulatory setting. Children admitted to either the PICU or the regular nursing floor were significantly more likely to be African-American ( $p < 0.001$ ) and to be younger ( $p < 0.01$ ) compared with children seen in the ambulatory setting.

**Conclusions.** Self-reported food allergy is an independent risk factor for potentially fatal childhood asthma. Asthmatic children or adolescents with food allergy are a target population for more aggressive asthma management.

## Efficacy and Safety of Indacaterol, a New 24-hour $\beta_2$ -Agonist, in Patients with Asthma: A Dose-Ranging Study

Frank Kanniss, Louis-Philippe Boulet, Wladyslaw Pierzchala, Ray Cameron, Roger Owen, and Mark Higgins

*Journal of Asthma 2008;45:887-892*

**Background.** Indacaterol is a new once-daily inhaled  $\beta_2$ -agonist in clinical development for asthma as a component of a fixed-dose combination with an inhaled corticosteroid.

**Objectives.** To investigate the efficacy and safety of indacaterol in patients with chronic persistent asthma.

**Methods.** A total of 115 patients were randomized in a double-blind, incomplete-block cross-over design to sequences of four 7-day treatment periods (separated by 7-day washouts) with indacaterol 100, 200, 300, 400, or 600  $\mu\text{g}$  or placebo, once daily, via single-dose dry-powder inhaler. After the fourth washout, patients received 1 day of open-label formoterol 12  $\mu\text{g}$  twice daily. Forced expiratory volume in 1 second ( $\text{FEV}_1$ ) was measured for 24 hours post-dose on days 1 and 7.

**Results.** For standardized (with respect to time)  $\text{FEV}_1$  area under the curve at 22 to 24 hours ( $\text{AUC}_{22-24\text{h}}$ ) on day 1, indacaterol doses  $\geq 200$   $\mu\text{g}$  were superior to placebo ( $p < 0.05$ ) and similar or greater than formoterol 12  $\mu\text{g}$  twice daily. By day 7, mean differences from placebo in  $\text{FEV}_1$  standardized  $\text{AUC}_{22-24\text{h}}$  were 0.08, 0.16, 0.15, 0.11, and 0.16 L for indacaterol 100, 200, 300, 400, and 600  $\mu\text{g}$ , respectively (all  $p < 0.05$  vs. placebo). Mean  $\text{FEV}_1$  for indacaterol doses  $\leq 200$   $\mu\text{g}$  on day 7 was higher than placebo ( $p < 0.05$ ) pre-dose and at all post-dose time points. AEs were generally mild in severity; no serious AEs occurred. No clinically meaningful differences were observed between treatments in any safety assessments.

**Conclusions.** Once-daily indacaterol demonstrated sustained 24-hour bronchodilator efficacy, with similar efficacy on days 1 and 7, and was generally well tolerated.

## Clinical Transplantation of a Tissue-engineered Airway

Paolo Macchiarini, Philipp Jungebluth, Tetsuhiko Go, M Adelaide Asnaghi, Louisa E Rees, Tristan A Cogan, Amanda Dodson, Jaume Martorell, Silvia Bellini, Pier Paolo Parnigotto, Sally C. Dickinson, Anthony P Hollander, Sara Mantero, Maria Teresa Conconi, Martin A Birchall

*Lancet 2008;372:2023-30*

**Background.** The loss of a normal airway is devastating. Attempts to replace large airways have met with serious problems. Prerequisites for a tissue-engineered replacement are a suitable matrix, cells, ideal mechanical properties, and the absence of antigenicity. We aimed to bioengineer tubular tracheal matrices, using a tissue-engineering protocol, and to assess the application of this technology in a patient with end-stage airway disease.

**Methods.** We removed cells and MHC antigens from a human donor trachea, which was then readily colonised by epithelial cells and mesenchymal stem-cell-derived chondrocytes that had been cultured from cells taken from the recipient (a 30-year old woman with end stage bronchomalacia). This graft was then

used to replace the recipient's left main bronchus.

**Findings.** The graft immediately provided the recipient with a functional airway, improved her quality of life, and had a normal appearance and mechanical properties at 4 months. The patient had no anti-donor antibodies and was not on immunosuppressive drugs.

**Interpretation.** The results show that we can produce a cellular, tissue-engineered airway with mechanical properties that allow normal functioning, and which is free from the risks of rejection. The findings suggest that autologous cells combined with appropriate biomaterials might provide successful treatment for patients with serious clinical disorders.

## Tracking Progress Towards Universal Childhood Immunisation and the Impact of Global Initiatives: A systematic Analysis of Three-dose Diphtheria, Tetanus, and Pertussis Immunisation Coverage

Stephen S. Lim, David B. Stein, Alexandra Charrow, Christopher J.L. Murray

*Lancet 2008;372:2031-46*

**Background.** Substantial resources have been invested in increasing childhood immunisation coverage through global initiatives such as the Universal Childhood Immunisation (UCI) campaign and the Global Alliance on Vaccines and Immunisations (GAVI). There are longstanding concerns that target-oriented and performance-oriented initiatives such as UCI and GAVI's immunisation services support (ISS) might encourage over-reporting. We estimated the coverage of three doses of diphtheria, tetanus, and pertussis vaccine (DTP3) based on surveys using all available data.

**Methods.** We estimated DTP3 coverage by analysing unit record data from surveys and supplemented this with reported coverage from other surveys and administrative data. We used bidirectional distance-dependent regression to estimate trends in survey-based coverage in 193 countries during 1986-2006. We used standard time-series cross-sectional analysis to investigate any association in the difference

between countries' official reports and survey-based coverage as the dependent variable and the presence of GAVI ISS as the independent variable, controlling for country and time effects.

**Findings.** Crude coverage of DTP3 based on surveys increased from 59% (95% uncertainty interval 51-65) in 1986 to 65% (60-68) in 1990, 70% (65-74) in 2000, and 74% (70-77) in 2006. There were substantial differences between officially reported and survey-based coverage during UCI. GAVI ISS significantly increased the difference between officially reported coverage and survey coverage. Up to 2006, in 51 countries receiving GAVI ISS payments, 7.4 million (5.7 million to 9.2 million) additional children were immunised with DTP3 based on surveys compared with officially reported estimates of 13.9 million. On the basis of the number of additional children immunised from surveys at a rate of US\$20 each, GAVI ISS payments are estimated at \$150 million (115 million to 184 million) compared with actual disbursements of \$290 million.

**Interpretation.** Survey-based DTP3 immunisation coverage has improved more gradually and not to the level suggested by countries' official reports or WHO and UNICEF estimates. There is an urgent need for

independent and contestable monitoring of health indicators in an era of global initiatives that are target-oriented and disburse funds based on performance.

## Financial Incentive-Based Approaches for Weight Loss: A Randomized Trial

Kevin G. Volpp, Leslie K. John, Andrea B. Troxel, Laurie Norton, Jennifer Fassbender, and George Loewenstein

*JAMA* 2008;300(22):2631-2637

**Context.** Identifying effective obesity treatment is both a clinical challenge and a public health priority due to the health consequences of obesity.

**Objective.** To determine whether common decision errors identified by behavioral economists such as prospect theory, loss aversion, and regret could be used to design an effective weight loss intervention.

**Design, Setting and Participants.** Fifty-seven healthy participants aged 30-70 years with a body mass index of 30-40 were randomized to 3 weight loss plans: monthly weigh-ins, a lottery incentive program, or a deposit contract that allowed for participant matching, with a weight loss goal of 1 lb (0.45 kg) a week for 16 weeks. Participants were recruited May-August 2007 at the Philadelphia VA Medical Center in Pennsylvania and were followed up through June 2008.

**Main Outcome Measures.** Weight loss after 16 weeks.

**Results.** The incentive groups lost significantly more weight than the control group (mean, 3.9 lb). Compared with the control group, the lottery group lost a mean of 13.1 lb (95% confidence interval [CI] of the difference in means, 1.95-16.40;  $P=.02$ ) and the

deposit contract group lost a mean of 14.0 lb (95% CI of the difference in means, 3.69-16.43;  $P=.006$ ). About half of those in both incentive groups met the 16-lb target weight loss: 47.4% (95% CI, 24.5%-71.1%) in the deposit contract group and 52.6% (95% CI, 28.9%-75.6%) in the lottery group, whereas 10.5% (95% CI, 1.3%-33.1%;  $P=.01$ ) in the control group met the 16-lb target. Although the net weight loss between enrollment in the study and at the end of 7 months was larger in the incentive groups (9.2 lb;  $t=1.21$ ; 95% CI, -3.20 to 12.66;  $P=.23$ , in the lottery group and 6.2lb;  $t=0.52$ ; 95% CI, -5.17 to 8.75;  $P=.61$  in the deposit contract group) than in the control group (4.4 lb), these differences were not statistically significant. However, incentive participants weighed significantly less at 7 months than at the study start ( $P=.01$  for the lottery group;  $P=.03$  for the deposit contract group) whereas controls did not.

**Conclusions.** The use of economic incentives produced significant weight loss during the 16 weeks of intervention that was not fully sustained. The longer-term use of incentives should be evaluated.

**Trial Registration** [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00520611

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The *Indian Journal of Chest Diseases and Allied Sciences* considers for publication original articles dealing with respiratory and cardiovascular diseases and in the fields of anatomy, biochemistry, microbiology, mycology, pathology, pharmacology, physiology, ultra-structure and virology of respiratory, and cardiovascular systems. However, only papers that make a significant contribution to the existing state of knowledge in a particular field will be published. The journal publishes original articles, case reports, radiology forum, short communications and book reviews.

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VI. **Discussion.** This should be limited to significance of results obtained and what can and what cannot be concluded and why. It should not be a repetition of the findings already given under 'Results'. Results should be

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VII. *Acknowledgements.* Acknowledgement should be brief and made specific for scientific/technical assistance and financial supports in the form of grants/drugs/equipment only and for not providing routine departmental facilities and for help in the preparation of manuscript (including typing/secretarial assistance).

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#### Articles in Journals

##### 1. *Standard journal article*

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002; 347: 284-7.

More than six authors:

Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, *et al*. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. *Brain Res* 2002; 935 (1-2): 40-6.

##### 2. *Article published electronically ahead of the print version*

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. *Blood* 2002 Nov 15; 100(10): 3828-31. Epub 2002 July 5.

##### 3. *Volume with supplement*

Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short-and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; 42 Suppl 2: S93-9.

##### 4. *Issue with supplement*

Glauser TA. Integrating clinical trial data into clinical practice. *Neurology* 2002; 58 (12 Suppl 7): S6-12.

##### 5. *Type of article indicated as needed*

Tor M, Turker H. International approaches to the prescription of long-term oxygen therapy [letter]. *Eur Respir J* 2002; 20(1): 242.

Lofwall MR, Strain EC, Brooner RK, Kindbom KA, Bigelow GE. Characteristics of older methadone maintenance (MM) patients [abstract]. *Drug Alcohol Depend* 2002; 66 Suppl 1: S105.

##### 6. *Volume with part*

Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. *Int J Psychoanal* 2002; 83 (Pt 2): 491-5.

##### 7. *Issue with part*

Ahrar K, Madoff DC, Gupta S, Wallace MJ, Price RE, Wright KC. Development of a large animal model for lung tumours. *J Vasc Interv Radiol.* 2002; 13(9 Pt 1): 923-8.

##### 8. *Issue with no volume*

Banit DM, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop* 2002; (401): 230-8.

##### 9. *No volume or issue*

Outreach: bringing HIV-positive individuals into care. *HRSA Careaction* 2002 Jun: 1-6.

##### 10. *Pagination in roman numerals*

Chadwick R, Schuklenk U. The politics of ethical consensus finding. *Bioethics* 2002; 16(2): iii-v.

##### 11. *Organization as author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; 40(5): 679-86.

12. *Both personal authors and an organization as author* (This example does not conform to NISO standards).

Vallancien G, Emberton M, Harving N, van Moorselaar RJ, Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; 169(6): 2257-61.

##### 13. *No author given*

21st century heart solution may have a sting in the tail. *BMJ* 2002; 325(7357): 184.

##### 14. *Article containing retraction*

Feifel D, Moutier CY, Perry W. Safety and tolerability of a rapidly escalating dose-loading regimen for risperidone. *J Clin Psychiatry* 2002; 63(2): 169. Retraction of: Feifel D, Moutier CY, Perry W. *J Clin Psychiatry* 2000; 61(12): 909-11.

15. *Article retracted*

Feifel D, Moutier CY, Perry W. Safety and tolerability of a rapidly escalating dose-loading regimen for risperidone. *J Clin Psychiatry* 2000; 61(12): 909-11. Retraction in: Feifel D, Moutier CY, Perry W. *J Clin Psychiatry* 2002; 63(2): 169.

16. *Article republished with corrections*

Mansharamani M, Chilton BS. The reproductive importance of P-type ATPases. *Mol Cell Endocrinol* 2002; 188(1-2): 22-5. Corrected and republished from: *Mol Cell Endocrinol* 2001; 183(1-2): 123-6.

17. *Article with published erratum*

Malinowski JM, Bolesta S. Rosiglitazone in the treatment of type 2 diabetes mellitus: a critical review. *Clin Ther* 2000; 22(10): 1151-68; discussion 1149-50. Erratum in : *Clin Ther* 2001; 23(2): 309.

18. *Article not in English*

(Note: NLM translates the title into English, encloses the translation in square brackets, and adds an abbreviated language designator.)

Ellingsen AE, Wilhelmsen I. *Sykdomsangst blant medisiner og jusstudenter. Tidsskr Nor Laegeforen* 2002; 122(8): 785-7.

**Personal Communication**

Name of the person and date of communication should be cited in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

**Unpublished Material**19. *In press*

(Note: NLM prefers "forthcoming" because not all items will be printed.)

Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Significance of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA*. In press 2002.

**Books and Other Monographs**20. *Chapter in a book*

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumours. In: Vogelstein B, Kinzler KW, editors. *The Genetic Basis of Human Cancer*. New York: McGraw-Hill. 2002; pp 93-113.

21. *Conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In : Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: *Proceedings of the 5th European Conference on Genetic Programming*; 2002 Apr 3-5; Kinsdale Ireland. Berlin: Springer.

2002; pp 182-91.

22. *Personal author(s)*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. *Medical Microbiology*; 4th ed. St. Louis: Mosby. 2002.

23. *Editor(s), compiler(s) as author*

Gilstrap LC (3rd), Cunningham FG, VanDorsten JP, editors. *Operative Obstetrics*. 2nd ed. New York: McGraw-Hill. 2002.

24. *Author(s) and editor(s)*

Breedlove GK, Schorfheide AM. *Adolescent Pregnancy*. 2nd ed. Wicczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

25. *Organization(s) as author*

Royal Adelaide Hospital; University of Adelaide, Department of Clinical Nursing. *Compendium of Nursing Research and Practice Development, 1999-2000*. Adelaide (Australia): Adelaide University; 2001.

26. *Conference proceedings*

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. *Proceedings of the 5th Germ Cell Tumour Conference*; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

27. *Scientific or technical report*

Issued by funding/sponsoring agency:

Yen GG (Oklahoma State University, School of Electrical and Computer Engineering, Stillwater, OK). Health monitoring on vibration signatures. Final report. Arlington (VA): Air Force Office of Scientific Research (US), Air Force Research Laboratory; 2002 Feb. Report No.: AFRLSRBLTR020123. Contract No.: F496209810049.

Issued by performing agency:

Russell ML, Goth-Goldstein R, Apte MG, Fisk WJ. Method for measuring the size distribution of airborne Rhinovirus. Berkeley (CA): Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; 2002 Jan. Report No.: LBNL49574. Contract No.: DEAC0376SF00098. Sponsored by the Department of Energy.

28. *Dissertation*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

29. *Patent*

Pegedas AC, inventor; Ancel Surgical R& D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1.

**Other Published Material**30. *Newspaper article*

Tynan T. Medical improvements lower homicide rate: study sees drop in assault rate. *The Washington Post*. 2002 Aug 12; Sect. A:2 (col. 4).

31. *Audiovisual material*

Chason KW, Sallustio S. Hospital preparedness for bioterrorism [videocassette]. Secaucus (NJ): Network for Continuing Medical Education; 2002.

32. *Legal Material*

Public law:

Veterans Hearing Loss Compensation Act of 2002, Pub.L.No. 107-9, 115 Stat. 11 (May 24, 2001).

Unenacted bill:

Healthy Children Learn Act, S. 1012, 107th Cong., 1st Sess. (2001).

Code of Federal Regulations:

Cardiopulmonary Bypass Intracardiac Suction Control, 21 C.F.R. Sect. 870.4430 (2002).

Hearing:

Arsenic in Drinking Water: An Update on the Science, Benefits and Cost: Hearing Before the Subcomm. on Environment, Technology and Standards of the House Comm. on Science, 107th Cong., 1st Sess. (Oct. 4, 2001).

33. *Map*

Pratt B, Flick, P, Vynne C, cartographers. Biodiversity hotspots [map]. Washington: Conservation International; 2000.

34. *Dictionary and similar references*

*Dorland's Illustrated Medical Dictionary*. 29th ed. Philadelphia: W.B. Saunders; 2000. Filamin; p. 675.

Electronic Material

35. *CD-ROM*

Anderson SC, Poulsen KB. *Anderson's Electronic Atlas of Hematology* [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

36. *Journal article on the Internet*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. *Am J Nurs* [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6) : [about 3 p.]. Available from: <http://www.nursingworld.org/AJN/2002/june/Wawatch.htm>

37. *Monograph on the Internet*

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: <http://www.nap.edu/books/0309074029/html/>.

38. *Homepage/Web site*

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: <http://www.cancer-pain.org/>.

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American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: <http://www.ama-assn.org/ama/pub/category1736.html>.

40. *Database on the Internet*

Open database:

Who's Certified [database on the Internet]. Evanston (IL): The American Board of Medical Specialists. c2000-[cited 2001 Mar 8]. Available from: <http://www.abms.org/newsearch.asp>

Closed database:

Jablonski S. Online Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes [database on the Internet]. Bethesda (MD): National Library of Medicine (US). c1999 [updated 2001 Nov 20; cited 2002 Aug 12]. Available from: [http://www.nlm.nih.gov/mesh/jablonski/syndrome\\_title.html](http://www.nlm.nih.gov/mesh/jablonski/syndrome_title.html)

41. *Part of a database on the Internet*

MeSH Browser [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2002 - [cited 2003 Jun 10]. Meta-analysis; unique ID: D015201; [about 3 p.]. Available from: <http://www.nlm.nih.gov/mesh/MBrowser.html> Files updated weekly.

MeSH Browser [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2002 - [cited 2003 Jun 10]. Meta-analysis; unique ID: D015201; [about 3 p.]. Available from: <http://www.nlm.nih.gov/mesh/MBrowser.html> Files updated weekly.

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