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## Globalisation and Respiratory Medicine in India

The practice of Respiratory Medicine in India has changed with times. Early on, the respiratory physicians in India were focused on managing tuberculosis, with non-tubercular lung diseases remaining largely in the domain of internists. The departments in the medical colleges and the postgraduate qualifications awarded by the universities were thus aptly named 'tuberculosis and chest diseases'. The modern day chest specialists like to be called a "pulmonologist" or "respiratory physician", as besides handling all the respiratory problems (both tubercular and non-tubercular), many chest physicians, particularly in cities are also practicing sleep medicine and critical care. The nomenclature associated with the departments as well postgraduate qualifications in the subject has also reflected this. This is not to say that importance or the burden of tuberculosis has decreased for us (as is perhaps the case with our colleagues in more developed nations). This expansion in the portfolio of chest physicians can be attributed to their inherent quest for knowledge and desire to emulate their colleagues from the west in the wake of increased awareness due to globalisation.

The rapid advancement and expansion in clinical commitments of a respiratory physician demands that he has to devote extra time and effort to keep abreast with the rapidly evolving practice of medicine. This is almost imperative in the current era of evidence based practice. Much as we would like to rely on evidence generated locally, however till the time quality data providing 'A' grade evidence are routinely generated locally, we have to keep ourselves updated with the similar information available globally. With the explosion of information technology, the availability and accessibility of educational resources has vastly improved. Gone are the days when we used to wait for 3-4 months to receive the latest journal copy in the library (personal subscriptions, were virtually impractical, both due to the high cost and the procedural hassles of remitting money in foreign exchange). The Internet has changed the way we acquire information. Every morning, you are greeted with the latest 'e-toc' (electronic table of contents) from the journals of your choice in your e-mails. Webcasts (publishing on the web), PDA (personal digital assistant or palm top) versions and now 'Podcasts' (information downloaded to mobile multimedia devices) have realised the seemingly impossible dream of getting the information wherever and whenever one wants and also to carry it along like a print journal in the hand/bag. The tedious search for references in the 'Index Medicus' has been replaced with a convenient click of

the 'mouse'. Basic access to the internet and the skill to extract information have become as important as possessing a stethoscope and ability to recognise rhonchi on auscultation of chest. Internet is also challenging the clinicians with its ability to offer clinical diagnosis, which till now was an absolute prerogative of the clinician.<sup>1</sup>

Virtual replacement of print media by electronic printing, has also resulted in drastic reduction of annual membership fees of several international societies. European Respiratory Society (ERS)<sup>2</sup> was among the first few to offer a reduced membership fee for various categories of members depending upon the per capita income of the country of their origin. For Indian nationals annual fees vary between 10-85 Euros only. American College of Chest Physicians (ACCP) has also offered similarly reduced membership dues for e-membership. The ACCP fee applicable in India is US \$ 72.00 for full fellows compared to annual fee of \$ 174.00 for traditional membership.<sup>3</sup> The reduced fees allow nearly full membership benefits and electronic access to all their publications, print copies are not included. Many of us may not be tuned into reading online, although there is a definite advantage of easy browsing and search option with electronic format access. Other societies of our interest, which offer affordable, yet very beneficial membership plans are Asia Pacific Society of Respiratory (US \$ 75)<sup>4</sup> and Infectious Disease Society of America (US \$ 25) with full access to journals like *Respirology and Clinical Infectious Disease* and *Journal of Infectious Diseases* respectively.<sup>5</sup> There are many more societies and resources which have either open (free) access or very nominal access fees.

Expansion and advancement of a specialty is also reflected in the strength and growth of its professional associations. We have also seen this phenomenon in India. Besides two major chest societies we have several smaller thematic societies catering to bronchology, sleep medicine, critical care, allergy, lung cancer, etc. These societies provide educational resources to their members in terms of journal and conferences, etc. The respiratory journals representing the two national societies have been made available online thereby providing easy accessibility to our publications.<sup>6,7</sup> However, onus is on all of us, the practicing respiratory specialists in India to stand up and be counted in the global arena of respiratory medicine. To achieve this goal we need to put our house in order, by striving hard to improve academic standards of our publications, conferences, etc. We also need more participation and collaborations at the national as well as international levels to generate quality research, which is tailor-made

to our peculiar needs. A change in attitude from 'I, ME and MY' to 'WE, US and OURS' is required to get respiratory medicine in India its due in the globalised world of medicine.

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# Impact of HIV Infection on Radiographic Features in Patients with Pulmonary Tuberculosis

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## ABSTRACT

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**Background.** There is insufficient data on the radiographic presentation of tuberculosis in human immunodeficiency virus (HIV) infected patients from India.

**Methods.** We examined the chest radiographs of 181 patients including 82 HIV positives with newly diagnosed sputum culture positive pulmonary tuberculosis before and after the completion of anti-tuberculosis treatment (ATT). Patients with smear/culture positive pulmonary tuberculosis were treated with Revised National Tuberculosis Control Programme (RNTCP) Cat-I regimen (2EHRZ<sub>3</sub>/4HR<sub>3</sub>). An independent assessor blinded to HIV and clinical status of patients read the radiographs.

**Results.** At presentation, HIV seropositive patients were significantly more likely to have normal chest radiographs (14.2% vs 0), miliary tuberculosis (10.7% vs 1%) and pleural effusion (16.6% vs 3%), and less likely to have cavitation (17.8% vs 39.4%) as compared to HIV negative patients. At the end of treatment, HIV positive patients were more likely to have normal radiographs (42.8% vs 1.2%), and less likely to have fibrosis (17.8% vs 42.5%).

**Conclusions.** The radiographic presentation of pulmonary tuberculosis in HIV-infected patients is atypical with less cavitation, and more dissemination. On completion of ATT, patients with HIV have less radiographic sequelae in the form of fibrosis. These features may be due to the reduced inflammatory response that patients with HIV infection may be able to mount. [Indian J Chest Dis Allied Sci 2007; 49: 133-136]

**Key words:** HIV/AIDS, Tuberculosis, Chest radiography.

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## INTRODUCTION

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Among factors contributing to the increased incidence of tuberculosis (TB) worldwide, HIV is one of the most important. Since control of tuberculosis in an individual depends on an intact cellular immune response, it is not surprising that HIV infection is a major risk factor for tuberculosis progressing from latent infection to clinical disease. In India, tuberculosis is the most common opportunistic infection among HIV seropositive patients.<sup>1</sup> Patients with HIV co-infection may not have typical radiographic features of pulmonary tuberculosis. Several studies from Africa, Europe, and South America have reported differences in radiographic manifestations of TB between HIV seropositive and seronegative groups.<sup>2,3,4-10</sup> A few studies have been conducted in India comparing the radiographic features of pulmonary tuberculosis between HIV seropositive and negative individuals.<sup>11,12</sup> We compared pre- and post-treatment radiological

features of tuberculosis in these two groups of patients to bring out any radiological outcomes.

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## MATERIAL AND METHODS

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Patients referred to the Tuberculosis Research Center Clinics in Chennai and Madurai between July 1999 and June 2002, and recruited into ongoing clinical trials of the center were included in this analysis. Patients with symptoms suggestive of pulmonary tuberculosis were investigated further. Three sputum specimens were collected for smear microscopy for acid-fast bacilli (AFB) and mycobacterial culture. Human immunodeficiency virus testing was done after pretest counseling and written informed consent. The diagnosis of HIV infection was based on three positive tests (Tridot, J. Mitra and Comb ADIS, Span Diagnostics) followed by an ELISA (Lab System, U.K.). A posteroanterior chest radiograph was done. The diagnosis of tuberculosis was based on sputum smear and culture results along with

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clinical and radiographic features. The CD4 count was done for all HIV positive patients by flow cytometry. Patients with long term steroid therapy, diabetes, and other causes of immunosuppression were excluded from the study. Based on HIV status, the patients were divided into two groups—positives and negatives.

Patients confirmed to have pulmonary tuberculosis were treated with standard short-course intermittent regimen with two months of ethambutol (1200 mg), INH (600 mg), rifampicin (450/600 mg) based on body weight < 60 kg: 450 mg and > 60 kg: 600 mg] pyrazinamide (1500 mg) given three times a week followed by four months of INH (600 mg) and rifampicin (450/600mg) given thrice weekly. Treatment was supervised completely in the initial intensive phase and once a week in the continuation phase.

The patients were followed up every month with a clinical examination and three sputum examinations. A chest radiograph was repeated at the end of treatment. An independent assessor (NMS) who did not know the clinical background of the patient including HIV status, CD4 and sputum smear status read all the chest radiographs. All patients included in this analysis had *Mycobacterium tuberculosis* isolated from at least one pre-treatment sputum culture specimen and were smear and culture negative at the end of treatment.

## Statistical Analysis

Data was entered into excel and analysis was done using SPSS software version 13. All tests were two-tailed and evaluated at a significance level of 0.05. Qualitative variables were expressed as percentage and were compared using the Chi-square test. Continuous variables were expressed as median and were compared using Mann-Whitney test.

## RESULTS

One hundred and eighty one patients who had culture confirmed tuberculosis were included in the study out of which 82 were HIV positive. Table 1 shows the demographic characteristics of the study population. The sex distribution was similar in both the groups of patients. The CD4 count was available for 71 HIV positive patients. The median CD4 count was 112 cells/

**Table 1. Demographic characteristics of study population**

	TB+ HIV- (n=99)	TB+ HIV+ (n=82)
<b>Sex</b>	Number (%)	Number(%)
Male	84 (85)	71 (84)
Female	15 (15)	11 (16)
<b>Age</b>		
< 30 years	45 (45)	28 (34)
31-50	38 (38)	51 (62)
> 50 years	16 (16)	3 (4)
<b>Smear Positivity</b>	99 (100)	49 (60)

mm<sup>3</sup> (Interquartile range 42-252). Sixty percent of patients with HIV-TB had sputum smears positive for AFB but all of them were culture positive.

Table 2 shows the initial radiographic features of patients in the two groups. Some patients had more than one abnormality. Diffuse pulmonary infiltrates/opacities was the most common radiological presentation in both the groups. Cavitation was more common in the HIV negatives pulmonary tuberculosis patients than in those with HIV co-infection. On the other hand, miliary pattern was more common in HIV positive patients. Radiographs were normal in 14.2% of HIV infected patients but in none of the seronegative patients with pulmonary tuberculosis.

**Table 2. Radiographic lesions at the time of diagnosis**

Type of Lesion	TB+ (n=99) Number (%)	TB+ HIV+ (n=82) Number (%)
Normal*	0	12 (14)
Diffuse infiltrate/opacities*	90 (91)	53 (65)
Cavity*	39 (39)	15 (18)
Pleural effusion*	3 (3)	14 (17)
Miliary TB*	1 (1)	9 (11)
Hilar/Mediastinal lymph nodes	3 (3)	8 (10)
Others	7 (8)	8 (10)

\*=<0.01

Radiographs at the end of therapy were evaluated in 80 TB and 82 HIV-TB positive patients. Fibrosis was more often seen in HIV negative TB patients (42.5% vs 17.8%). Cavities persisted in 15% of HIV negative TB patients and 8.7% of HIV positive patients. Over all, more HIV patients had a normal chest radiograph at the end of treatment as compared to HIV negative patients (42.8% vs 1.2%; p<0.05), table 3.

**Table 3. Radiographic lesions at the end of treatment**

Type of Lesion	TB+ HIV- (n=80)	TB+ HIV+ (n=82)
Normal**	1 (1)	36 (43)
Diffuse infiltrate/opacities**	62 (76)	27 (32)
Cavity	12 (15)	6 (9)
Fibrosis*	34 (43)	15 (18)
Calcification	1 (1)	0
Hilar nodes	3 (4)	8 (10)
Pleural effusion or thickening	3 (4)	1 (1)
Miliary TB	1 (1)	2 (2)

\*=p<0.05, \*\*=<0.01

The number of radiographic zones involved was less in HIV positives compared to HIV negative TB patients both at the beginning (67% vs 34% with < 3 zones involved, p<0.05) and the end of treatment (87% vs 52.5% with < 3 zones involved, p < 0.05). Among HIV-positive patients, the median CD4 count in patients without cavitation was 87 (IQR 40 to 161) whereas in those with cavity, it was 252 (IQR 160 to 468) (p<0.01).

**Table 4. Comparison of radiographic features in HIV positive and negative TB patients reported in series from different countries**

Radiological Patterns	Brazil		Rwanda		Zimbabwe		Tanzania		Uganda		Present Study	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Opacities/Infiltrates	66	80	16	55	-	-	84	75	46	26	65	91
Lymphadenopathy	10	3	31	0	26	15	22	6	26	06	10	3
Pleural effusion	15	8	43	9	26	13	31	32	23	11	17	3
Cavitation	18	50	39	91	40	64	23	40	18	57	18	39
Miliary	8	2	-	-	-	-	-	-	7	0	11	1
Normal	8	6	-	-	-	-	-	-	-	-	14	0

Note=All values are in percentages

Of the 82 patients with HIV-TB, 46 (56%) had sputum smear graded as negative or 1 + and 36 (44%) of them had a smear of 2 or 3 + grading, while of the 99 TB patients 80 had smears graded as 2 + or 3 + (80%). Sixty percent of the patients with CD4 counts of less than 200 cells/mm<sup>3</sup> had zero or 1 + smear, whereas in patients with CD4 counts of more than 200 cells/mm<sup>3</sup>, it was 30 percent. However, there was no significant difference between the median CD4 counts of patients with zero and 1 +, or 2 + and 3 + smear grading.

Table 4 is a comparative chart showing the prevalence of different radiographic features in HIV positive and negative TB patients, in reports from different countries, mostly from Africa.

## DISCUSSION

Infection with HIV has now emerged as the most strongest risk factor for the development of active tuberculosis.<sup>1</sup> With the increasing prevalence of HIV infection in India, physicians need to be aware of the different manifestations of tuberculosis in HIV positive patients. This study highlights the fact that radiographic features of tuberculosis are significantly different in HIV infected patients compared to those who are negatives. Tuberculosis can mimic many diseases and *vice-versa*. In HIV-infected individuals the radiographic manifestations of pulmonary tuberculosis can be atypical or different and the diagnosis requires a high index of suspicion.<sup>2,3</sup>

Our study compared radiographic findings at baseline and at the end of anti-tuberculosis therapy in HIV positive and HIV negative patients with tuberculosis. The commonest radiographic presentations among HIV patients were diffuse soft parenchymal opacities followed by cavities, pleural effusion, miliary tuberculosis and hilar adenopathy. A normal radiograph was also more commonly seen in the patients, in comparison to none in the HIV negative patients. Cavities were more frequent among tuberculosis patients without HIV infection. The higher occurrence of cavities, opacities, and fibrosis after treatment in HIV-negative patients may be related to the stronger inflammatory response mounted by these individuals. Those HIV patients who had a cavity had a

relatively higher median CD4 than those who did not have cavitation. In a study by Tripathy *et al*, presence of cavitation was related to higher CD4 counts, indicating that a robust immune response is required for cavitation to occur.<sup>13</sup> Further, extra-pulmonary tuberculosis by itself was not associated with decreased CD4 but patients with a combination of pulmonary and extra-pulmonary tuberculosis had significantly lower CD4 counts.<sup>6</sup> Features of dissemination including miliary, mediastinal adenopathy did not show a relationship with CD4 counts possibly due to the small number of patients in this study. There was also no relationship between the grade of sputum smear positivity and the radiographic findings. A unique feature of our study was the comparison of the pre- and post- treatment radiographs, not previously described. The post-treatment radiographic appearances showed that 42.8% had returned to normal in the doubly infected group compared to only 1.2% in the pulmonary tuberculosis group.

The fewer radiographic zones involved initially as well as the higher frequency of normal radiographs, at the end of treatment, indicate the poor cellular inflammatory response and fibrosis mounted by HIV positive persons. It is also known that the tissues are teeming with mycobacteria in HIV positive patients, even though sputum specimen may be smear negative.<sup>7</sup> Examination of bronchoalveolar lavage from involved lung segments in such patients reveals a failure of recruitment and activation of CD4+ lymphocytes (impaired CD4 alveolitis) compared to pulmonary tuberculosis patients seronegative for HIV. This may explain the paucity of consolidation and opacities seen. A number of HIV induced defects in granuloma assembly and function including impaired chemotaxis and proliferation of IFN- $\gamma$  secreting clones and decreased bactericidal activity of macrophages resulting in reduced granuloma formation, caseation and liquefaction which precede cavitation. Failure of containment and early and widespread dissemination may explain the increased prevalence of miliary tuberculosis in HIV patients.<sup>14</sup>

An earlier study from south India showed that cavitary form of pulmonary tuberculosis was seen in 8% of HIV patients and the miliary in 5 percent.<sup>11</sup> Studies by Debnath *et al*<sup>12</sup> showed that effusion (20% vs

10%) and miliary pattern (20% vs 10%) were more frequent, while cavitary forms were relatively less (8% vs 30%) in HIV-positive patients. Similar results have been reported from other studies in India<sup>15-17</sup> and various parts of the globe<sup>4-10</sup> (Table 4).

The presence of atypical and unusual lesions poses a clinical challenge. A negative tuberculin skin test may reflect the immunodeficiency status and does not rule out the presence of active tuberculosis. Sputum culture and blood culture may aid in the diagnosis in difficult cases. Mycobacteremia may be an uncommon event in immunocompetent individuals but an important cause of PUO in HIV infected patients as the CD4 declines. Ramachandran *et al* have reported a 10% positivity rate in isolating TB bacilli by blood culture in patients with CD4 below 100 cells/mm<sup>3</sup>.<sup>18</sup> The diagnosis of TB in HIV positive persons, therefore, requires a high index of suspicion and a combination of clinical, radiographic and bacteriologic investigations. While there could be a variety of infectious and non-infectious causes for an abnormal chest radiograph, a normal radiograph does not rule out tuberculosis. Efforts should be made to develop a clinical diagnostic algorithm to diagnose TB, which could be used in resource - constrained settings.

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# Evaluation of the Technical Details of Bronchoscopic Endobronchial Sealing: Review of 67 Patients

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## ABSTRACT

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**Background.** Management of haemoptysis not responding to conservative management is often difficult. Bronchial artery embolisation is costly and often not accessible, especially in the resource poor areas. Hence, surgery often remains the only therapeutic option despite its high morbidity and mortality. Therefore, an alternative easy but effective therapy is required. Endobronchial sealing is a recently described new method of therapy for haemoptysis.

**Methods.** We carried out transcatheter endobronchial sealing procedure using an injection of n-butyl cyanoacrylate in 67 patients of haemoptysis with the help of a fiberoptic bronchoscope. The patients were followed up for a mean period of six months to document the recurrence of bleeding or other complications.

**Results.** The success rate on long term follow up was 79.1 percent. There were procedure failures in 21.9%; the cause being false localisation (46.15%), proximal or inappropriate placement of the glue (30.79%) and difficult cannulation (23.0%).

**Conclusions.** Endobronchial gluing with n-butyl cyanoacrylate appears to be an efficient, safe and simple method for treating haemoptysis. The success depends on the proper identification of the bleeding bronchus and the appropriate placement of the glue. [Indian J Chest Dis Allied Sci 2007; 49: 137-141]

**Key words:** Haemoptysis, n-butyl cyanoacrylate, Endobronchial sealing.

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## INTRODUCTION

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Haemoptysis not responding to conservative management is often dealt with different bronchoscopic procedures. They include balloon tamponading of the bleeding bronchus,<sup>1</sup> local bronchoscopic instillation of haemostatic agents such as adrenaline,<sup>2</sup> fibrinogen thrombin,<sup>3</sup> thrombin,<sup>4</sup> or an ice-cold saline lavage.<sup>4,5</sup> But, none of these have qualified for widespread use. Endobronchial sealing of bleeding bronchus with cyanoacrylate glue is a new procedure reported recently.<sup>6</sup> We have tried this method on 67 patients to standardise the technical details, evaluate the causes of failures and to determine the efficacy of the procedure.

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## MATERIAL AND METHODS

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The study was carried out in a nursing home at Kolkata, India between February 2001 and March 2004. The initial selection was restricted to those patients with haemoptysis who continued to bleed despite an optimum conservative management for over seven days. Later we included patients not responding to conservative therapy for 48 hours or so. Patients with

profuse bleeding were not included as the chance of visualisation would be difficult and induction of cough would cause more bleeding while doing flexible bronchoscopy. Also patients with clinical or laboratory evidence of systemic coagulopathy or haemodynamic instability, and those not willing to sign the informed consent or otherwise having any serious problem that was a contraindication as per the American Thoracic Society Guidelines for fiberoptic bronchoscopy<sup>7</sup> were excluded. Any patient with radiological or bronchoscopic suspicion of malignancy was also not included. Thus out of 76 patients admitted or being referred for haemoptysis, a total of 67 patients (58 males and 9 females) were included. Blood loss was estimated from the statement of the patient and their relatives in terms of tea cup (with a capacity of 60 ml) while loss after admission was measured by collecting it. The patients were investigated with a chest radiograph (postero-anterior view), haemoglobin, packed cell volume, total and differential counts, prothrombin time, partial thromboplastin time, platelet count and creatinine. Sputum smear examination for acid-fast bacilli (AFB) was done only in suspected cases of tuberculosis. High resolution computed tomographic (HRCT) scan of chest was an optional evaluation for those who could afford it

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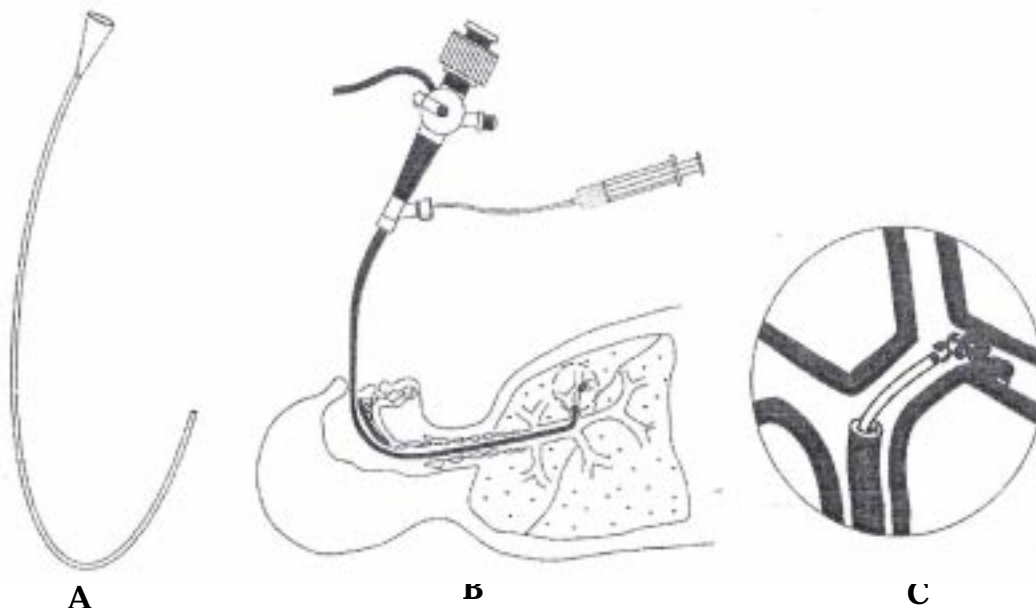
(done in eight cases). As the primary aim was to arrest the bleeding and to establish the validity and technical details of the procedure of endobronchial gluing developed by us,<sup>6</sup> extensive efforts to establish the cause were not made other than the above evaluations. One patient had a tracheal growth found during bronchoscopy. This patient was excluded also from the list.

Fiberoptic bronchoscopy was carried out usually in the morning hours after an overnight fasting or nil orally for at least three hours (except for two cases with a relapse of bleeding). The patients were prepared with sublingual alprazolam (0.25 mg) and 2% xylocaine nebulisation for 20 minutes. A Pentax 18P (Pentax, Tokyo, Japan) bronchoscope was introduced transnasally. We used an intra-airway spray of lignocaine (2% solution) as and when necessary to suppress coughing. Thereafter, blood and clots from the tracheo-bronchial tree were cleared with saline and the bleeding segment/sub-segment/site were approached slowly. The detection of the bleeding bronchus was confirmed by any of the following: (i) direct visualisation of the bleeding from a specific segment/subsegment; (ii) bleeding on removal of a tightly fitted clot from a suspected bronchus; (iii) bleeding on asking the patient to cough; (iv) bleeding on applying suction over a suspected bronchus; (v) active bleeding on cannulating a suspected bronchus; and (vi) finding a tightly fitted clot in a particular bronchus in non dependent area or a blood clot and old blood seen in an area suspected from the radiological investigations.

After the identification, a polyethylene catheter with an outer diameter of 2 mm was then passed through the

bronchoscope channel (2.2 mm) to place it slowly into the bleeding segment/bronchus (*see Figure*). Then the bronchoscope was withdrawn for two to three centimeters over the catheter keeping the catheter tip in the bleeding bronchus. Subsequently, 0.25 ml or 0.5 ml of n-butyl cyanoacrylate glue (Nectacryl, Dr. Reddy's Laboratory, India) was injected through the catheter slowly into the bronchus, followed by an injection of about 3 ml of air to flush the glue from the catheter lumen. The bronchoscope was then withdrawn quickly along with the catheter. Thereafter, the tip of the catheter was pulled out for a few more centimeters of its length distally to cut it with a pair of sharp scissors closed to the tip of the bronchoscope. Following this, the part of the catheter in the channel was pulled out sharply. The tip of the bronchoscope was then examined thoroughly for adherent glue, if any, and was cleaned with a sterile saline swab, before it was introduced again to confirm the absence/stoppage of bleeding. Non visibility of the glue assured desired and distal placement. The same procedure was repeated until the haemostasis was achieved to our satisfaction.

In case of rapid oozing of blood leading to difficulty in visualisation, instillation of adrenalin solution (1:20,000) or wedging or temporary suspension of the procedure was done as and when required. Oxygen supplementation was used, whenever it was necessary. Post procedure, the patients were given cough suppressant (dexamethorphan), whenever required for the next 3-5 days. The patients were meticulously observed for recurrence of bleeding and complications and were discharged following a period of observation for next 24 to 48 hours or even earlier, if there was no



**Figure.** Panel A shows the cannula used for instilling glue intrabronchially; Panel B shows the bronchoscope is placed at the origin of the bleeding bronchus and the cannula is passed deep into it followed by injection of the glue; and Panel C is the magnified view of cannula in the bronchus.

bleeding and if re-admission or re-intervention without delay could be arranged easily. We classified the relapse of bleeding as (i) early (relapse of bleeding before 48 hours of the procedure), (ii) delayed (relapse of bleeding between 48 hours to 7 days), and (iii) remote (relapse of bleeding beyond 7 days). All cases of relapse of bleeding (early and delayed) were tackled as before and attempt was made to determine the cause of the relapse in these.

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## RESULTS

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A total of 58 males and nine females with a mean age of  $49 \pm 17.27$  years were treated out of 76 patients admitted with haemoptysis. The mean duration of bleeding was  $12.2 \pm 9.26$  days with a mean volume of blood loss of  $555.22 \pm 506.09$  millilitre. The mean haemoglobin level was  $9.3 \pm 3.16$  g% with the mean packed cell volume of  $26.8 \pm 6.32$ . The source of bleeding was found to be predominantly from the right lung (62.68%), and most frequently from the posterior or apico-posterior segment of the upper lobes (47.8%), followed by the right middle lobe or lingular segment of the left upper lobe. We applied several methods to detect the sub-segmental source of bleeding. Oozing was obvious from the site in 32 patients (47.7%). In the remaining, one or more of the following findings guided us to the source of bleeding. Tightly fitting clot showing oozing after removal identified the bleeding bronchus in 15 (22.4%). Bleeding after induction of cough, cannulation of the suspected bronchus, and following application of suction helped to confirm the source in 14 (20.9%), six (8.9%) and four (5.9%) cases respectively. Deeply seated but loose clots were found in 35 (52.2%) of patients and in many of them, this appeared to be from blood pooled out of spillage from another area. These could be removed easily without producing any fresh oozing. On three occasions, because of difficult visualisation for active oozing, we had to suspend the procedure temporarily for about 30 minutes and then try it slowly but more cautiously again. In four patients it took more than 30 minutes to clear the clot slowly and reach the site of bleeding. In four patients, we sealed one or two adjacent sub-segmental bronchus or bronchi in the same sitting when there were doubts on the identification of the exact source. Radiological evaluation helped us in seven (10.4%) patients; one of them had a right upper lobe fibrotic scar and the rest had some local abnormalities in the form of bronchiectasis, consolidation, features of haemorrhage or infiltration.

Instillation of adrenalin solution (1 in 20,000) was used whenever required to slow the oozing and it helped in 17 (25.3%) cases. In three patients, the detection was obvious on removal of clots; the use of adrenalin solution and wedging together helped in these. The immediate success of the procedure appeared

to be 100 percent. A successful haemostasis was assumed by observing no bleeding following instillation of the glue before completing the procedure.

The patients were contacted on phone or through messenger to ensure a follow up visit whenever needed. Two patients (out of 67) did not visit us again; they had no recurrence according to telephonic contact. However, bleeding recurred in 17 patients within six months of follow-up. These cases were of early bleeding (13 patients), delayed bleeding (two patients) and remote bleeding (two patients). Out of 13 early re-bleeders there was one patient who expectorated loose and slightly blackish bloody material (15-20 ml) in the first few hours of the procedure. Repeat bronchoscopy within six hours showed no abnormality. We inferred it as expectoration of blood pent up inside the lungs and the patient responded to conservative treatment very well before being discharged on the 4th day following the procedure. This patient was excluded from the list of cases of relapse of bleeding. All the early relapse cases were re-examined with fiberoptic bronchoscopy within 24 hours and treated with the same technique of endobronchial sealing. Three patients required more than one (two) repeat procedures.

The causes of relapse of bleeding were analysed. In two patients with remote bleeding, it was recurrence from the same site that was found earlier. Both of them eventually required surgical resection of the affected bronchiectatic areas. It was a procedure failure in 14 cases; they had bleeding from the same area of the initially glued bronchus. The same procedure was repeated and they had no recurrence on subsequent follow up of more than six months. The reasons of such procedures failure were also analysed. There was false localisation in six, difficult cannulation in three and proximal or improper placement of glue in five cases. Two cases of delayed recurrence of bleeding were inferred as improper placement of the glue and in both of them repeat bronchoscopy revealed the bleeding source to be the same. On subsequent sealing, there was no more recurrence.

Further analysis of the cases of false localisation shows that the problem was improper identification of the source of bleeding. Mistake in identification was mostly in the same lobe or between adjacent segments of two different but adjacent lobes. Such mistakes took place mostly in the upper lobes (three on left side, two on right side) and a single case at the lingular lobe. On repeat gluing we had to seal multiple adjacent sites in two patients as there were difficulties in precise identification. None of the cases with repeated gluing required the intervention again.

The placement of the cannula was a problem in three cases, two of them required a repeat procedure twice. In one patient, the oozing was from a sub-segment of the posterior segment of the left upper lobe; the cannulation was done successfully using a thinner bronchoscope (Pentax 15P instead of 18P). Similarly, in another patient,

the cannulation was successful on second attempt for a bleeding sub-segment of the posterior division of the right upper lobe. In the third case, the placement of the cannula was impossible since the blood was coming from a small bronchus perpendicular to the posterior segmental bronchus of the right upper lobe. We flushed the whole area with 1 ml glue keeping the catheter tip at the proximity of the bleeding bronchus; there was no recurrence of haemoptysis.

Excluding the case of suspected pent-up bloody expectoration, most of the patients coughed out small old clots: 60% (40 cases) of these experienced cough requiring treatment with dextromethorphan and they reported granular watery expectorate for upto one week of the procedure.

The overall success of the procedure was 79.1% considering the early and delayed recurrence of bleeding as procedure failure.

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## DISCUSSION

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Management of haemoptysis at times poses a serious challenge. In cases of intractable haemorrhage; the treatment options are either bronchial artery embolisation or surgery. Transcatheter embolisation of bronchial artery is an established mode of treating massive haemoptysis with immediate control of bleeding in 75 to 90% of cases.<sup>11-13</sup> The results are further improved with super selective catheterisation.<sup>14</sup> However, the procedure is costly and technically difficult, sometimes not successful, and not easily available in most parts of the developing world.<sup>12,13,15,16</sup> In addition, it has definite complications.<sup>15</sup> When the scope of embolo-therapy is limited, surgery becomes the only plausible solution. Surgery is also recommended when bronchial embolisation is technically impossible or is unsuccessful or when the bleeding is so massive that any delay may be risky and also when the underlying putative cause is unlikely to be controlled by embolisation. However, surgery has significant mortality and morbidity related to it.<sup>5</sup>

Apart from these options, several bronchoscopic techniques have been attempted to ensure haemostasis. These include cold saline lavage with 50 ml aliquot or of iced saline at 4 °C (total of 500 ml),<sup>4</sup> wedging the bleeding segment with the bronchoscope tip to control bleeding after transbronchial biopsy,<sup>2</sup> local administration of adrenalin solution (1 in 20,000),<sup>2</sup> thrombin,<sup>3</sup> and fibrinogen-thrombin,<sup>3</sup> balloon tamponading of the bleeding bronchus.<sup>17,18</sup> Usually, the bronchoscopic techniques are used in control of iatrogenic bleeding and have not gained widespread acceptance for the management of haemoptysis when surgery or embolotherapy remains the currently recommended options.

Endobronchial gluing with n-butyl cyanoacrylate is a recent innovation that we used to manage six patients

of haemoptysis who failed to respond to conservative treatment for at least seven days.<sup>7,20</sup> We also reported successful treatment with endobronchial sealing in a case with massive haemoptysis.<sup>19</sup> The glue-n-butyl cyanoacrylate is biocompatible, solidifies quickly on exposure to moisture, has got an additional antibacterial effect<sup>21</sup> and is prothrombotic.<sup>22,23</sup> It has been used successfully in various deep tissue procedures including lung and heart surgery and also in treating variceal bleeding with high degree of success and safety.<sup>24-27</sup>

Proper placement of the glue is very important for the success of the procedure. As the glue does not probably stick on intact mucosal surface for a long time and the visibility of the glue following the procedure was found to be associated with procedural failure in many patients, we adopted a policy to place the sealant as distally as possible that improves chances of success. It is possible that the glue finds a raw area with blood to stick to it for a longer time or it enters into smaller bronchial branches and stays there for enough time to serve the purpose of haemostasis and healing. Patients may expectorate slightly opaque granular material within a few days of gluing; this may be the degraded glue. We have never faced any problem of atelectasis following the procedure. Distal placement of a small volume of the sealant and the sealing being likely a temporary phenomena, may explain this.

As our objective was to evaluate the technical details and outcomes of endobronchial gluing; and due to resource restraints, only limited efforts were made to establish the aetiology of bleeding. There was no coagulopathy in any of the patients. Endobronchial growth/suspected malignancies were practically excluded by chest radiograph. One patient having tracheal growth detected at bronchoscopy was also excluded. Only three out of 67 patients had confirmed pulmonary tuberculosis and 27 out of 67 patients had non-specific small patchy opacities suggestive of scar or pent up blood. It is interesting to observe that the upper lobes were the commonest site of bleeding. It is likely that in many of them were could be post infective scars or bronchiectasis. In two cases there were some consolidations that corresponded to the site of bleeding and subsequently resolved on treatment with antibiotics. Due to these limitations, a cause-specific analysis of outcome is not possible.

The amount of blood loss was variable in our patients with a mean 555.22 ml and a mean duration of 12.2 days. Less than half the patients required blood transfusion. The bronchoscopic approach was used more often for financial than medical reasons. It was offered as a practical option and the patients accepted it well.

In spite of the above limitations we believe that this treatment requires further evaluation due to the high success rate. It must be emphasised that the procedure is often not successful, if the bleeding is scanty. Our experience of performing it is limited in patients with

acute massive bleeding. We were able to do the procedure in a ward with limited instruments and the resuscitative facilities. It is possible that in a better equipped centre and a better protocol, the scope of the procedure can be expanded and its place in the management of haemoptysis can be defined.

Although cyanoacrylates are significantly safe, they are volatile and chemically active materials reported to cause eczema, rhinitis and asthma on occupational exposures.<sup>28</sup> Occupational contact dermatitis has also been reported.<sup>29</sup> Apart from endobronchial gluing there has been a recent report of another form of endobronchial topical haemostatic therapy (THT) with placement of oxidised regenerated cellulose with the help of rigid bronchoscope using general anaesthesia.<sup>30</sup> It has claimed a high initial success rate (100%) with about 10% chance of re-bleeding and 9% post obstructive pneumonia. The endobronchial sealing developed by us is simpler as it does not require general anaesthesia, and repeat procedures are not difficult because there is no problem of visualisation as is usual in cellulose THT. Further, we have not come across any post obstructive pneumonia.

In conclusion, n-butyl cyanoacrylate endobronchial gluing gives a success rate of about 80% percent. Give its relative ease, efficacy, low-cost and high safety, the procedure may substitute for bronchial artery embolisation in certain circumstances or it may be attempted where embolotherapy is not available or possible.

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# Epidemiological Aspects of Chronic Bronchitis in Shimla Hills

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## ABSTRACT

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**Objectives.** To study the prevalence and epidemiological aspects of chronic bronchitis in the rural and urban population residing in Shimla hills, and its relationship with various risk factors.

**Methods.** A cross-sectional study was conducted on 1330 subjects above 18 years of age in urban and rural areas of Shimla District, Himachal Pradesh. The study sample was selected equi-proportionately from rural and urban areas. Chronic bronchitis was defined based on clinical case definition given by Medical Research Council (MRC). A proforma based on MRC questionnaire was designed and pre-tested in both urban and rural population. Later, peak expiratory flow rate (PEFR) was measured for the cases diagnosed from the questionnaire.

**Results.** The overall prevalence of chronic bronchitis based on clinical case definition was 9.1 percent. The prevalence of chronic bronchitis was significantly more in males (11.1%) as compared to females (6.1%). It increased with age and was greater in rural areas (13.5%) as compared to urban areas (4.7%). Non-filtered cigarette smokers had significantly higher prevalence of chronic bronchitis as compared to filtered cigarette smokers.

**Conclusions.** After adjusting for other variables, prevalence of chronic bronchitis was significantly associated with heating source, age, area of residence and lower socio-economic status. [Indian J Chest Dis Allied Sci 2007; 49: 143-147]

**Key words:** Prevalence study, Chronic bronchitis, Clinical case definition.

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## INTRODUCTION

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Chronic bronchitis has been recognised as a major public health problem worldwide. In Great Britain, it is still the most common fatal respiratory disease, the number of deaths from this condition exceeding those from lung cancer. It was initially called as "chronic non specific lung disease".<sup>1</sup> Fletcher<sup>2</sup> defined it as a chronic cough with expectoration associated with recurrent attacks of infections of lower respiratory tract especially during winters, not caused by any specific or localised disease and present on most days for at least three months in a year for at least two consecutive years.

The prevalence of chronic bronchitis is showing an upward trend in most countries and the trend is likely to increase in future due to rapid urbanisation, increasing life expectancy, changing life styles and behavioural patterns. Developing countries are now warned to take appropriate steps to avoid the "epidemics" of such non communicable diseases likely to come with socio-economic and health development.<sup>3</sup> The prime objectives of the present study were to estimate the prevalence of chronic bronchitis among rural and urban

population of Shimla hills (Himachal Pradesh), and to study the relationship with various risk factors.

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## MATERIAL AND METHODS

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The study was conducted from January 2001 to December 2002 among rural and urban population of Shimla hills (Height 2148 meters) located in Northern India. In the study, Shimla city represented urban population and Basantpur Block (rural field practice area of Department of Community Medicine in district Shimla represented the rural population. The questionnaire was administered equi-proportionately in rural and urban areas (*i.e.*, 665 each in urban and rural area).

A sample size of 1330 was calculated based on a maximum allowable error of 20% and confidence limit of 95 percent.<sup>4</sup> The sample was equally drawn from urban and rural areas. Both males and females aged 18 years and above were included. Five sub-centre villages and seven wards were chosen using a simple random sampling technique out of a total 16 sub-centre villages and 25 wards, respectively. Thus, each selected ward

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was allocated a sample size of 95 whereas each sub-centre village was allocated a sample size of 133. Households were randomly selected in the study area. For selection, the Investigator reached the center of the selected village and a glass bottle was rotated on a hard surface. The direction in which the mouth of bottle pointed on stopping was chosen as the direction for survey. The last digit of a hundred rupees note was taken as the first household in that direction. Then every 3rd household was selected in the study sample. When the row of houses in a particular direction came to an end, the investigator took the left turn and proceeded in a similar manner until the required number of households was selected.

A proforma based on Medical Research Council (MRC) Questionnaire<sup>2</sup> and a Questionnaire developed by Department of Pulmonary Medicine, P.G.I., Chandigarh was designed and translated into local (Hindi) language. Necessary modifications were made after pre-testing and pilot-testing in both rural and urban population. The objectives and methods of the study were explained to each of the subjects and informed consent was obtained. No hazardous procedures were carried out and the confidentiality of the information was maintained. Questions were asked as per the study proforma and a detailed clinical examination of chest and a peak expiratory flow rate (PEFR) measurement by Wright's peak expiratory flow rate meter of the clinically confirmed cases was done.

Smokers were defined as those who regularly smoked one or more cigarettes or equivalents (*beedi*, tobacco and *hookah*) a day for at least one year. Smoking index was calculated as number of cigarettes smoked per day multiplied by duration of years of smoking.<sup>5</sup> The criteria for diagnosis of chronic bronchitis were followed strictly as prescribed by Medical Research Council, 1965 for symptoms which included history of cough with phlegm production for more than three months a year for atleast two consecutive years.<sup>2</sup> Campbell criteria were used for presence of physical signs.<sup>6</sup>

## Statistical Analysis

Analysis was done using the in SPSS software after checking for completeness and consistency of data. Association between categorical variables was determined by using Chi square tests. Multivariate analysis was done using logistic regression. Student's t test was performed for quantitative variables. A p value of less than 0.05 was considered to be significant.

## RESULTS

Out of the 1330 subjects, 791 (59.47%) were males and 539 (40.52%) were females. Majority of the population was in the age group of 18 to 30 years (42%). The

percentages in age groups 31-40, 41-50, 51-60 and greater than 60 years were 25.4%, 15.1%, 9.0% and 8.4%, respectively. A large number of the population surveyed was unemployed (45.9%). Among those employed, the majority consisted of government servants (24.5%) and agriculturists (10%). In the rural areas, 140 (21%) were illiterate, out of which, 98 (70%) were females and 42 (30%) were males. But in the urban areas, only 95 (14.3%) were illiterates. Most of the families (45.3%) belonged to Class IV of the Modified Prasad Classification<sup>3</sup> in rural areas (per capita monthly income Rs.330.00 to Rs.659.00) and Class I (38.2%) in urban areas (per capita monthly income > Rs.2200.00).

Based on the clinical case definition, 121 (9.1%) out of the 1330 subjects were identified to have chronic bronchitis (Table 1). The most common symptoms were morning cough (11.4%), cough with sputum (10.2%) and breathlessness (7.1%). These were followed by yellow coloured sputum (4.2%), wheeze (3.9%), pain chest (3.4%), paroxysmal nocturnal dyspnea (2%) and haemoptysis (0.7%). For the 121 cases of chronic bronchitis, the mean age, height, and weight were 47.36 years, 155.07 cm and 51.70 kg, respectively. Mean peak expiratory flow rate of the cases was 155.6 L/min (SD± 38.59).

The prevalence of chronic bronchitis increased with age. The highest prevalence of chronic bronchitis was

**Table 1. Relationship of chronic bronchitis with various epidemiological variables**

Age Group (in years)	Population Studied	Number of Patient (%)
18-30	559	10 (1.8)
31-40	338	22 (6.5)
41-50	201	19 (9.4)
51-60	120	27 (22.5)
>60	112	43 (38.4)
	<b><math>\chi^2 = 181.166</math></b>	<b><math>p &lt; 0.001</math></b>
<b>Occupation</b>		
Labourer	97	21 (21.6)
Agriculturist	133	28 (21.1)
Businessmen	49	5 (10.2)
Shopkeeper	115	8 (6.9)
Govt. Servant	326	27 (8.3)
Unemployed	610	32 (5.2)
<b>Literacy Status</b>		
Illiterate	235	47 (20)
Literate	1095	74 (6.7)
	<b><math>\chi^2 = 41.023</math></b>	<b><math>p &lt; 0.001</math></b>
<b>Socio-economic Class*</b>		
I	342	38 (11.1)
II	207	10 (4.8)
III	275	11 (4.0)
IV	408	46 (11.3)
V	98	16 (16.3)
<b>Total</b>	<b>1330</b>	<b>121 (9.1)</b>
	<b><math>\chi^2 = 23.539</math></b>	<b><math>p &lt; 0.001</math></b>

\*=Modified Prasad Classification

observed in the age group of greater than 60 years (38.4%). The distribution of chronic bronchitis was significantly higher in labourers (21.6%) and agriculturists (21.1%), in illiterates (20%) and among people in the lower socio-economic class (16.3%) (Table 1).

Table 2 shows that the prevalence of chronic

**Table 2. Relationship of smoking habits of chronic bronchitis cases with various epidemiological variables**

Variable	Cases		Total
	Smokers	Non-smokers	
<b>Sex</b>			
Male (S=376, NS=415)	87 (23.1)	1 (0.2)	88 (11.1)
Female (S=43, NS=496)	23 (53.5)	10 (2.0)	33 (6.1)
		$\chi^2 = 47.7$	$p < 0.001$
<b>Locality</b>			
Rural (S=190, NS=475)	82 (43.1)	8 (1.7)	90 (13.5)
Urban (S=229, NS=436)	28 (17.8)	3 (0.7)	31 (4.7)
		$\chi^2 = 659$	$p < 0.001$
<b>Cooking Fuel</b>			
No exposure (S=310, NS=365)	85 (27.4)	1 (0.2)	86 (12.7)
Coal (S=2, NS=12)	1 (0.5)	0 (0)	1 (7.1)
LPG (S=60, NS=291)	5 (8.3)	3 (1.0)	8 (2.3)
Wood/Cow Dung (S=42, NS=206)	19 (45.2)	6 (2.9)	25 (10.1)
Gobar gas (S=0, NS=7)	0 (0)	0 (0)	0 (0)
Electricity (S=0, NS=7)	0 (0)	0 (0)	0 (0)
Kerosene (S=5, NS=23)	0 (0)	1 (4.3)	1 (3.6)
<b>Total (S=419, NS=911)</b>	<b>110 (26.3)</b>	<b>11 (1.2)</b>	<b>121 (9.1)</b>
		$\chi^2 = 1675$	$p > 0.001$

\*=Figures in parentheses denote percentages

**Table 3. Multivariate step-wise regression analysis**

Model	Regression Coefficient (B)	T-value	Significance	R2	F Value	Significance
<b>Step-1</b>						
Constant	1.93	267.7	$p < 0.001$	0.266	481.2	$p < 0.001$
Smoking Index	-6.2	-21.9	$p < 0.001$			
<b>Step-2</b>						
Constant	2.05	139.7	$p < 0.001$	0.288	267.9	$p < 0.001$
Smoking Index	-6.0	-21.5	$p < 0.001$			
Heating Source	-4.2	-6.35	$p < 0.001$			
<b>Step-3</b>						
Constant	2.14	99.7	$p < 0.001$	0.304	193.0	$p < 0.001$
Smoking Index	-5.3	-17.6	$p < 0.001$			
Heating Source	-3.9	-5.9	$p < 0.001$			
Age	-2.7	-5.5	$p < 0.001$			
<b>Step-4</b>						
Constant	2.046	46.6	$p < 0.001$	0.307	146.9	$p < 0.001$
Smoking Index	-5.4	-17.8	$p < 0.001$			
Heating Source	-2.5	-2.8	$p < 0.001$			
Age	-2.6	-5.4	$p < 0.001$			
Area of Residence	4.4	2.5	$p < 0.001$			
<b>Step-5</b>						
Constant	2.05	46.6	$p < 0.001$	0.309	118.6	$p < 0.001$
Smoking Index	-5.4	-17.8	$p < 0.001$			
Heating Source	-2.8	-3.2	$p < 0.001$			
Age	-2.6	-5.2	$p < 0.001$			
Area of Residence	4.93	2.8	$P < 0.01$			
Income	-5.6	-2.0	$P < 0.01$			

Dependent variable – Chronic bronchitis

bronchitis was significantly higher among males (11.1%) as compared to females (6.1%) and in the rural population (13.5%) as compared to the urban population (4.7%). The prevalence was significantly higher ( $p < 0.001$ ) in subjects using wood/cow dung as cooking fuel (10%) as compared to those using coal (7.1%), kerosene (3.6%) and liquified petroleum gas (LPG) (2.3%). The prevalence of chronic bronchitis was significantly higher among smokers (26.3%) as compared to non-smokers (1.2%). Among smokers, it was significantly higher in females (53.5%) as compared to males (23.1%), in rural area (43.1%) as compared to urban area (17.8%), in agriculturists (43.3%) as compared to those with their occupations and those using wood/cow dung as cooking fuel (45.2%) as compared to other fuels users (8.8%) (Table 2). The comparison of smoker and non-smoker group with relation to various epidemiological variables is shown in table 2.

In the present study, the overall population attributable risk was 26.2% and was higher in females compared to males. Thirty-five (13%) cases were mild smokers (smoking index 1-100) and 75 (49.7%) cases were heavy smokers (smoking index  $> 300$ ). The difference in the prevalence of chronic bronchitis between the two groups was found to be highly significant ( $p < 0.001$ ). The prevalence of chronic bronchitis was found to be significantly higher among unfiltered cigarette smokers (41.2%) as compared to filtered cigarette smokers (14.8%).

It was observed that smoking, source of heating, age,

area of residence and income remained significantly associated with chronic bronchitis on step-wise univariate analysis while other factors turned out to be non-significant.

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## DISCUSSION

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The present study included population aged 18 years and above and gave an overall prevalence rate of 9.1 percent. The high prevalence of chronic bronchitis observed in our study is in conformity with earlier studies from northern parts of India (1% to 21%)<sup>7-10</sup> and other international studies (7% to 32%).<sup>11-13</sup> Differences in prevalence can be explained by differences in smoking habits, diagnosis and reporting of disease, genetic susceptibility and other environmental influences, such as poor ventilation and wood burning on respiratory health.<sup>7-11</sup>

Symptoms of chronic bronchitis (*i.e.*, cough and sputum) reported from United States<sup>14-15</sup> and Britain<sup>17</sup> are higher (10-48%) than in our study (10.2%) and studies of other developing countries (12%),<sup>18-19</sup> as subjects in these studies were more than 45 years of age and they had more exposure to industrial pollution.

It is a well established fact that there is a significant association between cigarette smoking and chronic bronchitis. This view is supported in studies by Medical Research Council (U.K.), Wig *et al*<sup>20</sup>, Viswanathan *et al*<sup>1</sup>, Bhattacharya<sup>9</sup> and Jindal *et al*<sup>10</sup>. In the present study, the overall population attributable risk was 26.2% and was higher in females. Other population based studies have given similar results with population attributable risk varying between 46 percent to 70 percent.<sup>21-23</sup> This is due to the fact that men and women differ with regards to their susceptibility to mucus hyper secretion when exposed to tobacco smoke.<sup>2</sup> In the present study, the prevalence of chronic bronchitis among heavy smokers was about four times greater than in light smokers. This association has been proved by majority of workers in their studies.<sup>8,20,24</sup>

The information on the relative effects of filter *versus* non-filter cigarette on pulmonary function is insufficient. In our study, it was observed that the prevalence of chronic bronchitis was greater among unfiltered cigarette smokers as compared to filtered cigarette smokers. Similar observations were also made in a study conducted in Brazil by Menezes *et al*<sup>25</sup>. A filtered cigarette delivers low yield of tar and nicotine, thus causing less broncho-constriction and minimal mucus formation in lungs. Moreover, it minimises the adverse effects of cigarette smoking on elastase-inhibitory activity of alpha-antitrypsin.<sup>20,25</sup>

In almost all studies conducted in India and abroad, prevalence of chronic bronchitis has been found to increase with age.<sup>8-10</sup> The results are similar in our study. Age related decline in lung functions and cumulative effect of smoking and other environmental factors on

pulmonary functions with age explains the increase in its prevalence.<sup>8</sup>

The high prevalence of chronic bronchitis among rural population (13.5%) as compared to urban population (4.7%) in our study is in conformity with a study by Yamaguchi *et al*.<sup>26</sup> Most of the subjects in rural areas are agriculturists and thus exposed to various allergens and dusts, that are incremental in the causation of chronic bronchitis. Moreover, they are exposed to indoor air pollution, especially from unvented cooking fuel.<sup>26</sup> Higher prevalence of chronic bronchitis among rural smokers (43.1%) than in urban smokers (17.8%) in our study may be due to the confounding effects of occupation and greater exposure to biomass fuel.

Chronic bronchitis in general was seen more often among the poor social groups because of several adverse environmental conditions such as poor housing, over crowding, inhabitation in the more polluted areas of the city and higher prevalence of smoking.<sup>25-29</sup> In our study, prevalence of chronic bronchitis was significantly higher in the extremes of social class, *viz.* socio-economic class I (11.1%) and class V (16.3%) of Modified Prasad's classification (based on per capita income).<sup>3</sup> It was seen in the study that the extremes of the classes indulged in smoking more frequently than middle class population. Further, in higher socio-economic class, greater access to medical care and consequently greater likelihood of recognition and diagnosis of chronic bronchitis may possibly lead to increased diagnosis of chronic bronchitis.

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## CONCLUSIONS

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The overall prevalence rate of chronic bronchitis in the sample selected in Shimla is 9.1 percent. Prevalence of chronic bronchitis was significant related to smoking, source of heating, age, area of residence and income. Smoking is a leading risk factor in causation of chronic bronchitis and measures should be taken to discourage the habit at teenage.

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# New Approach to the Treatment of Lung Cancer: The Molecular Targeted Therapy

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## ABSTRACT

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Lung cancer is a leading cause of death worldwide and is increasing both in the developed and developing nations including India. A large proportion of these cases are diagnosed with advanced or metastatic stage. Although chemotherapy can extend life and provide good quality of life with palliation, the median survival time remains poor. A number of good regimens provide similar benefit to patients with stage IIIB/IV non-small cell lung cancer. On the other hand, there are inherent risks associated with such therapy. Thus, there is a need for newer agents to tackle advanced lung cancer. Remarkable progress has been made in the recent times in identifying molecular targets for cancer drug development. A number of such agents that target compelling pathways involved in lung cancer growth and progression have been identified and used in clinical practice recently. It is hoped that addition of such novel targeted agents to conventional chemotherapy would produce significant survival benefit for patients with advanced non-small cell lung cancer. These agents include inhibitors of the epidermal growth factor receptor (EGFR) vascular inhibitors endothelial growth factor (VEGF), and the proteasome, as well as other agents. This review gives a brief account of these agents. [Indian J Chest Dis Allied Sci 2007; 49: 149-158]

**Key words:** Lung cancer, Chemotherapy, Drug, Epidemic, Surgery, Malignant.

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## INTRODUCTION

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Lung cancer is the most commonly diagnosed malignancy in the world today.<sup>1</sup> It has been the most common cancer in the world since 1985<sup>2</sup> and; by 2002 there were 1.35 million new cases, representing 12.4% of all new cancers. It is also the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the world total. Almost half (49.9%) of the cases occur in the developing countries — a big change since 1980, when it was estimated that 69% of the cases were in the developed countries. Worldwide, it is by far the most common cancer of men, with the highest rates observed in North America and Europe (especially Eastern Europe). With increasing prevalence of smoking, lung cancer has reached epidemic proportions in India. It has surpassed the earlier commonest form of cancer of oropharynx and now is the commonest malignancy in males in many hospitals as documented by the Cancer Registry and Cancer Atlas programmes of the Indian Council of Medical Research. Majority of the Indian patients have locally advanced or disseminated disease at presentation and are not candidates for surgery. Chemotherapy applied as an adjunct to radiation improves survival and the quality of life to some extent but that is not very impressive. New anti-cancer drugs,

which have emerged during the last decade, have shown an improved efficacy-toxicity ratio.<sup>3</sup>

The treatment of lung cancer can be summarised as given in the table. In advanced non-small cell lung cancer (NSCLC), which is most often encountered in clinical practice, chemotherapy offers symptomatic relief and modest improvement in survival.<sup>4</sup> No curative treatment is available for advanced disease (Stage III and IV non-small cell type) and chemotherapy is broadly used for the treatment at this stage. The drugs usually consist of a platinum-containing compound (cisplatin for carboplatin) combined with gemcitabine, a taxane (paclitaxel, docetaxel), or vinorelbine.<sup>5-8</sup> However even with these modern chemotherapeutic drugs, the response rates are poor with a median time to progression of only three to five months. Second-line chemotherapy with docetaxel can prolong survival marginally after platinum-based therapy for NSCLC.<sup>9,10</sup> At present, there is no defined role for the three-drug combination chemotherapy, and reports indicate unimpressive benefit.<sup>11,12</sup> The potential benefit of improved tumour size, symptoms, and quality of life are mitigated by the disadvantages of increased hospitalisation, inconvenience, cost and serious adverse events.<sup>13</sup> Survival at five years measured by the Surveillance Epidemiology and End Results (SEER)

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**Table. Treatment approaches to lung cancer**

Cell Type	Treatment Approach	Comments
Small cell lung cancer		
Localised disease	Chemo-radiotherapy	In patients with complete response, prophylactic cranial irradiation
Extensive disease	Chemotherapy	
Non-small cell lung cancer		
Stage I and II	Surgery	Adjuvant chemotherapy is superior
Stage IIIA	Neoadjuvant chemotherapy followed by surgery	
Stage IIIB	Local radiotherapy followed by chemotherapy Molecular targeted therapy	
Stage IV	Chemotherapy Molecular targeted therapy	

Chemotherapy for stage IIIB and IV disease can be of 1st line (any of the platinum-based combination therapy) or 2nd line (Docetaxel or pemetrexed)

programme in the United States is 15% the best recorded at the population level. The average survival in Europe is 10%, not much better than the 8.9% observed in developing countries. This information indicates that chemotherapy has not substantially altered the long-term outcome for most lung cancer patients in the past decade and it is likely that the results of chemotherapy have reached a plateau.<sup>12</sup> Despite some advancement, a plateau of effectiveness appears to have been reached for the treatment of NSCLC with standard chemotherapy,<sup>14</sup> and substituting one agent for another in combination chemotherapy regimens. It does not necessarily guarantee a significantly improved overall response rate and survival.<sup>15</sup> Therefore, there is a need for alternative form of therapy and the development of new treatment strategies.

There has been an explosion in our knowledge of the genetic and biologic understanding of lung cancer. Cancer results from an accumulation of genetic mutations and carcinogenesis and is a multi-step process reflecting genetic mutations that drives the normal human cells into malignant derivatives. This knowledge has provided many new targets for lung cancer therapy and prevention. Many of these targets involve the signal transduction pathways associated with changes in oncogenes and tumour suppressor genes. Receptor tyrosine kinase genes such as the erbB/HER family including erbB1 or the EGFR are excellent therapeutic targets.<sup>16</sup> Based on this information, newer molecular targeted agents are developed which have become a therapeutic reality. Such agents can be of the following types:

1. Targeting or intervening along the pathways of tumorigenesis—Epidermal growth factor receptor (EGFR) inhibitors (gefitinib, erlotinib and cetuximab)
2. Targeting angiogenesis and cell proliferation — Anti vascular endothelial growth factors (VEGF) (Bevacizumab, Celecoxib-a COX2 inhibitor, ZD6474)
3. Combination of 1 and 2.
4. Proteasome inhibition (Bortezomib)

5. Reginoid agonists (Bexarotene)
6. Apoptosis targets
7. Vaccines
8. Other targeting agents (Dipeptidyl peptidase inhibitor - talabostat; Farnesyl transferase-Lonafarnib)

### 1. Epidermal Growth Factor Receptor (EGFR) Inhibitors

Epidermal growth factor receptor, a member of the HER/Erb-B family of receptor tyrosine kinases, mediates cell proliferation, differentiation, survival, angiogenesis, and migration.<sup>17</sup> This molecule consists of an extra-cellular domain that binds EGF, transforming growth factor alpha (TGF- $\alpha$ ), and other growth factors; a short transmembrane region; and an intracellular tyrosine kinase domain. Ligand binding leads to homodimerisation of EGFR or heterodimerisation of EGFR with another receptor of the Erb-B family and phosphorylation of specific EGFR tyrosine residues.<sup>17</sup> Tyrosine-phosphorylated receptors then recruit intracellular signaling proteins, converting extra-cellular signals to intra-cellular signal transduction events. Epidermal growth factor receptor is expressed more abundantly in malignant than in normal tissues, and has been shown in 40%-80% of NSCLCs.<sup>18</sup>

There are two main types of EGFR inhibitors that are available currently: (i) monoclonal antibodies (MAbs) directed at the extra-cellular domain of the receptor, and (ii) small molecule intra-cellular EGFR tyrosine kinase inhibitors. The MAbs include drugs, like cetuximab, panitumumab (ABX-EGF) and matuzumab (EMD 72000). The later two are currently in early phases of investigation.<sup>19-22</sup> The kinase inhibitors gefitinib and erlotinib have been studied extensively throughout the world in different population groups.<sup>23</sup> Patient characteristics from these trials that have been associated with responsiveness to EGFR inhibitors include adenocarcinoma histology, female sex, absence of history of smoking, and Asian ethnicity.<sup>24</sup> Further, immunohistochemistry and FISH (Flourescent - *in situ*

hybridisation) studies on the somatic mutations in the regions of EGFR that encodes the tyrosine kinase domain of the receptor have identified subgroups of patients who will benefit from such therapy.<sup>25</sup> The presence of an EGFR mutation may increase responsiveness to the agent, erlotinib.<sup>26,17</sup> There is recent evidence of a correlation between epidermal growth factor receptor (EGFR) mutations at exons<sup>18-21</sup> and the clinical response of advanced non-small cancer to gefitinib therapy. Gefitinib is recommended in a dose of 250 mg per day and erlotinib in a dose of 150 mg per day.

### **Anti-EGFR MABs**

Antibodies generally have the advantages of less frequent administration, induction of receptor down regulation, the potential to engage the host immune response in direct tumour cell cytotoxicity, and a favourable toxicity profile (notably the absence of gastrointestinal adverse effects). Antibodies specific for EGFR are among the first targeted therapies to demonstrate effectiveness in treating cancer, including NSCLC.

### **Cetuximab**

The monoclonal antibody, cetuximab, is an IgG1 MAB that binds specifically and with high affinity to the extra-cellular portion of the EGFR and acts as a competitive antagonist, preventing endogenous ligand binding. This EGFR blockade affects all cellular functions implicated in tumour biology, such as cell proliferation, cell survival, DNA repair, tumour angiogenesis, cell motility, and cell invasion. Internalisation of EGFR may lead to down regulation of cell surface receptors and reduced receptor signaling. The drug also exerts an antibody-dependent cell-mediated cytotoxicity (ADCC). The drug is useful as a single agent as well as in combination with other concomitant chemotherapeutic agents. It is given as an initial 2-hour infusion of 400 mg/m<sup>2</sup>. On day 1, week 1 and subsequent weekly 1-hour infusions, starting at week 2, each of 250 mg/m<sup>2</sup>. All the above three EGFR antagonists are well tolerated with a good safety profile. The only notable adverse reaction is skin rash of mild to moderate severity.

Pre-clinical studies with cetuximab have shown that it enhances the activity of cytotoxic drugs<sup>28-30</sup> and radiotherapy.<sup>30-32</sup> This may be related to its ability to block the nuclear import of EGFR and activation of DNA-dependent kinase (DNA-PK) necessary for the repair of radiation- and chemotherapy-induced DNA damage. Early clinical studies in advanced NSCLC have reported promising responses for cetuximab administered as monotherapy or in combination with chemotherapy in chemotherapy-naïve and previously treated patients.

**Cetuximab Monotherapy.** A phase II study of cetuximab monotherapy in recurrent or metastatic EGFR-detectable NSCLC patients with one or more prior chemotherapy regimens demonstrated two of 29 (6.9%) partial responses and five patients (17.2%) with stable disease.<sup>33</sup> Similar response rates were shown in a subsequent phase II trial in patients with stage IIIB/IV recurrent or metastatic disease.<sup>34</sup> These studies showed that cetuximab is well tolerated, with rash being the most common toxicity.

**Cetuximab in Combination with Chemotherapy Regimens.** The efficacy of cetuximab plus chemotherapy has also shown good results. In a phase I study in advanced NSCLC two out of 19 patients (10.5%) receiving multiple doses of cetuximab plus cisplatin had shown partial responses.<sup>35</sup> A randomised, controlled trial in previously untreated patients with advanced, EGFR-expressing NSCLC showed higher response rates for the cetuximab plus vinorelbine plus cisplatin regimen than for the later two drugs alone (31.7% vs 20.00%).<sup>36</sup> In another study, cetuximab combined with docetaxel in chemotherapy-refractory/resistant NSCLC resulted in a 28% partial response rate and 17% stable disease rate.<sup>37</sup> Cetuximab added to paclitaxel plus carboplatin or to gemcitabine plus carboplatin in untreated NSCLC led to response rates of 26% and 28.6%, respectively.<sup>38, 39</sup>

Cetuximab has been shown to be well tolerated in all the clinical trials carried out till now. The most common treatment-related adverse effect, that occurs in most patients, is a self-limiting acneiform rash generally occurring in the first 2-3 weeks. The rash stabilises or resolves with continued therapy and disappears completely without scarring once the treatment is stopped. The occurrence of rash with cetuximab reflects the widespread distribution of EGFR in epithelial tissues, and a number of studies have reported a correlation between the rash and the response to cetuximab. Less commonly infusion reactions have occurred in some patients. These reactions generally respond to treatment with corticosteroids, anti-histamines, and bronchodilators administered alone or in combination and are rarely fatal (<1 in 1,000).

### **EGFR TKIs**

Small-molecule TKIs are another class of EGFR-targeted agents. The TKIs can be orally administered, have a rapid onset of action, and potentially have better tumour penetration than mAbs.<sup>15</sup> Among drugs of this class, the two most extensively evaluated in NSCLC are gefitinib and erlotinib. Both have demonstrated single-agent activity in NSCLC, and a greater sensitivity to either gefitinib or erlotinib has been correlated with somatic mutations in the receptor kinase domain and/or increased EGFR gene copy number. Other TKIs undergoing testing in early-phase clinical trials include PKI 166, GW 572016, EKB 569, and CI-1033.<sup>40</sup> In pre-clinical studies, all these agents inhibited the growth of

EGFR-expressing human cancer cell lines and showed additive or synergistic growth inhibitory effects when combined with chemotherapeutic agents or radiotherapy.

### **Gefitinib**

Gefitinib, an anilinoquinazoline, was the first TKI selective for EGFR evaluated in NSCLC. It is orally active and given once daily.

**Gefitinib Monotherapy.** Two randomised, double-blind trials of gefitinib monotherapy in daily doses of 250 mg or 500 mg given to patients with advanced NSCLC who had previously received chemotherapy regimens, the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL)-1 and IDEAL-2, showed objective response rates of 10 percent to 19 percent.<sup>41,42</sup> In both the studies, symptoms improved in 35%-43% of patients. Although no significant differences in efficacy were found between the 250 mg and 500 mg daily doses of gefitinib, adverse effects occurred more frequently with the higher dosage.<sup>41,42</sup> In the first study, greater efficacy was found in Japanese than in non-Japanese patients (27.5% vs 10.4%).<sup>41</sup>

Results from three institutional studies of single-agent gefitinib therapy used on a compassionate basis in patients with advanced NSCLC for whom standard treatment had failed or who were not suitable for systemic chemotherapy are available.<sup>43-45</sup> In the largest of these studies, involving 21,064 patients with stage III/IV NSCLC who received one or more doses of gefitinib, the median survival was 5.3 months, and the one-year survival rate was 29.9% percent.<sup>44</sup> These results are comparable with those obtained with chemotherapy in a second-line clinical setting.

A recent phase III randomised, multicenter study of gefitinib in refractory advanced NSCLC, the Iressa Survival Evaluation in Lung Cancer (ISEL) trial, concluded that gefitinib provided no significant survival benefit over the best supportive care across the total population of patients studied.<sup>46</sup> However, significant survival benefit was observed in specific sub-populations, including patients of Asian descent ( $n=342$ ; median survival 9.5 vs 5.5 months) and patients with no smoking history ( $n=375$ ; median survival 8.9 vs 6.1 months).<sup>46</sup> A study in patients with advanced bronchioalveolar cell carcinoma (BAC), a subtype of NSCLC with distinctive clinical, pathologic, and radiographic characteristics that is generally considered chemoresistant, found that single-agent therapy with gefitinib (500 mg daily) achieved tumour response rates of 21% and 10% in chemotherapy-naïve and previously treated patients, respectively. Median survival times were 12 and 10 months, respectively.<sup>47</sup> In the same study, increased EGFR gene copy number, as detected by fluorescence *in situ* hybridisation (FISH), was associated with longer survival (median survival > 18 months vs 8 months).

### **Gefitinib in Combination with Chemotherapy Regimens.**

Two double-blind, placebo-controlled trials, the Iressa NSCLC Trial Assessing Combination Therapy (INTACT)-1 and INTACT-2 trials, evaluated whether the addition of gefitinib to gemcitabine plus cisplatin or paclitaxel plus carboplatin provides additional clinical efficacy over chemotherapy alone in chemotherapy-naïve patients with advanced NSCLC. Both indicated no benefit from gefitinib in objective response rates or survival.<sup>48,49</sup> One potential explanation for the failure of gefitinib to provide clinical benefit is that concurrent cytotoxic agents abrogate its efficacy by directly or indirectly altering EGFR expression.<sup>50</sup> It has been suggested, therefore, that sequential therapy, in which chemotherapy regimens are preceded or followed by gefitinib, or intercalated therapy, in which higher doses of gefitinib are given as a bolus between chemotherapy regimens, may be better strategies. Trials to test these hypotheses are currently in progress.<sup>15</sup>

Preliminary results from other studies of gefitinib used in combination with chemotherapy have provided encouraging results.<sup>51-53</sup> In one study, in which gefitinib was given in combination with concurrent paclitaxel plus carboplatin and radiation therapy in patients with stage III NSCLC, a complete response rate of 27% and a partial response rate of 64% were achieved in 11 patients.<sup>51</sup>

Measurement of EGFR expression by immunohistochemistry was not useful for predicting responsiveness to gefitinib in patients enrolled in the IDEAL or INTACT studies.<sup>54,55</sup> However, immunohistochemistry coupled with FISH to detect increased EGFR gene copy number may help to predict which patients are likely to benefit from gefitinib therapy.<sup>56</sup> Other factors that might be predictive of responsiveness include a better performance status and the appearance of rash while on gefitinib treatment.<sup>57,58</sup>

Gefitinib has been generally well tolerated, with skin rash and diarrhea occurring in 40%-60% of patients. Other less common adverse effects include nausea, vomiting, pruritus dry skin, and asthenia.<sup>59,60</sup> Potential danger of gefitinib-associated lung toxicity (interstitial pulmonary fibrosis) in a subset of NSCLC patients with previous thoracic irradiation or poor performance status has also been reported.<sup>61</sup>

### **Erlotinib**

Like gefitinib, erlotinib is an orally-active, EGFR-specific quinazoline TKI that demonstrated anti-tumour activity in xenograft models.<sup>14,15,18,62</sup> In addition to the first-line treatment for advanced pancreatic cancer, erlotinib is currently approved for second-line treatment of locally advanced or metastatic NSCLC.

**Erlotinib as Monotherapy.** A phase II study of erlotinib (150 mg daily) in 57 advanced NSCLC patients demonstrated complete responses in 4% and partial response in 9% of patients. The median overall survival

time was 8.4 months, with a 40% one-year survival rate. Patients with skin rash survived significantly longer than those without rash, suggesting skin rash as a potential marker of erlotinib response.<sup>63</sup> Erlotinib (150 mg daily) resulted in a 25.4% partial response rate in 59 patients of bronchioloalveolar cell carcinoma. Greater erlotinib responsiveness was shown in non-smokers (37%) and adenocarcinoma with bronchioloalveolar cell carcinoma features.<sup>64</sup>

A recent double-blind, placebo-controlled phase III study comparing erlotinib with placebo in 731 patients with stage IIIB/IV NSCLC and one to two prior chemotherapy regimens [National Cancer Institute of Canada Clinical Trials Group, (NCIC CTG) trial BR. 21] reported the first evidence of an EGFR inhibitor prolonging survival in chemotherapy-refractory NSCLC.<sup>65,66</sup> Patients receiving erlotinib (n=488) at 150 mg daily demonstrated significantly longer overall survival (6.7 months vs 4.7 months) and progression free survival (2.2 months vs 1.8 months) than those receiving placebo. The overall erlotinib response rate was 8.9 percent. The median response duration was 34.2 weeks. Response rates were higher among specific subpopulations, including women, Asians, non-smokers, and patients with adenocarcinoma, reminiscent of similar results with gefitinib.<sup>66</sup> Response was associated with higher EGFR gene copy number, but no survival advantage was seen in patients with higher EGFR expression or mutations in exons 19 and 21.<sup>67</sup> Mutation frequency in EGFR or *K-ras* was not correlated with tumour sensitivity or responsiveness to erlotinib in one study.<sup>68</sup> In another study, nine out of 37 patients with EGFR mutations responded well to erlotinib, while four out of 34 patients with *K-ras* mutations did not respond to it.<sup>69</sup>

#### *Erlotinib in Combination with Chemotherapy Regimens.*

As with the gefitinib INTACT studies,<sup>48,49</sup> erlotinib showed no survival advantage when combined with a two-drug chemotherapy regimen. In a randomised, placebo-controlled study of 1,059 previously untreated advanced NSCLC patients, erlotinib (150 mg daily) with six cycles of paclitaxel plus carboplatin followed by maintenance monotherapy showed no significant differences in overall response rates, response duration, median survival, or time to progression compared with paclitaxel plus carboplatin alone.<sup>70</sup> However, patients who had never smoked showed a longer survival with erlotinib (23 vs 10 months).<sup>71</sup> A placebo-controlled study of erlotinib (150 mg daily) plus gemcitabine plus cisplatin in 1,172 patients with previously untreated, advanced NSCLC showed no improvement in overall survival or time to progression compared with gemcitabine plus cisplatin.<sup>72</sup>

Erlotinib tolerability is similar to that of gefitinib. Skin rash and diarrhea are the most common adverse effects.<sup>40</sup> Preliminary results of a study of erlotinib administered at 1,200, 1,600, or 2,000 mg weekly suggest that the 1,600 mg per week dose is tolerable for

advanced NSCLC patients refractory to previous chemotherapy.

## **2. Antiangiogenesis in NSCLC Treatment**

Angiogenesis is a very attractive target, especially the VEGF pathway including VEGF and VEGF receptors.<sup>73</sup> At least four isoforms of VEGF exist, VEGF-A through VEGF-D, and three isoforms of membrane-bound VEGF receptors have been identified (VEGFR-1, VEGFR-2, and VEGFR-3), each with distinct roles in angiogenesis. Several angiogenesis inhibitors have been studied in NSCLC. These include antibodies to VEGF and VEGFR and inhibitors of VEGFR tyrosine kinase.<sup>74</sup> The best-studied angiogenesis inhibitor is bevacizumab (rHumAb-VEGF), an anti-VEGF antibody that has been evaluated in combination with chemotherapeutic agents and erlotinib in advanced or recurrent NSCLC. Randomised phase II trials of bevacizumab in combination with chemotherapy suggested superior survival compared to chemotherapy alone. In a randomised, controlled trial involving 99 patients with previously untreated stage IIIB/IV or recurrent NSCLC, bevacizumab added to paclitaxel plus carboplatin improved the overall response and time to progression compared with paclitaxel plus carboplatin alone. The median time to progression was significantly greater for patients receiving a high-dose (15 mg/kg) bevacizumab regimen than those receiving a low-dose (7.5 mg/kg) regimen (7.4 vs 4.2 months). In contrast, no significant difference in time to progression was found for the low-dose bevacizumab group *versus* paclitaxel plus carboplatin alone.<sup>75</sup> However, there were more pulmonary haemorrhagic events in patients randomised to initial bevacizumab and these were most increased in patients with central tumours and squamous cell histology.

Several other humanised monoclonal antibodies to the VEGF receptor (VEGFR) are now in clinical trials. There are also several small molecule tyrosine kinase inhibitors of VEGFR that are currently in clinical trials. Several of these inhibit other tyrosine kinases as well. For example, ZD6474 inhibits both VEGFR and EGFR. Phase I and II trials have shown objective responses to ZD6474 and clinical trials are continuing. The ZD6474 is an orally available inhibitor of the above-mentioned key pathways in tumour growth. Other small molecule, VEGFR TKIs such as vitalanib (PTK 787), SU 11248, AG 013736, and AZD 2171 are in Phase I clinical trials. The VEGF trap decoy receptor fusion protein is also in Phase I trial. Other anti-angiogenic agents in clinical trials include thalidomide, squalamine, TNP-470 combretastatin and ZD 6126. The BAY 43-906 (sorafenib) is a potent inhibitor of Raf-1 and also active against VEGFR-2, VEGFR-3 and PDGFR-beta. The ras/Raf signalling pathway is an important mediator of tumour cell proliferation and angiogenesis.<sup>16</sup>

The most successful use of antiangiogenic agents has

been seen in combination with conventional chemotherapy in colorectal and advanced non-small cell lung cancer. The combination of these agents is biologically quite attractive, as they target two important components of tumour development, cell proliferation and vascularisation. These strategies will help in reducing acquired drug resistance and also allow the use of lower dosages of chemotherapeutic agents. This approach also helps in the normalisation effect of antiangiogenic therapy on the tumour vasculature. Tumour blood vessels are functionally and structurally abnormal resulting in heterogenous blood flow throughout the tumour and regions of hypoxia. The hyperpermeable blood vessels in the tumour result in insufficient pressure gradients that prevents effective flow of drugs from the vessel lumen to the tumour cells. Inhibition of VEGF and its receptor may result in reduced vessel density and permeability that would reduce interstitial pressure and increase oxygen uptake. Antiangiogenic therapy actually increases tumour blood flow and oxygen delivery during the first week of therapy. These also enhance the therapeutic efficacy of radiotherapy. The VEGF inhibitor bevacizumab (15 mg/kg intravenously given every 21 days) has been investigated in combination with the EGFR tyrosine kinase inhibitor erlotinib (150 mg orally daily) in stage III/IV or recurrent NSCLC of non-squamous histology. The median survival has been 12.6 months and 52% of the patients were alive at one year.<sup>76</sup> Hypertension and bleeding are the two common adverse events that have been observed with several angiogenesis inhibitors due to their effect on the physiological angiogenesis too. They may have some cardiogenic (asymptomatic QTc prolongation) and neurological effects. Preliminary results from a phase I/II study of bevacizumab plus erlotinib in previously treated stage IIIB/IV or recurrent NSCLC patients showed partial response in eight out of 40 (20%) and stable disease in 26 out of 40 (65%) patients. The median overall survival time and time to progression were 12.6 and 6.2 months, respectively.<sup>76</sup> The recent Eastern Cooperative Oncology Group (ECOG) E4599 trial compared paclitaxel plus carboplatin with and without bevacizumab (PCB) in advanced NSCLC.<sup>77</sup> This was the first phase III trial to demonstrate a survival advantage obtained from a first-line treatment combining a targeted biologic with chemotherapy, reporting encouraging tumour response rates (27% for PCB vs 10% for PC), progression-free survival (6.4 vs 4.5 months) and median survival rates (12.5 vs 10.3 months) with bevacizumab.

Bevacizumab appears to be generally well tolerated. Combination with paclitaxel plus carboplatin showed modest changes in the chemotherapy regimen toxicity profile.<sup>75</sup> However, some bevacizumab-associated adverse effects warrant special attention, including hypertension, proteinuria, and haemorrhage. Most cases of haemorrhage with bevacizumab have been minor, but some serious pulmonary haemorrhages have

occurred, which often result from angiogenesis inhibition; also, poorly developed neovessels in large, centrally located tumours may be more prone to haemorrhage into the necrotic tumour cavity.<sup>75</sup> Eligibility restrictions in clinical trials of bevacizumab in NSCLC have included a history of myocardial infarction or stroke, significant peripheral vascular disease, central nervous system or brain metastasis, lung carcinoma of squamous cell histology or close proximity to a major vessel, and use of anticoagulants, aspirin, or non-steroidal anti-inflammatory drugs.

The ZD6474, an orally available small-molecule kinase inhibitor of both EGFR and VEGFR, is being explored for efficacy in NSCLC and other cancers. Phase II trials of ZD6474 in combination with standard chemotherapies in first- and second-line settings for advanced or metastatic NSCLC are ongoing. Preliminary data have shown that ZD6474 combined with docetaxel provided an 18.2% (2/11) partial response rate and a 63.4% (7/11) stable disease rate for greater than 12 weeks in NSCLC patients who had previously failed at first-line platinum-based chemotherapy.<sup>78</sup> The ZD6474 combined with carboplatin plus paclitaxel as a first-line therapy in NSCLC (IIIB-IV) demonstrated a 39% partial response rate in a randomised, double-blind trial.<sup>79</sup>

### 3. EGFR and Tumour Angiogenesis (Combination treatment)

New blood vessel formation is required for the growth and progression of most tumours. The EGFR is also involved in angiogenesis: the EGFR ligands, EGF and TGF- $\alpha$ , induce angiogenesis, and TGF- $\alpha$  promotes the expression of VEGF, which induces vascular growth and vascular cell permeability,<sup>80</sup> providing a strong rationale for combined anti-VEGF/anti-EGFR therapy. The VEGF expression is upregulated in many tumours, resulting in an imbalance between pro- and anti-angiogenic factors in the tumour microenvironment, promoting vascularisation and growth.

### 4. Retinoid Agonists

Lung cancers are known to be defective in retinoic acid signalling with low levels of RAR $\beta$  and RXR $\alpha$ . Patients with low levels of RXR $\alpha$  have a shorter survival than those with normal levels. Bexarotene is a retinoid agonist that produced long disease stabilisation (> 3 months in 36%) in Phase I single agent trials and produced long time to progression in a randomised maintenance study. When combined with vinorelbine and cisplatin a 25% response rate, a 13.7 month median survival and a 61% one-year survival was observed in a Phase II trial. These results led to two completed randomised Phase III trials comparing chemotherapy alone to chemotherapy with bexarotene. Unfortunately, these trials were both negative.<sup>16</sup>

## 5. Apoptosis Targets and Proteasome Inhibition

A number of new agents targeting apoptosis including cell surface molecules such as TRAIL involved in the extrinsic apoptotic pathway and BCL-2 and other inhibitors of the intrinsic pathway have entered clinical trials. Both apo2/Ligand/TRAIL and a TRAIL monoclonal agonist are in Phase I and Phase II trials. The antisense molecule genasense or G3139 is also in clinical trial. The proapoptotic agent, exisulind, did not improve lung cancer outcome but more potent analogs are in development.<sup>16</sup>

The development of targeted inhibitors of signalling transduced by *RAS*, *p53* and other oncogenes has been more problematic. Another strategy is the interference with intracellular signal transduction. Farnesyl transferase inhibitors exert their action by interfering with either pro-RAS or RhoB farnesylation. Several clinical studies in different phases have been carried out with compounds belonging to this class, either alone or in combination with chemotherapy; unfortunately, all of them have turned out to be disappointing. Cell cycle inhibitors, such as CYC-202 and BMS-387032, represent a class of interesting compounds which are in the early phase of development and whose clinical results are eagerly awaited. Suberoylanilide hydroxamic acid is another small molecular weight inhibitor of HDAC activity. Phase I/II clinical trials have shown low toxicity and evidence of anti-tumour activity; on the other hand, this compound has a potential for synergism with radiotherapy, chemotherapy and biologicals.<sup>81</sup>

Inhibitors of many downstream targets, such as PI3 kinase, MEK, Raf and MTOR, are now being studied. Many tumour suppressor genes are degraded by the proteasome. Proteasome inhibitors such as bortezomib have shown activity in lung cancer and additional studies are ongoing. Similarly, transcription factors may require histone deacetylation for activity. Histone deacetylase inhibitors have shown activity in lung cancer and mesothelioma and are under further Phase II study.

## 6. COX2 Inhibitors

Lung cancers frequently over express COX2 and PGE<sub>2</sub>. The COX2 inhibitors are under investigation, alone and in combination with other chemotherapeutic agents, such as taxanes and with other targeted therapies, such as erlotinib.

## 7. Vaccines

Cancer immunotherapy aims to direct the patient's immune system to recognise tumour-associated antigens and attack cancer cells, offering a promising adjunct to other therapies. Several vaccines continue to show promise for lung cancer therapy. The MUC1

mucinous glycoprotein has a broad distribution in a variety of normal and abnormal tissues, and in many cancers including that of lung it is both over-expressed, under- or aberrantly-glycosylated, and expressed over the whole cell surface of tumour cells. The tumour associated MUC1 is antigenically distinct from normal MUC1. A liposomal vaccine using the MUC1 antigen (L-BLP25) has shown promise both in pre-clinical and clinical studies.<sup>82</sup> The vaccine has been evaluated in a randomised trial with chemotherapy (stage IV) or chemo-radiotherapy (stage III). Patients randomised to the vaccine arm had a longer survival (median 17.2 months vs 13.0 months) but these differences were not significant for the entire group. The differences were significant in a subset of stage III patients where median survival was greater than 30 months in the vaccine arm and 13.3 months in the control arm. Another multicenter Phase IIB randomised study of the vaccine in 171 patients with stage IIIB or stage IV disease has shown a median survival of 17.4 months as against 13 months in those with best supportive care. No significant toxicity has been observed except minor injection site reactions. Vaccines based on heat shock proteins (Antigenics), mutated RAS antigens in yeast (Globeimmune) and autologous tumour antigens with GM-CSF (Cell Genesys) are in Phase I or II clinical trials. The EORTC is listing a vaccine as adjuvant therapy in resected lung cancer patients.<sup>16</sup>

The National Cancer Institute (USA) has set the goal of eliminating suffering and death due to cancer by 2015. Cancer might be controlled and even cured by combining three potential therapeutic strategies aimed at (i) cancer-specific targets, (ii) universally-vital targets with selective protection of normal cells (the selective combinations) and (iii) tissue-specific targets. Although targeting cancer-specific pathways (e.g. by imatinib and gefitinib) is probable, it alone will not be sufficient to control cancer. This strategy is limited to oncogene (kinase)-dependent cancers and is further limited by therapy-induced resistance and tumour progression. Thus, targeting cancer-specific pathways needs to be complemented by two divergent therapeutic strategies: (i) selective combinations and (ii) tissue-selective therapy. With selective protection of normal cells (based on cell cycle and apoptosis manipulation), combinations of selective and chemotherapeutic drugs can be effective in most common cancers. Alternatively, tissue-selective therapy can suppress cancer cells in a tissue-selective manner, sparing other tissues. While individually each therapeutic strategy may cause drug resistance and even tumour progression; these obstacles can be overcome and even exploited by using all the three strategies in sequence. And finally, these strategies will benefit from molecular diagnostics and can be used for chemoprevention.<sup>83</sup>

In summary, targeted therapies are now approved and are part of the standard care of lung cancer patients.

They have far fewer side effects as compared to standard chemotherapy. Many targeted therapies are in clinical development and should further improve the outcomes of lung cancer patients. However, it must be remembered that these drugs/strategies should be cost-effective, non-toxic and widely available. Recognition of subsets of patients who will benefit from such therapy is also necessary and for that advanced technological facilities need to be made available widely. The EGFR inhibitor gefitinib has become available for clinical use in India recently and is affordable. Initial results are encouraging,<sup>84</sup> but experience with large number of patients is essential.

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# Late Onset Bronchopleural Fistula After Pneumonectomy for Tubercular Bronchiectasis

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## CLINICAL SUMMARY

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A 63-year-old male presented to the chest clinic with complaints of intermittent fullness of the chest on the left side for the past one year. He underwent left-sided pneumonectomy for tubercular bronchiectasis 20 years back and he was since then asymptomatic. He had a history of expectoration of copious, mucoid fluid on bending forward for the past one year, and this manoeuvre used to relieve his chest discomfort. There was a no history of cough, fever or frank haemoptysis. He was a known diabetic for the last 22 years and was on oral hypoglycemic agents. His general examination was unremarkable. Left side of the chest revealed an operative scar with loss of volume. Trachea was deviated to the left side. On auscultation, amphoric breath sounds were heard over the left upper zone but were reduced over the left middle and lower zones. Normal vesicular breathing was present on the right side. Cardiovascular examination was normal.

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## INVESTIGATIONS

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Laboratory investigations revealed a haemoglobin of 11.2 gm%, a total leukocyte count of 8200/cc with 61% polymorphs and a fasting blood sugar of 119 mg%. Sputum and pleural fluid cytology were negative for malignant cells and acid-fast bacilli (AFB). Chest radiograph showed post-operative changes in the left chest with ipsilateral mediastinal shift. Air fluid level was seen in the left pleural cavity with marked pleural thickening (Figure 1). A long bronchial stump was also noted on the chest radiograph. Multi-detector computed tomographic (MDCT) coupled with virtual bronchoscopy demonstrated a communication between the left bronchial stump and pleural space suggestive of a bronchopleural fistula. In addition, empyema with air fluid level was also seen (Figure 2). The right lung was normal. Minimum intensity projection in the coronal plane delineated the presence of bronchopleural fistula (Figure 3).



Figure 1. Chest radiograph shows post-operative changes in the left chest with ipsilateral mediastinal shift. Air fluid level is seen in left pleural cavity with marked pleural thickening suggestive of a loculated pyopneumothorax (arrow). Also note the long bronchial stump left after surgery.

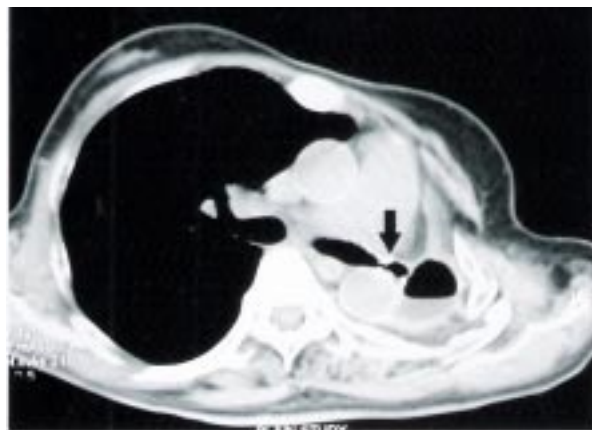


Figure 2. CT scan axial section (mediastinal window) showing empyema with air fluid level. Note the presence of surgical clips around the left bronchial stump (arrow).

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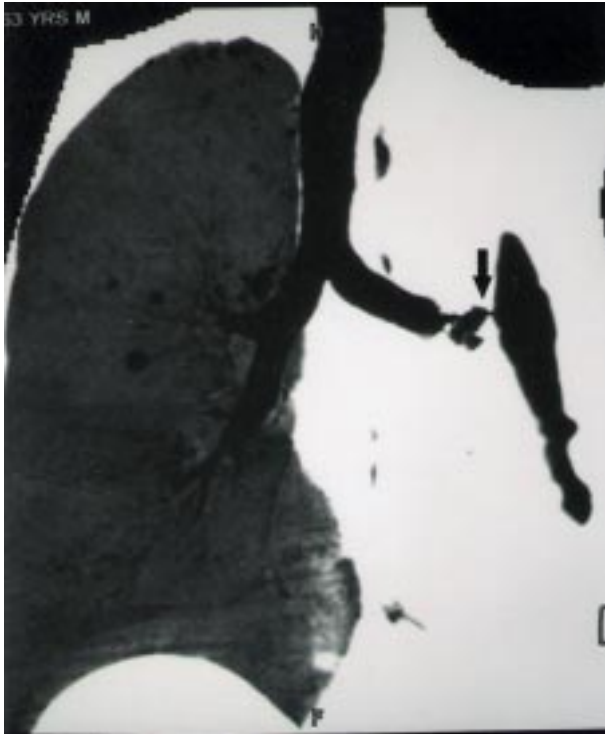


Figure 3. Frontal view of 3-D CT scan minimum-intensity-projection reconstruction showing the fistulous communication (arrow).

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## DIAGNOSIS

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### *Post pneumonectomy bronchopleural fistula (BPF)*

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## DISCUSSION

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Bronchopleural fistula (BPF) is a rare complication after pneumonectomy and carries significant morbidity and mortality. It has been known to occur after pulmonary resection for tuberculosis or carcinoma lung.<sup>1</sup> Incidence of BPF is significantly higher following pulmonary resection for tubercular conditions, ranging from 2.7 to 10.5 percent.<sup>1,2</sup> The possible risk factors for the development of BPF include pre-operative radiotherapy, pre-operative pleuropulmonary infection, completion pneumonectomy, and the necessity for post-operative ventilation.<sup>3</sup> In the immediate post-operative period it usually occurs due to a faulty closure of the bronchus.<sup>4</sup> Delayed BPF is usually due to infection or recurrent tumour of the bronchial stump. The most common cause of death associated with this condition is aspiration pneumonia with subsequent adult respiratory distress syndrome.<sup>4</sup> Bronchopleural fistula is also the main cause of postpneumonectomy empyema.

Computed tomography (CT) is the imaging technique of choice for visualising and characterising bronchopleural fistulas.<sup>5</sup> With the advent of MDCT, volume acquisition with three-dimensional

reconstruction has been used to display the entire course of a bronchopleural fistula.<sup>6</sup> Although fistulous communication is usually not seen on chest radiographs, they are valuable in suggesting possibility of a BPF and for monitoring the efficacy of therapy. Chest radiograph findings in BPF consist of a continuous increase in size of the residual intrapleural airspace, changes in an already present air-fluid level, development of tension pneumothorax, and a drop in the air-fluid level exceeding 2 cm in a patient who has undergone pneumonectomy.<sup>4</sup> Return of the mediastinum back towards its pre-operative position with leaked air, may be an evidence of BPF. In delayed BPF scarring usually prevents the mediastinum from returning to the midline. Computed tomographic findings in BPF include air and fluid collections in the pleural space and demonstration of a tract from an airway or the lung parenchyma to the pleural space.<sup>4</sup>

The present case highlights the utility of MDCT in the diagnosis of bronchopleural fistula. The likely cause of BPF in our case in the long bronchial stump left by the surgeon, as it is a well known risk factor for the development of BPF.<sup>7</sup> A long bronchial stump causes mucus accumulation leading to a high risk of infection and impaired healing of bronchus. The incidence of late post-pneumonectomy BPF is very small due to the progressive fibrosis after surgery. However, in one series of patients with lung carcinoma, BPF was reported as late as 1-10 years after pneumonectomy without any evidence of tumour recurrence.<sup>8</sup> Although the presentation was unusually late in our case, it is not implied that the BPF was of recent origin and the initial symptoms may have been ignored as the thorax got contracted and patient may have been living with this condition for many years. Successful closure of post-resection BPF can be obtained by a two-stage approach.<sup>9</sup> First, the pleural cavity is thoroughly drained by closed or open thoracostomy. In the next stage, the BPF is closed by sutures and buttressed by a vascular flap (omentum or muscle). A long bronchial stump is reamputated and closed. The residual pleural space may be obliterated by myoplasty or thoracoplasty, if required.

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# Spondylocostal Dysostosis and Complex Congenital Heart Disease

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## ABSTRACT

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Spondylocostal dysostosis is a rare genetic disorder characterised by multiple morphological abnormalities of the vertebrae and the ribs. The association of this disorder with congenital heart disease is extremely rare and very few cases have been reported so far. We report herein, a case of autosomal recessive form of spondylocostal dysostosis in association with complex congenital heart diseases, who underwent cardiac surgery successfully. [Indian J Chest Dis Allied Sci 2007; 49: 163-164]

**Key words:** Dysostosis, Spondylocostal, Congenital, Surgery, Genetic.

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## INTRODUCTION

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Spondylocostal dysostosis (SCD) is a rare heterogeneous group of disorders, characterised by typical morphological abnormalities coupled with characteristic clinical picture and radiological features. The term spondylocostal dysostosis has been recommended in the revised international nomenclature of constitutional diseases of bone.<sup>1</sup> Only few cases of SCD have been reported to be associated with congenital heart disease.<sup>2-5</sup> We report herein, a rare case of autosomal recessive form of SCD in association with complex congenital cyanotic heart disease in an infant.

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## CASE REPORT

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An 11-month-old Saudi girl, who was the first child of her parents, presented with a history of cyanosis while crying since one month of age and a failure to thrive. Her parents were first cousins. The birth weight and head circumference were 2.5 kg and 32 cm, respectively. There was no family history of congenital spinal abnormality. On examination, the baby had dysmorphic features particularly a short neck with a low posterior hairline, short trunk and thick curly hair (Figure 1). In addition, she had a depressed nasal bridge, and puffiness of the dorsum of the feet. The length, weight and head circumference of the infant were less than 5th percentile on standard growth charts. The inter nipple distance was 10 cm (5-50th percentile). The child also exhibited a mild developmental delay. Central cyanosis



**Figure 1.** Photograph of the patient showing dysmorphic features of spondylocostal dystosis, namely, a short neck, posterior hairline, thick curly hair and short trunk.

was noted with an oxygen saturation of 80% on room air.

A 2-dimensional echocardiogram and angiogram revealed double outlet right ventricle, an unbalanced complete atrioventricular septal defect, mild hypoplasia of the left ventricle, mild hypoplasia of

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the main and branch pulmonary arteries, and a small patent ductus arteriosus. The skeletal survey showed hemi-vertebrae in the lower dorsal spine and fusion of the posterior portion of lower ribs with scoliosis (Figure 2). However, abdominal ultrasonography, chromosomal karyotyping, FISH studies for chromosome 22q micro deletions, magnetic resonance imaging (MRI) brain and biochemical studies were normal. The child underwent a successful bi-directional cavo-pulmonary shunt operation on cardiopulmonary bypass. The patient is being followed up for her long-term medical and surgical management in a satisfactory condition.



**Figure 2.** Radiograph of thoracolumbar region (PA view) showing fused, hemi vertebrae and fused or bifid ribs.

## DISCUSSION

Spondylocostal dysostosis is characterised by multiple morphological abnormalities of the vertebrae and ribs due to the mal-segmentation of the axial skeleton, probably before the 20th day of gestation.<sup>6</sup> As in our patient, affected individuals present with a short, immobile neck, short trunk, dwarfism and spinal deformity including kyphoscoliosis.

Other features described in association with this disorder include protuberant abdomen, muscular hypotonia, lumbar lordosis or inguinal hernia. Radiological features of SCD comprise mainly, hemi or

fused vertebrae and absent, bifid or fused ribs. The mode of inheritance may be autosomal dominant or recessive with varying levels of severity.<sup>7,8</sup> The presence of first-degree parental consanguinity in the present case suggests an autosomal recessive inheritance.

The association between SCD and congenital heart disease has been reported only in a few case studies, which were mostly cardiac positional anomalies.<sup>2-5</sup> The most severe form of autosomal recessive type of SCD, Jarcho-Levin syndrome has been reported to be associated double outlet right ventricle or atrio-ventricular septal defect.<sup>2,4</sup> The heart in our patient had similar defects, in addition to the presence of pulmonary valvular and subvalvular stenosis and hypoplasia.

The surgical implications and long-term outcome of management of such patients is not clear and the presence of spinal or genetic abnormalities might have a bearing on patient selection, surgical procedure and outcomes especially in view of the possible altered dynamics of the chest wall and remains a challenge.

## ACKNOWLEDGEMENTS

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# Acute Superior Vena Cava Obstruction due to Tubercular Mediastinal Abscess

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## ABSTRACT

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Acute superior vena cava (SVC) syndrome is most commonly due to thrombosis following central venous catheterisation. We report an immunocompetent, young host presenting with high-grade fever and SVC obstruction of acute onset, that was proved to be due to a tubercular mediastinal abscess and responded well to treatment. [Indian J Chest Dis Allied Sci 2007; 49: 165-167]

**Key words:** Superior vena cava, Mediastinum, Abscess, Tuberculosis.

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## INTRODUCTION

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The commonest cause of slowly developing superior vena cava obstruction (SVCO) is bronchogenic carcinoma. Lymphoma, thymoma and germ cell tumours are other frequent causes of this syndrome. In children, lymphoblastic leukaemia and non-Hodgkin's lymphoma account for most of the cases. However, acute onset SVCO is uncommon. Unlike the usual causes of SVCO, the majority of cases of acute onset SVCO are due to a benign aetiology. Most often, it is due to SVC thrombosis caused by central venous catheters.<sup>1-3</sup> It has also been reported following cardiac operations<sup>4,5</sup> and due to other rare causes.<sup>6-12</sup> There are only two reports mentioning tuberculosis as a cause of SVCO, one due to pulmonary tuberculosis and the other due to a tubercular mediastinal lymphadenopathy.<sup>14,15</sup> However, acute SVCO due to a tubercular mediastinal abscess has not been reported in the literature. We report a case of an immuno-competent young male who presented with SVC obstruction of acute onset that was proved to be due to tubercular mediastinal abscess.

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## CASE REPORT

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A 28-year-old, non-smoker, male presented with a two days history of sudden onset, high-grade fever without any localising symptoms. Physical examination was unremarkable and there were no localising signs. Before presenting to this hospital, he was provisionally diagnosed as a case of viral fever and was prescribed antipyretics for symptomatic relief. Two days later, he was brought to the emergency room with sudden onset

of breathlessness and swelling over the face. High-grade fever continued. General physical examination revealed a dyspnoeic patient with facial oedema and distended non-pulsatile superficial veins over the neck and chest. There was no peripheral lymphadenopathy and systemic examination was unremarkable. On investigation, hemoglobin was 12.4 gm/dl, total leukocyte count was 9,000/mm<sup>3</sup>, erythrocyte sedimentation rate was 60 mm in 1st hour (Westergren). Chest radiograph revealed marked widening of the mediastinum without any lung parenchymal lesion. Computed tomographic (CT) scan of the chest revealed a conglomerate lymph nodal mass in the anterior mediastinum compressing the SVC (Figure 1). There

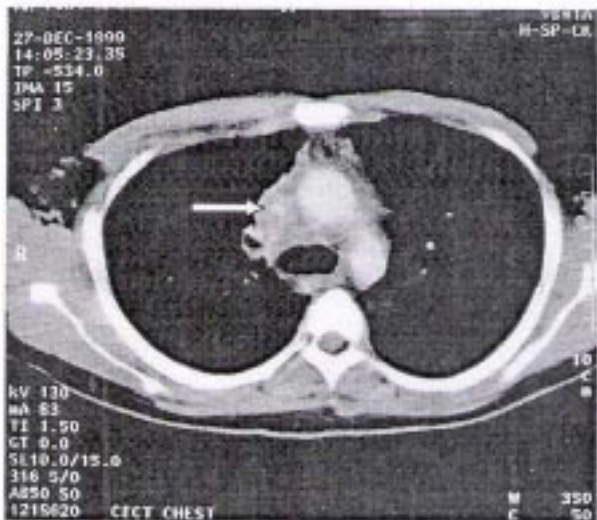


Figure 1. CT scan of the chest showing a conglomerate mass in the anterior mediastinum encasing and compressing the superior vena cava (arrow).

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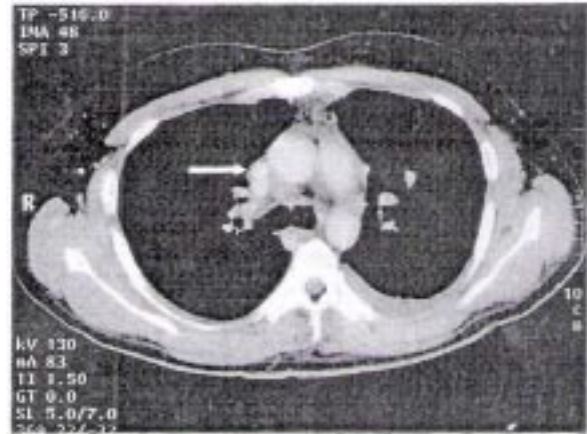
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was evidence of central necrosis in the mass but no rim enhancement or calcification was seen. In view of the short history and SVCO with a large mediastinal lymphnode mass, possibilities of lymphoma, pyogenic bacterial infection or tuberculosis were considered. CT guided fine needle aspiration cytology (FNAC) from the lymphnodal mass did not reveal any malignant cells or acid-fast bacilli. Subsequently, a cervical mediastinoscopic biopsy of the mass was performed. During the procedure, while dissecting in the right paratracheal area, an abscess cavity was entered and approximately 30 ml of thick yellowish pus was drained. Multiple biopsies were taken from the lymph nodal mass. The pus was positive for acid-fast bacilli on Ziehl-Neelsen staining. There were no malignant cells and the bacterial culture was sterile. The histopathology of the biopsy specimen revealed caseating granulomas with necrosis and giant and epithelioid cells consistent with tuberculosis. Serology for human immunodeficiency virus (HIV) 1 and 2 was negative. Immediately after mediastinoscopy, the patient showed marked symptomatic improvement. His fever subsided and the dyspnoea and facial congestion diminished markedly. Anti-tuberculosis therapy (ATT) with isoniazid, rifampicin, pyrazinamide and ethambutol (RHZE regimen) was started. CT scan of the chest on the 13th post-operative day showed considerable reduction in the size of the mediastinal mass (Figure 2). Over the next three weeks, his symptoms subsided completely. He was treated with four drugs (RHZE) for two months



**Figure 2.** Follow-up CT scan of the chest (two weeks post-operatively) showing considerable reduction in the size of the mass but superior vena cava still compressed (arrow).

and thereafter with two drugs (RH) for four months. Another CT scan of the chest at five-month follow-up revealed near complete regression of the lymph nodal mass (Figure 3). He completed six month's course of ATT and was well at three years follow-up.



**Figure 3.** Follow-up CT scan of the chest (five months post-operatively) showing complete resolution of the mass. Superior vena cava is well visualised.

## DISCUSSION

Acute onset superior vena cava obstruction (SVCO) is a serious disorder. It has usually been reported to be due to thrombosis related to central venous catheters<sup>1-3</sup> and following cardiac operations.<sup>4,5</sup> It has also been reported due to other causes, such as a primary tumour of the SVC, rupture of bronchial and innominate artery aneurysms, aortic dissection, following cervical mediastinoscopy, Behcet's disease, hemothorax and a retained knife blade.<sup>6-12</sup> Tubercular mediastinal lymphadenopathy has been reported to cause SVCO,<sup>15</sup> but an abscess has not been reported as a cause of acute SVCO.

Acute SVCO with fever in a previously healthy young adult is extremely rare. Lymphoma is the most plausible diagnosis in such a presentation. However, the condition is not acute. An aggressive approach for a tissue diagnosis should be undertaken because of the acuteness of the condition. Percutaneous tissue biopsy is the initial procedure of choice failing which cervical mediastinoscopy can be performed. It is a safe procedure and has a high yield. In the present case cervical mediastinoscopy not only provided the tissue for diagnosis but also provided a therapeutic opportunity for drainage of the tubercular abscess, thereby reducing the extrinsic compression on the SVC and leading to immediate symptomatic improvement. In literature, we could come across only one case of SVCO due to suppurative mediastinitis caused by mixed anaerobic organisms.<sup>13</sup> The diagnosis and drainage in that case was achieved by anterior mediastinoscopy with a successful outcome.<sup>13</sup> Acute SVCO due to mediastinal abscess is rare but an eminently treatable disease. This unusual case highlights the fact that tuberculosis should also be kept in mind as a differential diagnosis in patients presenting with acute onset SVC obstruction. A timely diagnosis and appropriate treatment leads to cure.

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# Malignant Fibrous Histiocytoma Developing During Pregnancy

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## ABSTRACT

Cancer may present during pregnancy in less than 0.1% of cases. Among all cancers, sarcoma in pregnancy is rare. We present a case of a young pregnant woman with widespread pulmonary metastasis due to malignant fibrous histiocytoma in the lower extremity. [Indian J Chest Dis Allied Sci 2007; 49: 169-171]

**Key words:** Malignant fibrous histiocytoma, Pregnancy.

## INTRODUCTION

The term malignant fibrous histiocytoma (MFH) was first introduced in 1963 by Ozzello *et al* and later by O'Brien and Stout to refer to a group of aggressive soft tissue tumours characterised by a storiform growth pattern.<sup>1</sup> It is the most common soft tissue sarcoma in late adult life. The tumour occurs more commonly in the skeletal muscle of the lower extremity, especially the thigh followed by upper extremity and retroperitoneum. This is a case report of a young female, who had accelerated growth of this tumour during pregnancy.

## CASE REPORT

A 24-year-old primigravida with 24 weeks of gestation, presented with difficulty in breathing and cough of one week duration to the emergency room of our hospital with ulceration of the left calf muscle. On examination, she was orthopnoeic and pale, with no palpable lymph nodes. Examination of the respiratory system revealed features suggestive of pleural effusion on the right side without mediastinal shift. There was a large ulcerated vascular swelling measuring 8 cm × 4 cm in the left calf muscle. One-and-a-half-year ago she had noticed a painless swelling (1 cm in size) in the left calf muscle. In the 4th month of pregnancy she noticed that the swelling had suddenly increased in size to about 5 to 6 centimeters. Wide excision biopsy of the swelling revealed a malignant fibrous histiocytoma (MFH). She

was not a diabetic. Her younger sister had died of cancer at the age of 12 years, the details of which were not available.

As the patient showed features of Type 1 respiratory failure, she was intubated and was put on assisted ventilatory support. Ultrasound examination of abdomen showed intrauterine death of foetus. Chest radiograph (Figure 1) and computerised tomographic (CT) scan of thorax showed multiple nodular opacities with a right side pleural effusion suggesting widespread metastasis. Biopsy of the lesion in the calf muscle showed a tumour with storiform pattern with spindle cells arranged in short fascicles in a cartwheel pattern and round plump pleomorphic histiocytic cells with

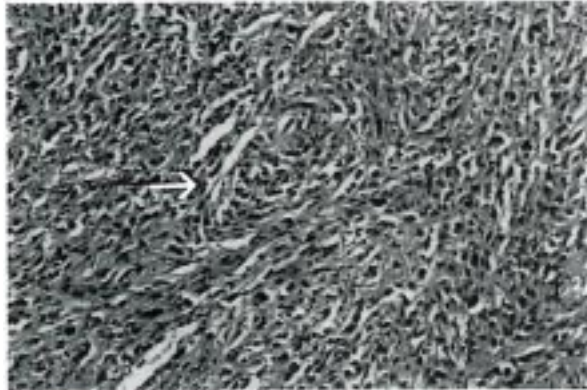


Figure 1. Chest radiograph showing multiple nodular opacities with pleural effusion.

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haphazard arrangement admixed with giant cells (Figure 2). There was increased mitotic activity. A diagnosis of pleomorphic storiform type of MFH was made.



**Figure 2.** Photomicrograph of the tumour showing storiform pattern and cells with pleomorphic, hyperchromatic nuclei (H&E x200).

In view of the dead foetus in utero, termination of pregnancy was decided upon. After evaluation, prostaglandin E<sub>1</sub> tablets (misoprostol) was administered and the dead foetus was expelled within five hours. There was no post-partum obstetric complications. However, despite aggressive supportive therapy, patient expired on the 7th post admission day due to cardio-respiratory arrest.

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## DISCUSSION

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Malignant fibrous histiocytoma (MFH) is recognised since 1963 and occurs principally as a mass in the extremity (lower extremity 49%, upper extremity 19%) or in the abdominal cavity or retroperitoneum (16%) of adults with a peak incidence at 61-70 years of age. It involves deep fascia (19%) or skeletal muscle (59%) and only 7% confines to subcutis without fascial involvement. The most common clinical presentation is an enlarged painless soft tissue mass in the thigh, typically 5 cm - 10 cm in diameter. Two-thirds of the tumours are intramuscular. Rare symptoms and signs include episodic hypoglycaemia and rapid tumour enlargement during pregnancy.<sup>2</sup> Rapid acceleration of the growth rate during pregnancy prompts the patient to seek medical attention quickly. The histogenesis is uncertain. Both histiocytic and primitive mesenchymal cell theories in origin have been proposed. In general, the tumour contains both fibroblast and histiocyte like cells in varying proportions with spindle and rounded cells exhibiting storiform arrangement. Five histologic subtypes have been described: storiform/pleomorphic (most common), myxoid, giant cell, inflammatory and angiomatoid.

Tumour grade, size and distant metastases at initial

presentation remain the most important prognostic factors for MFH.<sup>3</sup> Histologic subtype and methods of surgical treatment are also important prognostic factors. The prognostic relevance of the anatomic site and depth of the primary tumour is controversial. Patients with low grade, intermediate and high grade tumours have 10-year survival rates of 90%, 60% and 20%, respectively.<sup>2</sup> The primary tumour size is also an important factor in the 5-year survival rate; tumours smaller than 5 cm have survival rate of 82%, 5 to 10 cm, 68%, and larger than 10 cm, 51 percent.<sup>4</sup>

Distant metastasis most commonly occurs to the lung (90%), bone (8%) and liver (1%). The rate of metastasis varies with the histologic subtype from 23% (myxoid) to 50% (Giant cell). Resection with negative microscopic margins decreases the incidence of local recurrence. The appearance of distant metastasis is a fatal sign in patients with MFH. Histological vascular invasion by tumours is a risk factor associated with distant metastases that appear in MFH.<sup>5</sup> Tumours that are small, superficially located or have a prominent inflammatory component, metastasises less frequently than the larger and more deeply located tumours.<sup>6</sup>

Outcomes for wide-margin excision of tumours less than 5 cm in diameter are equivalent whether or not adjuvant radiation therapy is employed. In contrast, high-grade tumours larger than 5 cm in diameter require wide surgical excision plus radiation therapy administered either pre-operatively or post-operatively. Large tumours close to vascular, bony or nerve structures may be resected more successfully when radiation therapy is used pre-operatively. Although radiation therapy decreases local recurrence dramatically, it may not affect survival because the high-grade tumours trend to metastasise early.<sup>7</sup>

To conclude, prognosis for the foetus as well as mother is adversely affected by the diagnosis of sarcoma during pregnancy. Growth rate acceleration has been observed in sarcomas during pregnancy. Our patient presented with a rapid course due to pregnancy. We document this case for the rare presentation of malignant fibrous histiocytoma during pregnancy with a rapid downhill course and early widespread pulmonary metastases.

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# Myotonic Dystrophy and Sleep Apnea

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## ABSTRACT

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A 35-year-old woman presented with complaints of backache, shortness of breath, weakness, excessive day-time sleepiness and difficulty in walking was admitted to our clinic. She was diagnosed as a case of myotonic dystrophy accompanied by obstructive sleep apnea syndrome. [*Indian J Chest Dis Allied Sci* 2007; 49: 173-175]

**Key words:** Myotonic dystrophy, Sleep-apnea syndrome.

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## INTRODUCTION

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Myotonic dystrophy is a progressive, multi-systemic, autosomal dominantly inherited disease. It has several clinical forms. The diagnosis is based on clinical signs, electromyography (EMG) and genetic analysis.<sup>1</sup>

In its mild forms, symptoms and signs, like fatigue, weakness, lumbago, gait abnormalities, dyspnoea and cyanosis may be very subtle and go unnoticed. These cases can only be diagnosed with clinical suspicion and a detailed analysis thereafter. Anaesthesia in patients with myotonic dystrophy may be associated with grave complications, such as acute respiratory failure. Also, pregnancy and parturition can endanger both the mother and the child. Therefore, it is important to diagnose the conditions in patients who have disorders of the respiratory and locomotor systems, before any complication occurs. In any patient with such a presentation, myotonic dystrophy should be considered in the differential diagnosis. Family members of the patient should also be screened and genetic counseling should be available for subjects in the risk groups.

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## CASE REPORT

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A 35-year-old woman was admitted to our clinic with complaints of shortness of breath, fatigue, increased somnolence and difficulty in walking. Her complaints were progressively persistent during the past 10 days. In her past, she had an operation for polycystic ovarian syndrome and hyperparathyroidism six years ago. Her mother and one of her sisters also had similar sleepiness.

On physical examination, she was prone to doze off but responsive to verbal stimulation. She had excess hair as beard and moustache and was cyanotic. Chest revealed respiratory rales in basal and mid zones of both hemithoraces. Bilateral upward eye movements and right eye lateral movements were restricted. There was bilateral ptosis. She had a nasal speech. The global assessment of muscle strength of distal extremities revealed significant weakness. The muscle strength increased with exercise. She had a duck-like gait. Chest radiography (postero-anterior view) revealed cardiomegaly, bilateral patchy interstitial and acinar infiltrations in mid and lower zones. In the high resolution computerised tomography, dilatation of heart chambers, bilateral diffuse peribronchial and septal thickening and ground-glass attenuation were detected. Electrocardiography showed sinus rhythm. Heart rate was 90 beats per minute. There was counter clock-wise rotation of the heart as well as pathologic Q wave in standard leads, V<sub>1</sub> and aVL and negative T waves in some precordial leads. Twenty-four hour rhythm holter examination revealed sinus rhythm. There was one nodal rhythm record lasting for one hour with 62 beats per minute. There were 214 single multifocal ventricular and occasional single supraventricular premature beats with only one bigeminated premature beat. The maximum heart rate reached 109 and minimum 47 beats per minute.

Arterial blood gas analysis revealed hypoxemia resistant to nasal oxygen treatment as well as hypercapnia. Therefore considering the possibility of an intracardiac shunt, echocardiographic examination was done that showed left ventricular systolic functions to be normal with an ejection fraction of 73% and pulmonary arterial pressure of 40 mmHg. As

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echocardiography failed to show an intracardiac shunt, cardiac catheterisation was carried out, that demonstrated normal coronary arteries and normal left ventricular function. There was no intracardiac shunt but she did have pulmonary hypertension (50 mmHg). Respiratory function tests revealed a ventilatory defect in restrictive pattern. PI max and PE max, which reflect respiratory muscle strength, were found to be decreased. Fundi examination was normal but she had posterior subcapsular cataract.

Full polysomnographic examination was performed during the night that detected 111 obstructive type hypopneas along with one obstructive apnea (AHI: 48.6) as well as desaturations and arousals (57 per hour). Oxygen saturation was under 60% for 19.6% of total sleep time. It was detected that sound sleep and rapid eye movement (REM) phases of sleep were extremely decreased.

Concentric needle electromyography showed excessive myotonic discharges and short motor unit potentials on all of the muscles examined. Muscle biopsy of the left deltoid revealed diffuse necrosis and necrobiosis, atrophy and interstitial oedema of the myofibriles. Genetic examination was performed by polymerase chain reaction (PCR) and Southern Blot Method cytosine-thymine-guanine (CTG) repeat as 900 times was demonstrated.

Screening of family members revealed bilateral posterior subcapsular cataract in her sister. Her EMG showed myotonic discharges in all the muscles. Genetic analysis had 1300 CTG repeats. The patient had a clinically healthy son. Her uncle's child had myotonic dystrophy, diagnosed at another center. One of her brothers had normal tests. The other members of the family could not be followed-up (Figure).

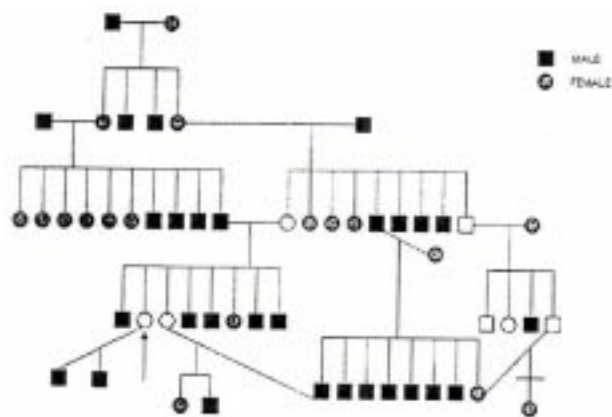


Figure. The patient's pedigree is shown. The present case is indicated with arrow and all the sick relatives are shown in black.

## DISCUSSION

Myotonic dystrophy is a multi-system genetic disorder that affects skeletal and smooth muscle as well as the

eye, heart, endocrine system, and central nervous system. The myotonic dystrophy gene, codes for a protein kinase that is found in the skeletal muscle, where it likely plays a regulatory role. In 98% of the patients, there is an increased repeat of nontranslation CTG at the third end of myotonic dystrophy protein kinase gene which is found at the chromosomes 19 and 13.3 location. In unaffected population there can be 5-34 repeats, whereas in the affected population it can be a thousand times. In our patient the repeat sequence was 900. There is a positive correlation between the severity of clinical symptoms and repeat number.<sup>1</sup>

There are three distinct clinical forms: congenital, classic, and minimal. This variance of clinical presentation has been linked to multiple genetic changes and loci.<sup>1</sup> The clinical picture of our patient was consistent with minimal form.

Several organs involvement is present in myotonic dystrophy. Abnormalities of conduction, rhythm abnormalities and rarely myocardium involvement may be there. The most common arrhythmias are atrial flutter and fibrillation. The patients are commonly asymptomatic, therefore, ECG evaluation is important for early diagnosis.<sup>2,3</sup> Electrocardiographical changes have been observed in 37% to 80% of myotonic dystrophic patients. Cardiac involvement has been related to the severity of neuromuscular disease as well as the increase of the gene repetition.<sup>2,3</sup> Our patient had normal coronary arteries but there were Q waves in standard V<sub>1</sub> and aVL and negative T waves in pre-cordial leads as well as few ventricular and supra-ventricular premature beats in 24 hour-holter recordings. Cardiac disorder is progressive.<sup>2,3</sup>

Patients with myotonic dystrophy generally suffer from excessive drowsiness in day-time.<sup>4</sup> Our patient had this symptom for years. This may be due to interruption of the sleep because of impaired respiratory function, central nervous system dysfunction and sleep-apnea syndrome.<sup>4</sup> Sleep examination in our patient revealed obstructive type sleep apnea syndrome. Cranial imaging studies demonstrate a correlation between day-time sleep and atrophy of the anterior region of corpus collosum.<sup>4</sup> We could not demonstrate any pathology in our patient's cranial imaging.

Although chronic respiratory insufficiency is common, especially in later stages, the incidence is not known. Arterial blood gas analysis of our patient was concordant with chronic respiratory insufficiency. The main reason for this may be either the involvement of respiratory tract, the incapability of responding to central neurogenic stimulants or the insufficiency of inspiratory muscles and the diaphragm.<sup>5</sup>

The diagnostic value of spirometry and arterial blood gas analysis is little. Restrictive type of ventilation disorder is frequent in patients. Our patient also had restriction. The value of intraoral occlusion pressure is limited especially in patients with facial weakness. PE<sub>max</sub> is affected more than PI<sub>max</sub> in patients with myotonic

dystrophy. Weakness of expiratory and abdominal muscles is held responsible from this damage. The myotony of respiratory muscles causes a decrease in compliance of the chest wall and this results in an increase in respiratory work and precipitates of muscle weakness. Patients are tachypnoeic and carbon dioxide (CO<sub>2</sub>) retention is present in most of the patients, especially during sleep. We observed hypercarbia and low saturation in our patient that was evident at nights. Chronic respiratory insufficiency is increased during the late phase of the disease.<sup>5</sup> Our patient's blood gas analysis was consistent with chronic respiratory insufficiency. There is a relationship between hypercapnia and degree of muscle weakness.<sup>2</sup> Inspiratory muscle weakness, progressive increase in inspiratory elasticity and low central stimulus have an important role in pathogenesis of hypercapnia.<sup>2, 5, 7</sup>

Nearly all patients have subcapsular lens opacity that can enlarge and obstruct vision.<sup>6</sup> Our patient had bilateral subcapsular cataract and pytosis and her fundi were normal.

For diagnosis, clinical signs, EMG, muscle biopsy and genetic analysis are important. Before the development of genetic techniques, definite diagnosis was made by muscle biopsy.<sup>7</sup> Yet, muscle biopsy results may be non-specific.<sup>7, 8</sup> Histological examination of muscle biopsy samples were non-specific and CTG repeat sequence was 900 that supported the diagnosis in our case.

The aim of myotonia treatment is to control the disease without reducing the strength as well as controlling the systemic manifestations. Thus, myotonia can be treated symptomatically by various Na channel blockers, mexiletine, phenytoin, and carbamazepine.<sup>9</sup>

In conclusion, myotonic dystrophy is a rarely encountered disease that can have grave consequences,

if not diagnosed. Sleep apnea syndrome can accompany this disease as was seen in our patient. Since the diagnosis is based mainly on clinical suspicion, the differential diagnosis should include myotonic dystrophy in any patient with respiratory and locomotor system disorders.

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## ACKNOWLEDGEMENTS

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We thank Dr Rumezka Kazancioglu, for her support and help for this study.

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## **1<sup>ST</sup> NATIONAL UPDATE IN RESPIRATORY MEDICINE**

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# Hepatic Hydrothorax without Ascitis

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## ABSTRACT

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A transudative pleural effusion may complicate cirrhosis of liver following the development of ascitis. However, hepatic hydrothorax without associated ascitis is very rare. We report one such case, occurring in a 62-year-old female who presented with dyspnoea on exertion. [Indian J Chest Dis Allied Sci 2007; 49: 177-179]

**Key words:** Cirrhosis, Pleural effusion, Transudate.

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## INTRODUCTION

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Hepatic hydrothorax, the presence in a cirrhotic patient of a significant pleural effusion in the absence of primary pulmonary or cardiac disease is uncommon, the incidence ranging between 0.4 percent to 12 percent.<sup>1-3</sup> Clinical ascitis is almost always evident and the pleural effusion is usually on the right side, although bilateral effusions may also be seen.<sup>4</sup> Hepatic hydrothorax without associated ascitis (HHAA) is a very rare complication of decompensated liver cirrhosis.<sup>5-7</sup> In earlier reports, ascitis was excluded on clinical grounds that could miss small quantities of fluid<sup>5,6</sup> while in another reported case<sup>7</sup>, other possible causes such as hypoalbuminaemia, were not excluded. Thus, true HHAA without any other cause for the pleural collection is likely to be even rare. We report one such case.

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## CASE REPORT

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A 62-year-old female presented with complaints of gradually progressive dyspnoea and dry cough for three years. Four years prior to this, she was diagnosed as a case of liver cirrhosis of unknown aetiology, confirmed by biopsy. The liver biopsy revealed altered architecture with pseudolobule formation and fibrous bands infiltrated with chronic inflammatory cells. The patient had not undergone upper gastro-intestinal (GI) endoscopy. However, a contrast enhanced computed tomographic (CECT) scan of the abdomen showed evidence of portal hypertension. The portal vein was engorged, measuring 15 mm in diameter in the region of porta hepatis. Multiple enhancing collaterals were

seen in perigastric and paraoesophageal regions, interlobar fissure of liver, the splenic hilum and in the retroperitoneal area. HBsAG and anti-HCV antibodies were negative. Other antibodies such as anti-LKM, ANA, antimitochondrial and anti-smooth muscle antibodies were not investigated. A chest radiograph taken earlier had revealed a right-sided pleural effusion that was tapped twice in another hospital six months back and had turned out to be a transudate. Physical examination followed by a plain chest radiograph confirmed the presence of a free effusion.

Blood counts were normal. Ultrasound examination confirmed the pleural effusion but did not reveal any evidence of ascitis. A diagnostic tap showed slightly yellowish but clear fluid that was a transudate with a total protein 1.6 mg%, sugar 70 mg%, total cells 350 cells per mm<sup>3</sup> with 90% lymphocytes and an adenosine deaminase level of 34 IU/L (normal range less than 40 IU/L, borderline upto 60 IU/L, positive above 60 IU/L). No pyogenic or acid-fast bacilli organisms were found on smears and culture. The blood sugar, and renal function tests were within normal limits. The liver function tests revealed a total bilirubin of 1.4 mg% with conjugated being 0.6 mg%, SGOT 82 IU/L, SGPT 42 IU/L, alkaline phosphatase 192U/L, serum total protein 7.2 g% and albumin 3.6 g%. A repeat serum albumin estimation one month later showed levels of 3.4 g%. Urine examination was not remarkable. Human immunodeficiency virus (HIV) ELISA was not done as it was not clinically indicated.

Echocardiography showed an ejection fraction of 58%, with no structural and wall motion abnormality. The thyroid status was also normal. Contrast computed tomography (CT) scan of the chest and abdomen showed a right-sided pleural effusion with a shrunken

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liver, splenomegaly with absence of ascitis (Figures 1 and 2). Based on the previous diagnosis of cirrhosis of liver absence of ascitis on CT, a transudate pleural effusion and exclusion of other causes for such an effusion, a diagnosis of hepatic hydrothorax without associated ascitis (HHAA) was made. The patient was put on diuretics (furosemide and spironolactone) with salt restriction. The symptoms gradually subsided. However, a plain chest radiograph taken 12 weeks later showed only a partial resolution of the effusion.

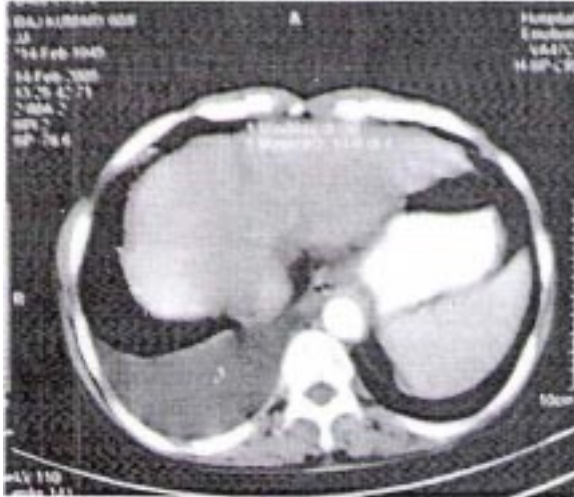


Figure 1. Contrast enhanced computed tomographic (CECT) scan of the lower chest and upper abdomen showing a right-sided pleural effusion with a shrunken liver and splenomegaly.



Figure 2. Contrast enhanced tomographic (CECT) scan of the lower abdomen showing absence of ascitis.

## DISCUSSION

Pleural effusion in patients with decompensated cirrhosis of liver may present asymptotically and be

discovered incidentally on a chest radiograph or the patient may have dyspnoea, cough and even hypoxaemia and overt respiratory failure.<sup>8</sup> Rarely, there may be an effusion without any detectable ascitis.<sup>5-7</sup> This entity has been labeled as hepatic hydrothorax without associated ascitis (HHAA). Rubinstein *et al*<sup>5</sup> documented two such cases in which the diagnosis was made by injection of radioisotope colloid demonstrating a one-way transdiaphragmatic flow of fluid from the peritoneal to pleural cavity. The possibility of small amount of ascitic fluid remained as ultrasonography was not done. Serrat *et al*<sup>7</sup> recently reported a case of HHAA in a 58-year-old female with hepatic cirrhosis, developing acutely after a right crural hernia surgery. She, however, had minimal ascitis on ultrasonography. In 27 cases reported between 1937 to 1997, only two had serum albumin concentrations above 3.5 g%.<sup>6</sup> Hypoalbuminaemia itself may cause a pleural effusion. Thus, true HHAA without any other explanation for effusion is likely to be even rarer.

While demonstration of a peritoneal-pleural communication using a radiolabelled colloid is diagnostic, the history of biopsy-confirmed cirrhosis with a transudative right-sided pleural effusion, exclusion of all causes of such a fluid and CT confirmation of absence of ascitis gave a virtually certain diagnosis of HHAA in the present case.

Existence of diaphragmatic defects in the tendinous portion of the diaphragm through which a unidirectional flow occurs is the likely mechanism for the development of pleural effusion in patients with cirrhosis.<sup>9</sup> Formation of HHAA would be favoured when the fluid moves to the pleural space before it can accumulate in the peritoneal cavity.<sup>10</sup> Other proposed mechanisms include hypoproteinemia, leakage of plasma through hypertensive azygos system or lymphatic leakage from thoracic duct.

Management of hepatic hydrothorax is difficult as diuretics and salt-water restriction usually fail to clear the fluid completely. However, it usually runs a benign course as was observed in our patient. In patients with disabling dyspnoea, a more aggressive approach may be required. Treatment options in such cases include repeated thoracentesis as a palliative measure and more definitive modalities such as tube thoracostomy with pleurodesis, peritoneovenous shunts, thoracoscopic diaphragmatic repair and liver transplantation.<sup>8</sup> Each of these treatments has limitations, technical difficulties and variable success rate.

While the occurrence of a right-sided pleural effusion in a patient with cirrhosis and ascitis is likely to be a complication of the latter, a search for other causes should still be made as in upto 30% of cases, there may be another cause.<sup>11</sup> Similarly, in HHAA, other causes of a transudative effusion must be ruled out as a potentially treatable cause may be found.

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# Treatment of Probable Idiopathic Pulmonary Fibrosis with Long Term Doxycycline, a Matrix Metalloproteinase Inhibitor

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[Indian J Chest Dis Allied Sci 2007; 49: 180]

Idiopathic pulmonary fibrosis (IPF) is a disease of significant mortality and morbidity without a known aetiology. The prevailing pathophysiological concept has shifted from inflammation induced fibrosis<sup>1</sup> to a disease of fibroblast proliferation and dysregulated fibrogenesis.<sup>2</sup> One of the proposed mechanisms is that an abnormal lung remodelling ensues from accumulation of extracellular matrix following epithelial injury.<sup>3</sup> This is associated with a simultaneous dysregulated activity of matrix metalloproteinases (MMPs), a group of enzymes that can be related to release of fibroblast growth factor which is important for continuous stimulation of fibrogenesis.<sup>4,5</sup> Hence, prevention of MMP activity could therapeutically benefit patients with IPF.

A 60-year-old male ex-smoker presented with dry cough and progressive shortness of breath for one-and-a-half months. On investigation, he was found to have interstitial lung disease with the high resolution computed tomographic (HRCT) scan of chest suggesting IPF. The patient refused any invasive test and treatment with steroids or cytotoxic drugs. He was therefore, advised empirically doxycycline, a matrix metalloproteinase inhibitor with consent. In the following months the patient has shown a significant improvement in symptoms, physiological and radiological parameters. His cough and dyspnoea have virtually disappeared. On the first visit arterial oxygen saturation (SpO<sub>2</sub>) at rest had dropped from a baseline of 98% on room air to 92% following walking a distance of only 20 yards. After treatments for two years, he did not show any fall in SpO<sub>2</sub> even after walking a distance of 500 yards. His forced vital capacity improved from 2.12 L to 2.45 L after seven months with the corresponding TLCO (%) and TLCO/VA improving from 49.4% to 58.9% and 102.6 to 127.9, respectively. Serial chest radiographic have also shown significant improvement. The patient has been stable with a functionally improved state and has shown no radiological deterioration over the two years of follow-up.

Since, the benefit of conventional treatment of IPF with steroid and immunosuppressive agents is unsatisfactory<sup>6</sup> with significant toxicities, we decided to treat the patient with doxycycline, a known MMPs inhibitor<sup>7</sup> after he refused the option of conventional therapy. Doxycycline has been approved by the FDA for use in the periodontal diseases<sup>7</sup> and the long term use of doxycycline in several disease states has been found to have minimal side effects. Although we did not perform lung biopsy or bronchoalveolar lavage, an antibiotic effect of doxycycline is unlikely in this case. The remission in this patient suggests that the drug merits further evaluation with an ethically sound randomised clinical trial.

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## **Exploiting Immunology and Molecular Genetics for Rational Vaccine Design Against Tuberculosis**

**S.H.E. Kaufmann, S. Baumann and A. Nasser Eddine**

*The International Journal of Tuberculosis and Lung Disease 2006; 10: 1068-79*

One hundred years after the Nobel Prize was awarded to Robert Koch for his work on tuberculosis (TB) and 85 years after the development of the attenuated vaccine strain, *Mycobacterium bovis* bacille Calmette-Guerin (BCG), by Albert Calmette and Camille Guerin, effective prevention measures against TB are still not available. However, the first decade of the 21st century will witness the implementation of clinical trials with several novel vaccine candidates. These candidates fall into two groups. (1) subunit vaccines aimed at boosting the immune response induced by a BCG prime, and 2) recombinant (r)BCG improved to replace the current

BCG vaccine strain. For boosting, protein and DNA vaccines in suitable adjuvant or delivery systems, respectively, as well as recombinant viral carriers, such as recombinant modified vaccinia virus Ankara, are being tested. For rBCG prime, a vaccine strain with higher immunogenicity and a strain overexpressing a dominant antigen have been developed. These vaccine candidates will have passed phase I clinical trials before the end of 2006. The goal for the future would be to have these novel vaccine candidates tested in different combinations to facilitate the design of the most efficacious vaccination protocol.

## **Introduction and Diagnosis of Tuberculosis in Children**

### **Stop TB Partnership Childhood TB Subgroup**

*World Health Organization, Geneva, Switzerland: Guidance for National Tuberculosis Programmes on the management of tuberculosis in children*

*The International Journal of Tuberculosis and Lung Disease 2006; 10: 1091-7*

About one million children develop tuberculosis (TB) annually worldwide, accounting for about 11% of all TB cases. Children with TB differ from adults in their immunological and pathophysiological response in ways that may have important implications for the prevention, diagnosis and treatment of TB in children. There is an urgent need to improve the diagnosis and management of children with TB, and the prevention of TB in children, by ensuring their inclusion under the implementation of the Stop TB strategy by National TB Programmes. Critical areas for further research include a better understanding of the epidemiology of childhood TB, vaccine development, the development of better diagnostic techniques, new drug development, and the optimal formulations and dosing of first- and

second-line TB drugs in children.

Specifically regarding the diagnosis of TB in children, this relies on a careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g., tuberculin skin test, chest radiograph and sputum smear microscopy. Although bacteriological confirmation of TB is not always possible, it should be sought whenever possible, e.g., by sputum microscopy in children with suspected pulmonary TB who are old enough to produce a sputum sample. A trial of treatment with TB medications is not generally recommended as a method to diagnose TB in children. New, improved diagnostic tests are urgently needed.

## **Symptom-Based Questionnaire for Differentiating COPD and Asthma**

**David G. Tinkelman, David B. Price, Robert J. Nordyke, R.J. Halbert, Sharon Isonaka, Dmitry Nonikov, Elizabeth F. Juniper, Daryl Freeman, Thomas Hausen, Mark L. Levy, Anders Ostrem, Thys van der Molen and Constant P. van Schayck**

*Respiration 2006; 73: 296-305*

**Background.** Many patients with obstructive lung disease (OLD) carry an inaccurate diagnostic label. Symptom-

tom-based questionnaires could identify persons likely to need spirometry.

**Objectives.** We prospectively tested questions derived from a comprehensive literature review and an international Delphi panel to help identify chronic OLD (COPD) in persons with prior evidence of OLD.

**Methods.** Subjects were recruited via random mailing to primary-care practices in Aberdeen, Scotland, and Denver, Colorado. Persons aged 40 and older reporting any prior diagnosis of OLD or any respiratory medications in the past year were enrolled. Participants answered 54 questions covering demographics and symptoms and underwent spirometry with reversibility testing. A study diagnosis of COPD was defined by fixed airway obstruction as measured by post-bronchodilator  $FEV_1/FVC < 0.70$ . We examined ability of individual questions in a multivariate framework to discriminate between persons with and without the

study diagnosis of COPD.

**Results.** 597 persons completed all investigations and proceeded to analysis. The list of 54 questions yielded 52 items for analyses, which was reduced to 19 items for entry into a multivariate regression model. Nine items had significant relationships with the study diagnosis of COPD, including increased age, pack-years, worsening cough, breathing-related disability or hospitalization, worsening dyspnea, phlegm quantity, cold going to the chest, and receipt of treatment for breathing. Individual items yielded odds ratios ranging from 0.33 to 20.7. This questionnaire demonstrated a sensitivity of 72.0 and a specificity 82.7.

**Conclusions.** A short, symptom-based questionnaire identifies persons more likely to have COPD among persons with prior evidence of OLD.

## Symptom-Based Questionnaire for Identifying COPD in Smokers

David B. Price, David G. Tinkelman, R.J. Halbert, Robert J. Nordyke, Sharon Isonaka, Dmitry Nonikov, Elizabeth F. Juniper, Daryl Freeman, Thomas Hausen, Mark L. Levy, Anders Ostrem, Thys van der Molen and Constant P. van Schayck

*Respiration 2006; 73: 285-95*

**Background.** Symptom-based questionnaires may enhance chronic obstructive pulmonary disease (COPD) screening in primary care.

**Objectives.** We prospectively tested questions to help identify COPD among smokers without prior history of lung disease.

**Methods.** Subjects were recruited via random mailing to primary care practices in Aberdeen, UK, and Denver, Colo., USA. Current and former smokers aged 40 or older with no prior respiratory diagnosis and no respiratory medications in the past year were enrolled. Participants answered questions covering demographics and symptoms and then underwent spirometry with reversibility testing. A study diagnosis of COPD was defined as fixed airway obstruction as measured by postbronchodilator  $FEV_1/FVC < 0.70$ . We examined the ability of individual questions in a multivariate framework to correctly discriminate between

persons with and without COPD.

**Results.** 818 subjects completed all investigations and proceeded to analysis. The list of 54 questions yielded 52 items for analysis, which was reduced to 17 items for entry into multivariate regression. Eight items had significant relationships with the study diagnosis of COPD, including age, pack-years, body mass index, weather-affected cough, phlegm with out a cold, morning phlegm, wheeze frequency, and history of any allergies. Individual items yielded odds ratios ranging from 0.23 to 12. This questionnaire demonstrated a sensitivity of 80.4 and specificity of 72.0.

**Conclusions.** A simple patient self-administered questionnaire can be used to identify patients with a high likelihood of having COPD, for whom spirometric testing is particularly important. Implementation of this questionnaire could enhance the efficiency and diagnostic accuracy of current screening efforts.

## The Future in Diagnosis and Staging of Lung Cancer: Positron Emission Tomography

Barbara M. Fischer and Jann Mortensen

*Respiration 2006; 73: 267-76*

Since its introduction in 1974, positron emission tomography (PET) has gained widespread use, especially in diagnosis and staging of lung cancer. In this respect,  $^{18}F$ -fluorodeoxyglucose (FDG) is by far the most used PET

tracer exploiting the increased glucose uptake and metabolism in malignant cells. A large number of studies have suggested that addition of FDG-PET to conventional workup can improve diagnosis and

staging in patients with non-small cell lung cancer (NSCLC). In meta-analysis, the sensitivity and specificity of PET in diagnosing single pulmonary nodules and masses is found to be 96 and 78%, respectively. In mediastinal staging, the sensitivity and specificity of PET is estimated to be 83 and 92%. In order to achieve high diagnostic values from PET, it is necessary to pay attention to a number of pitfalls, e.g., the uptake of FDG by inflammatory cells causing false-positive results, as well as size and histology of the tumour in order to avoid false-negative results. In 2001,

the first integrated PET/computed tomography (CT) was installed, and since then, the use of this modality has expanded steadily, thereby decreasing examination time and overcoming the lack of anatomical details on PET. Recently, PET and PET/CT have become increasingly integrated in therapy planning and evaluation: response evaluation during and after chemotherapy, restaging after neoadjuvant therapy, planning of radiotherapy and detection of recurrent disease are all examples of emerging indications for PET and PET/CT in managing patients with lung cancer.

## Tuberculosis in Patients Receiving Anti-TNF Agents Despite Chemoprophylaxis

L. Sichletidis, L. Settas, D. Spyrtatos, D. Chloros and D. Patakas

*The International Journal of Tuberculosis and Lung Disease 2006; 10: 1127-32*

**Setting.** A major concern surrounding the use of tumor necrosis factor-alpha (TNF- $\alpha$ ) inhibitors is their potential to increase the risk of opportunistic infections, particularly tuberculosis (TB).

**Objective.** To estimate the incidence of active TB in patients with rheumatic diseases receiving anti-TNF drug therapy and to evaluate the effectiveness of an antituberculosis chemoprophylaxis regimen.

**Design.** Retrospective study of the files of 613 patients with rheumatic diseases who had received anti-TNF agent (etanercept, infliximab and adalimumab) therapy from July 2000 to June 2004 at the Aristotle University of Thessaloniki, Greece. All patients had a tuberculin skin test (TST) and a postero-anterior chest radiograph (CXR) prior to anti-TNF therapy. When indicated (TST  $\geq$ 10 mm

and/or fibrotic lesions on CXR), treatment for latent TB was established (6 months isoniazid [INH] or three months INH and rifampicin [RMP]). Anti-TNF agent therapy was started again 2 months later.

**Results.** Of 45 patients who fulfilled the criteria for chemoprophylaxis, only 36 were treated correctly. Eleven patients developed active TB 2–35 months after the beginning of anti-TNF therapy. Six patients developed pulmonary and five extra-pulmonary TB. Eight of these had received infliximab and three adalimumab.

**Conclusions.** The incidence of active TB in this study population was estimated at 449 cases per 100 000 population annually. Anti-tuberculosis chemoprophylaxis was only of partial preventive success in these patients.

## Position of a Chest Tube at Video-Assisted Thoracoscopic Surgery for Spontaneous Pneumothorax

Fengshi Chen, Tetsu Yamada, Akihiro Aoyama, Noritaka Isowa and Koji Chihara

*Respiration 2006; 73: 329-33*

**Background.** Video-assisted thoracoscopic surgery (VATS) is a good therapeutic option for young patients with primary spontaneous pneumothorax (PSP), but there sometimes exists unexpected prolonged hospital stay due to air leak after the operation.

**Objectives.** The goal of this retrospective study was to clarify if the position of the chest tube placed at VATS for PSP affected the periods of postoperative hospital stay.

**Methods.** Seventy-one cases with PSP under age 40 who undertook VATS from January 1994 to February 2001 were examined for several factors. They were

classified into two groups by the location of the tip of the chest tube placed at VATS as follows: upper medial pleural space (group I) and outside of there (group II).

**Results.** Fifty-three of the 71 cases (75%) were classified in group I and 18 (25%) were in group II. Between the two groups, there were no differences as to preoperative characteristics of the patients and intraoperative findings of blebs or bullae. On the other hand, postoperative air leak-related complications were more frequent in group II than in group I ( $p=0.004$ ). Mean postoperative hospital stay was  $5.1 \pm 1.9$  days in group I and

8.4 ± 4.3 days in group II (p<0.0001).

**Conclusions.** Patients with the tip of the chest tube in the upper medial pleural space at VATS could be

discharged earlier than the other patients. The chest tube placement is one of the important factors for the outcome of VATS for PSP.

## Relationship Between Calcium-Activated Chloride Channel 1 and MUC5AC in Goblet Cell Hyperplasia Induced by Interleukin-13 in Human Bronchial Epithelial Cells

Masanori Yasuo, Keisaku Fujimoto, Tsuyoshi Tanabe, Hironobu Yaegashi, Kenji Tsushima, Keiichirou Takasuna, Takeshi Koike, Mutsuo Yamaya and Toshio Nikaido

*Respiration* 2006; 73: 347-59

**Background.** Interleukin (IL)-13 has recently been reported as the major T-helper 2 cytokine involved in mucus overproduction and oversecretion in allergic airways. However, the relationship between human calcium-activated chloride channel-1 (hCLCA 1) and MUC5AC induced by IL-13 in vitro has not been fully investigated.

**Objectives.** The present study examines whether IL-13 induces the expression of hCLCA1 in normal human bronchial epithelial (NHBE) cells. We also investigated the relationship between hCLCA1 and MUC5AC expression and the development of goblet cell hyperplasia (GCH).

**Methods.** NHBE cells were isolated from human bronchi, and cultured with an air-liquid interface. hCLCA1 and MUC5AC gene and protein expression, as well as GCH were examined in the cells after exposure to IL-13.

**Results.** Incubation with IL-13 for 14 and 21 days increased the total number of epithelial cells, the number of periodic acid-Schiff (PAS)-stained epithelial cells, the number of goblet cells, as well as expression of mRNA and protein of hCLCA1 and MUC5AC. The number of goblet cells with secretory granules also increased after 21 days of incubation with IL-13. Niflumic acid, a chloride channel inhibitor, reduced mRNA expression of hCLCA1 and MUC5AC, and reduced the number of PAS-positive cells after incubation with IL-13. NHBE cells exposed or not to IL-13 expressed IL-13 receptor  $\alpha_1$  (IL-13R $\alpha_1$ ), and an antibody to IL-13R $\alpha_1$  also reduced the number of PAS-positive cells after exposure to IL-13.

**Conclusions.** IL-13, might induce the expression of MUC5AC and hCLCA1 gene and protein in well-differentiated NHBE cells. These cells might also differentiate into goblet cells and become hyperplastic.

## *OBITUARY*

### **Dr Hans Kumar**

With deep sense of sorrow, the Secretary, NCCP(I), informs that Professor Hans Kumar, Founder Fellow of the National College of Chest Physicians (India) left for heavenly abode. We deeply mourn the sudden and untimely demise of Professor Kumar and pray to God for peace to the departed Soul.

Professor Kumar was an excellent Teacher, Research worker, good Administrator and Cardiothoracic Surgeon.

He was Ex-Principal and Professor of Tuberculosis and Chest Diseases, SMS Medical College, Jaipur.

Professor Kumar was a source of encouragement and inspiration to most of us.

A 2-minute silence was observed at the Governing Council and General Body meetings of the NCCP(I) meeting to pay our respect to a noble Soul.

### **Dr Janki Prasad Srivastava**

With deep sense of sorrow, the Secretary, NCCP(I), informs that Dr Janki Prasad Srivastava, Founder Fellow of the National College of Chest Physicians (India) left for heavenly abode. We deeply mourn the sudden and untimely demise of Dr Srivastava and pray to God for peace to the departed Soul.

Dr Srivastava was an excellent Teacher, Research worker and good Administrator.

He was Ex-Consultant of Tuberculosis and Chest Diseases.

Dr Srivastava was a source of encouragement and inspiration to most of us.

A 2-minute silence was observed at the Governing Council and General Body meetings of the NCCP(I) meeting to pay our respect to a noble Soul.

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More than six authors:

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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.

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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.

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

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

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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.

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

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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.

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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.

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**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, Pfaffler 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/>.

39. *Part of a homepage/Web site*

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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