

## ATTENTION SUBSCRIBERS

Due to substantial increase in the cost of printing, paper, postal charges and other overhead expenses, it has been felt necessary to revise the subscription rates w.e.f. January, 2011. New rates are given below:

### **Subscription Rates**

[w.e.f. 1st January, 2011]

	Individual		Institutes/Hospitals/Colleges, etc.	
	India (in ₹)	Overseas (Airmail) (in US \$)	India (in ₹)	Overseas (Airmail) (in US \$)
Single Issue	400.00	60.00	500.00	100.00
Per Volume (4 issues)	1300.00	200.00	1800.00	350.00

1. Overseas subscription rates include airmail postal charges.
2. Subscription Agencies are eligible for a 10% discount on annual rates for institutional subscription only. Agencies must provide complete address of the institution for which subscription is sent in their subscription order.
3. Payments should be made only by **Banker's Cheque/Demand Draft**; drawn in favour of **The Director, V.P. Chest Institute, Delhi**.
4. **Subscription rates are not subject to any Tax Deduction at Source.**
5. Subscribers are advised to get their copies by "**Registered Post**" by making an advance payment of ₹400/- per year in addition to Subscription rates, if subscription is made for one year (in case of a single copy, ₹100/- to be added).
6. The rates are subject to revision at any time by announcement in the Journal.
7. Subscription can be enrolled only on receipt of full payment in advance. Copies will not be sent if part payment is received.
8. Our responsibility ceases once we hand over the copies to the Post/Courier Office. We are not responsible for any delay/loss/damage in transit. We hold the receipt from the Post/Courier Office as proof. The Journal Office is not liable to replace copies lost in transit.
9. **Requests for missing issues will be considered if made within one month of the publication of a particular issue (i.e. for January-March issue → upto April, for April-June issue → upto July, for July-September issue → upto October and for October-December issue → upto January). Supply of replacement copy will be subject to availability.**

*Publishers/Editor-in-Chief*

# THE INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES

**Editor-in-Chief**S.N. GAUR, *Delhi***Editors**

S.K. Jindal, *Chandigarh*  
 Ashok Shah, *Delhi*  
 S.K. Sharma, *New Delhi*  
 Alladi Mohan, *Tirupati*  
 S.K. Chhabra, *Delhi*

**Associate Editors**

Dheeraj Gupta, *Chandigarh*  
 J.M. Joshi, *Mumbai*  
 J.C. Suri, *New Delhi*

*Founded by:* Professor R. Viswanathan  
 Founder-Director, V.P. Chest Institute

THE INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES (ISSN 0377-9343) is published quarterly, by the Vallabhbhai Patel Chest Institute, University of Delhi, Delhi in association with the National College of Chest Physicians (India). The Journal covers the Clinical and Experimental work dealing with all aspects of Chest Diseases and Allied Sciences. It publishes Original Articles, Review Articles, Radiology Forum, Case Reports, Short Communications, Book Reviews.

Copyright © with Vallabhbhai Patel Chest Institute, University of Delhi, Delhi. All rights reserved; no part of this publication should be reproduced and/or stored in a retrieved system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission from the Publishers in India and/or in the USA by the *Copyright Clearance Center*, 222, Rosewood Drive, Danvers, MA 01923.

The statements and opinions contained in this Journal are solely those of the authors/advertisers. The Publishers and Editor-in-Chief, its Editorial Board Members, and employees disown all responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements contained in this Journal.

*The Journal has a wide International and National Circulation/ Exchange and is abstracted and indexed in Index Medicus, Medline, IndMed, INSEAR, and Ulrich's Directory.*

**Editorial Board**

R. Agarwal, *Chandigarh*  
 A.N. Aggarwal, *Chandigarh*  
 G. Ahluwalia, *Ludhiana*  
 J.N. Banavaliker, *Delhi*  
 R.S. Bedi, *Patiala*  
 D. Behera, *New Delhi*  
 Arati Bhatia, *Delhi*  
 Mridula Bose, *Delhi*  
 Dhruva Chaudhry, *Rohtak*  
 Anuradha Chowdhary, *Delhi*  
 D.J. Christopher, *Vellore*

R.K. Dewan, *New Delhi*  
 R. Guleria, *New Delhi*  
 K.B. Gupta, *Rohtak*  
 V.K. Jain, *Bikaner*  
 A.K. Janmeja, *Chandigarh*  
 T. Kadiravan, *Puducherry*  
 S. Kashyap, *Shimla*  
 G.C. Khilnani, *New Delhi*  
 Jai Kishan, *Patiala*  
 Raj Kumar, *Delhi*  
 T. Mohan Kumar, *Coimbatore*

A.A. Mahashur, *Mumbai*  
 B.K. Menon, *Delhi*  
 B.N. Panda, *Bhubneshwar*  
 R. Prasad, *Lucknow*  
 M. Rahman, *Delhi*  
 G.K. Rath, *New Delhi*  
 J.K. Samaria, *Varanasi*  
 R. Sarin, *New Delhi*  
 Raj B. Singh, *Chennai*  
 Virendra Singh, *Jaipur*  
 Z.F. Udawadia, *Mumbai*

**Journal Coordinators**

R.K. Gupta, *Delhi*  
 D.K. Sahu, *Delhi*

## NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

### GOVERNING COUNCIL

*[w.e.f.: 1st April 2011]*

**President** (2011-2012)

Dr G.C. Khilnani  
New Delhi

**Vice-President** (2010-2012)

Dr J.C. Suri  
New Delhi

**President-Elect** (2012-2013)

Vacant  
Due to death of Dr R.C. Jain

**Immediate Past President** (2010-2011)

Dr D. Behera  
New Delhi

**Secretary** (2010-2013)

Dr S.N. Gaur  
Delhi

**Joint Secretary** (2010-2012)

Dr Rajesh N. Solanki  
Ahmedabad

**Treasurer** (2009-2012)

Dr V.K. Singh  
Delhi

#### Councillors (2011-2013)

Dr Bharat Gopal  
New Delhi

Dr Dheeraj Gupta  
Chandigarh

Dr Rajendra Prasad  
Lucknow

Dr K.B. Gupta  
Rohtak  
(upto 2012)

Dr V.K. Jain  
Bikaner

Dr A.K. Janmeja  
Chandigarh

#### Zonal Chairmen

**North**

Dr J.C. Suri  
New Delhi

**South**

Dr P. Ravindran  
Trivandrum

**Central**

Dr S.K. Katiyar  
Kanpur

**East**

Dr S.N. Tripathy  
Cuttack

**West**

Dr N.K. Jain  
Jaipur

#### Co-opted Member (NAPCON-2011)

Dr Raj Kumar  
Delhi

---

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


---

**Vol.53****October–December 2011****No.4**


---

## CONTENTS

Pages

**Editorial**

Allergen immunotherapy: the scientific facts

*S.N. Gaur*

.. 205

**Original Articles**

Prevalence of venous thromboembolism in acute exacerbations of chronic obstructive pulmonary disease: an Indian perspective

*T.S. Dutt and Z.F. Udhwadia*

.. 207

Assessment of severity of methaemoglobinemia following fiberoptic bronchoscopy with lidocaine

*Sajal De*

.. 211

Breath carbon monoxide level of non-smokers exposed to environmental tobacco smoke

*R. Kumar, G.C. Mahakud, J.K. Nagar, S.P. Singh, N. Raj, K. Gopal and V.K. Vijayan*

.. 215

**Radiology Forum**

Bone scintigraphy in pulmonary alveolar microlithiasis

*M. Shah and J.M. Joshi*

.. 221

**Case Reports**

Mediastinal haematoma: a rare complication following insertion of central venous catheter

*P. Gupta, S. Guleria and S. Sharma*

.. 225

Polymyositis presenting with respiratory failure

*J. Maclean, R.B. Singh and Z.A. Sayeed*

.. 229

Type A thymoma with generalised *Myasthenia gravis**Manjiri Karandikar and R.M. Swami*

.. 233

Intrapulmonary teratoma presenting with tricoptysis: a case report and review of the literature

*J. Rawat, S. Saini, S. Raghuvanshi, G. Sindhwani and V. Kesarwani*

.. 237

**Brief Communication**

Difference in the outcome of patients with different grades of initial sputum positivity under the revised national tuberculosis control programme

*A. Mukherjee, R. Singla, I. Saha, A. Sarkar and P. Bhattacharyya*

.. 241

**Book Review***NCCP Textbook of Respiratory Medicine*

.. 243

**Correspondence***Burkholderia pseudomallei*: an uncommon cause of bacteraemic pneumonia in a diabetic

.. 244

**Abstracts' Service**

.. 245

**Authors' Index**

.. 248

**Guidelines to Authors**

.. 251

**Announcements**202, 204, 210, 220, 223,  
224, 232, 236, 240

## THE INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES

Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110 007

- Editor-in-Chief & Publisher : **Prof. S.N. Gaur**  
 Place of Publication : Delhi, India  
 Web Address : <http://www.vpci.org.in>  
 ISSN No. : 0377-9343  
 Language : English  
 Periodicity : Quarterly (Published in the months of January, April, July and October)  
 Method of Printing : Offset Process  
 Overall Size : 27.5 cm x 20.5 cm  
**Print Area** : **24.0 cm x 17.0 cm** (Advertisement materials required in Print Area size only)
- Spectrum of Readership : The readership comprises faculty members of medical colleges/research institutions, chest physicians, cardiologists, medical practitioners, postgraduate students, research scholars, biomedical scientists and libraries of medical colleges/hospitals; including 800 fellows/members of the National College of Chest Physicians (India)
- Countries where it is Circulated : India, USA, Canada, South American countries, USSR, UK, The Netherlands, Germany, Italy, African countries, Middle East, Japan, China, Australia and New Zealand
- International Standing : Abstracted and indexed in the globally reputed abstracting periodicals such as Index Medicus, Medline, IndMed, INSEAR, and Ulrich's Directory, etc

### ADVERTISEMENT RATES\*(w.e.f. 1<sup>st</sup> January 2011)

	<i>Per Issue</i>	<i>Per Volume (4 issues)</i>
Ordinary Full Page	₹ 8,000.00	₹ 25,000.00
Back Cover	₹ 15,000.00	₹ 55,000.00
Inside Cover	₹ 12,000.00	₹ 45,000.00
Facing Contents	₹ 15,000.00	₹ 55,000.00
<b>Colour Ads</b>	<b>50% extra on above rates</b>	

- \*Note:**
1. *The above rates are not subject to any Tax Deduction at Source.*
  2. *Advertisement materials (four positives in case of colour ads) are to be provided by the advertiser in a CD with a print out (hard copy) of the advertisement.*
  3. *A discount of 10% will be offered to Advertising Agencies only.*
  4. *Advertisement Payments (along with the space order and advertisement material) should be made in advance through Banker's Cheque / Bank Drafts only and should be drawn in favour of the **DIRECTOR, V. P. CHEST INSTITUTE, DELHI.***

## Allergen Immunotherapy: The Scientific Facts

Allergy affects various systems of the body but primarily involves lung, nose and skin. The mediators released immune reaction of antigens and immuno-globulin (Ig) E produces symptoms of allergy in genetically pre-determined system. The methods of combating IgE-mediated allergic disease is allergic immunotherapy.

Immunotherapy, was previously known as desensitisation and/or hyposensitisation is a treatment modality to suppress IgE-mediated symptoms by directing the immune system to produce blocking (IgG) antibodies instead of IgE. This is achieved gradually by administering the increasing doses of antigen(s) from a very diluted amount to the maintenance dose for that particular patient. The maintenance dose varies from person to person. The concept of immunotherapy is very old and goes back to the inducing of *Vish-kanyas* in Indian literature, where a girl was given increasing doses of poison starting from the diluted one and ultimately, she could tolerate the large amount of poison sufficient to kill a strongly built person. In scientific world, first human experiment using immunotherapy for hay-fever was done by Noon and Freeman in 1911. The concept got approval from the Federal Drug Authority (FDA) (USA) in the year 1949.

Since then there have been several trials on immunotherapy and most of them demonstrated favourable results. Laboratory experiments also supported the benefit showing a decrease in IgE, an increase in IgG, a decrease in histamine release by basophil after exposure to antigen, and a decrease in airway reactivity apart from the improvement in the clinical symptoms.

According to recent concept, allergen acts through T-helper 2 (TH2) cells resulting an increase in their number and increased interleukin-4 (IL-4), which then leads to production of more IgE. Simultaneously, there is lowering of interferon-gamma (IFN- $\gamma$ ). It has been demonstrated that specific immunotherapy generates TH1 response reducing IL-4 and IgE production. The TH1 cytokines upregulates cell mediated immune defence mechanisms, promoting phagocytosis and natural killer cell activity (IFN- $\gamma$  and IL-12) and cross inhibit TH2 responses.<sup>1</sup>

The methods followed for detecting the offending allergens prior to immunotherapy are skin tests. Skin testing is usually done by intradermal injection of antigen or by prick test. The intradermal tests have more chances of false positive, whereas prick tests yield more false negative results. In our opinion, intradermal tests should be done first and prick tests may be performed later for further confirmation. Recently, it has been shown that chances of anaphylaxis is more with prick test method than intradermal method. *In*

*vitro* methods, e.g. RAST/ELISA can also be used for appropriate diagnosis alongwith *in-vivo* procedures.

An unbiased approach is very much needed in practising immunotherapy. Unfortunately, as the concept floated in the community more and more misuse, overuse of immunotherapy has started, resulting in the controversies. The believers were sticking to its usefulness, whereas others were having contradictory or unequivocal statements. There was a time when persons laughed as to how an insect as large as cockroach can enter the respiratory tract to produce allergy. Now insect allergy, mainly of antigenic proteins from faeces and urine of the insects is an established identity.

Allergy practice, *i.e.* specific immunotherapy requires plenty of time for probing the patient to record detailed history of illness, proper skin testing, unbiased interpretation, judicious prescription writing, precautions of side effects and adequate follow-up.

Immunotherapy has an important drawback, *i.e.* risk of developing anaphylaxis, though in rare occasions especially while skin testing, during increase in the dose of antigen and/or peak season for that antigen, during acute attacks, injecting antigen intravenously (IV) or intramuscularly (IM) by mistake or by ignoring signs of side effects in previous dose, etc. Deaths due to above reasons has cautioned that person practicing allergy should be trained and the set-up should have requisite facilities for managing anaphylaxis. Safer methods of immunotherapy, like modification of allergen to retain antigenicity and almost negligible allergenicity are being developed, e.g. polymerised antigens, which will be quite safe and provide better results. Recently, trials are underway to produce antibodies against IL-4, which is raised after antigen exposure. Use of such antibodies will block IL-4, and thus, IL4 will not be available for further reaction *i.e.* production of IgE.

The safer and easier method for drug delivery in immunotherapy is being tried—oral, nasal, spit methods.<sup>3-6</sup> Presently, sublingual immunotherapy (SLIT) which was introduced in 1986 is providing encouraging results.<sup>7</sup> However, the dose has been uniformly standardised in India. SLIT has been allowed to be used for research purpose to accumulate data for consideration by the Controller-General of India for recommending use of SLIT in population. Guidelines for practising allergen immunotherapy in India has been published in 2009.<sup>8</sup>

There is no method for the management of bronchial asthma and rhinitis, which can maintain a normal level of airway reactivity even after discontinuation of therapy except immunotherapy, where the airway reactivity was found to be normal upto 3 to 5 years

after discontinuation of immunotherapy. Therefore, the stay should be made to use, achieved through specific immunotherapy. However, the antigens (prescription) should be administered by properly trained persons for adequate period of time. There is no point in arguing about the usefulness of immunotherapy, since it has already been well established by several workers<sup>9</sup>. In support, may we quote a paragraph written by Richard F. Locky (1997) in the Allergy Advocates of American College of Allergy and Applied Immunology:

*"Allergen immunotherapy alter the immunological reaction responsible for insect allergy, hay fever and allergic asthma. Such therapy decreases the symptoms and the amount of medication necessary to control the allergic diseases, and in the case of insect allergy, stops the life-threatening reactions from occurring when a patient is stung.<sup>10</sup> Newer methods under investigation will eventually result in better therapy with fewer injections and a prolonged effect that lasts even when the injections are discontinued."*

The WHO has endorsed effectiveness of allergen immunotherapy by issuing position statement paper in 1998.<sup>11</sup>

In studies carried out at V.P. Chest Institute, Delhi, specific immunotherapy provided benefit in about 50% cases of nasobronchial allergy in 1 to 2 year's time,<sup>12</sup> with mixed and single insect antigen.<sup>13,14</sup> Standardisation of allergen extracts will further improve the response of immunotherapy by mini-mising the batch to batch variations of commercially available extracts. There is also a need to reduce the number of allergens used for allergy diagnosis and immunotherapy by isolating common allergenic moieties (proteins). This will also avoid mixing of irrelevant allergens. Storage and transport of extracts is another aspect which needs to be looked after very seriously. We expect few peptides and/or recombi-nant allergens or easy IgE delivery method will be in use for combating allergy ailments through specific immunotherapy.

**S.N. Gaur**  
Editor-in-Chief, IJCDAS  
and  
Director (Acting)  
V.P. Chest Institute  
University of Delhi, Delhi - 110 007

---

## REFERENCES

---

1. Durhan SR. Immunotherapy mechanism, planary immunotherapy: is it a shot in the dark, or just a drop, do we know when to star and when to stop? American College of Allergy, Asthma and Immunology 2006, Annual Meeting Nov., 6-15, 2006, Philadelphia, USA.
2. Wells JH. Systemic reactions to immunotherapy: comparisons between two large allergy practices. *J Allergy Clin Immunol* 1996;97:1030-2.
3. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003;III:437-48.
4. Oppenheimer J, Areson JG, Nelson HS. Safety and efficacy of oral immunotherapy with standardized cat product. *J Allergy Clin Immunol* 1994;93:61-7.
5. Passalacqua G, Albano M, Pronzato C, Riccio AM, Scordamaglia A, Falagiani P *et al.* Long-term follow-up of nasal immunotherapy to *Parietaria*: clinical and local immunological effects. *Clin Exp Allergy* 1997;27:904-8.
6. Brown JL, Frew AJ. The efficacy of oromucosal immunotherapy in respiratory allergy. *Clin Exp Allergy* 2001; 31:8-10.
7. Mailing HJ. Is sublingual immunotherapy clinically effective? *Curr Opin Allergy Clin Immunol* 2002;2:523-31.
8. Gaur SN, Singh BP, Singh AB, Vijayan VK, Agarwal MK. Guidelines for practice of allergen immunotherapy in India. *Indian J Allergy Asthma Immunol* 2009;23:1-20.
9. Abramson MJ, Puy MR, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003, CD001186.
10. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial in insect hypersensitivity. *N Engl J Med* 1978;299:157-61.
11. Bousquet J, Lockey RF, Mailing H-J, editors. WHO position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998; 53(Suppl. 44): 1-42.
12. Gaur SN, Gupta S. Clinical response of immunotherapy in cases of nasobronchial allergy. *Indian J Allergy Asthma Immunol* 1966;10:65-8.
13. Srivastava D, Singh BP, Sudha VT, Arora Naveen, Gaur SN. immunotherapy with mosquito (*Culex quinquefasciatus*) extract. *Ann Allergy Asthma Immunol* 2001;31:1391-7.
14. Srivastava D, Singh BP, Sudha VT, Arora N, Gaur SN. Clinico-immunologic study on immunotherapy with mixed and single insect allergens. *J Clin Immunol* 2009;29:665-73.

# Prevalence of Venous Thromboembolism in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: An Indian Perspective

Tiyas Sen Dutt and Zarir F. Udwadia

P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, India

---

## ABSTRACT

---

**Background.** Chronic obstructive pulmonary disease (COPD) will be the third leading cause of death by 2020. Recent studies reveal that pulmonary embolism (PE) may be a trigger of acute deterioration in patients with COPD. Patients with COPD have approximately twice the risk of PE than those without COPD.

**Objective.** The primary objective was to assess the prevalence of venous thromboembolism (VTE) in patients with acute exacerbation of COPD (AE-COPD) in India.

**Methods.** We conducted this prospective study on patients admitted for AE-COPD in a tertiary care hospital in Mumbai, India. We considered the prevalence of deep venous thrombosis (DVT) to reflect the occurrence of VTE. The screening tool used was a colour Doppler of the bilateral lower limbs.

**Results.** One hundred patients enrolled, were in stage II to stage IV COPD; 9% had DVT. Eight of these nine patients had unilateral DVT. Two patients had developed PE and died.

**Conclusions.** Our results show a lower prevalence of unsuspected DVT in Indian patients admitted for AE-COPD. Future prospective, randomised studies are needed to confirm the findings of the present study and to determine whether a systematic evaluation for VTE is justified in these patients, and hence, be recommended. [*Indian J Chest Dis Allied Sci* 2011;53:207-210]

**Key words:** COPD exacerbation, Venous thromboembolism.

---

## INTRODUCTION

---

Chronic obstructive pulmonary disease (COPD) is a major public health burden worldwide. It is the fourth leading cause of mortality and morbidity, accounting for more than three million deaths annually. By 2020, COPD will be the third leading cause of death, after ischaemic heart disease and stroke.<sup>1</sup> Most COPD related deaths occur during periods of exacerbation.<sup>2,3</sup> Earlier estimates<sup>2</sup> suggest that 50% to 70% of all exacerbations of COPD are precipitated by an infectious process, while 10% are due to environmental pollution; up to 30% of exacerbations are caused by an unknown aetiology. Thus, the cause of acute exacerbation of COPD (AE-COPD) is often difficult to determine.

Pulmonary embolism (PE) may be a trigger of acute dyspnoea in patients with COPD. A study<sup>4</sup> suggests that patients with COPD have approxi-

mately twice the risk of PE and other venous thromboembolic events than those without COPD. Since thromboembolic events can lead to cough and dyspnoea (similar presentation as infectious events), PE may be another common cause of AE-COPD.<sup>5</sup>

Unlike infectious aetiologies, which are effectively treated by antimicrobial agents, bronchodilators, inhaled corticosteroids and systemic corticosteroids, thromboembolic diseases require specific anticoagulant therapy. Studies have revealed that significant delays in the treatment are associated with poor outcomes.<sup>6,7</sup>

There are no Indian data looking into the prevalence of PE in patients with of AE-COPD. The primary objective of our study was to assess the prevalence of venous thromboembolism (VTE) in patients with AE-COPD in Mumbai, India who required hospitalisation for their disease.

---

[Received: February 28, 2011; accepted after revision: June 16, 2011]

**Correspondence and reprint requests:** Dr Zarir F. Udwadia, P.D. Hinduja National Hospital and Medical Research Centre, Veer Savarkar Marg, Mahim, Mumbai-400 016, India; Phone: 91-22-24451515, 91-22-24449199, Fax: 022-24457353; E-mail: zfu@hindujahospital.com, zarirfudwadia@gmail.com

---

## MATERIAL AND METHODS

---

We conducted a prospective, observational, epidemiological study to determine the prevalence of VTE on patients admitted with AE-COPD, in the wards and intensive care units (ICUs) of a tertiary care referral hospital in Mumbai. Since deep venous thrombosis (DVT) and PE are part of the spectrum of the same disease, we looked into the prevalence of DVT in patients admitted with AE-COPD as a reflection of the occurrence of a VTE in this subgroup of patients.

A sample size calculation was not performed a priori.

This prospective observational epidemiological study included consecutive patients (n=100) who required hospital admission for AE-COPD between February 2005 and February 2007.

Clearance of the Ethics Committee of our hospital was taken and informed consent of all the patients enrolled in the study was obtained.

The AE-COPD was defined as an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum production that is beyond the normal day-to-day variations, acute in onset, and warranting a change in regular medication in a patient with underlying COPD. Spirometric classification of the severity and stages of COPD was done according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) classification<sup>8</sup> as follows:

**Stage I:** mild COPD; ratio of forced expiratory volume in the first second (FEV<sub>1</sub>) to forced vital capacity (FVC) less than 0.70, FEV<sub>1</sub> greater than or equal to 80% predicted;

**Stage II:** moderate COPD; FEV<sub>1</sub>/FVC less than 0.70, FEV<sub>1</sub> less than 80%, more than 50% predicted;

**Stage III:** severe COPD; FEV<sub>1</sub>/FVC less than 0.70, FEV<sub>1</sub> less than 50%, more than 30% predicted; and

**Stage IV:** very severe COPD; FEV<sub>1</sub>/FVC less than 0.70, FEV<sub>1</sub> less than 30% or FEV<sub>1</sub> less than 50% with signs of respiratory failure or cor-pulmonale.

Patients with COPD who had an associated malignancy, cardiac failure, pneumothorax or a neurological disease were excluded from the study.

The primary outcome studied was the prevalence of DVT among patients who required hospitalisation for AE-COPD. Venous Doppler examination of both the lower limbs were done from the common femoral vein up to the calf vein. Lack of compressibility of the veins, presence of filling defects and ecogenic material within the veins were considered as evidence suggestive of DVT. This was done on two occasions; first on the day of admission and for the second time on the seventh day of hospital stay, or on the day of discharge, whichever was earlier. Venous Doppler examination of both the lower limbs was done on the

first day of hospitalisation to determine the prevalence of DVT at initial presentation. The test was repeated on the seventh day of hospital stay or at the time of discharge from the hospital (whichever was earlier), in order to identify the occurrence of new onset DVT during hospital stay.

Other details recorded includes the age at presentation, duration of hospitalisation, the microbiological aetiology of AE-COPD, details of various therapeutic options, such as, antibiotics, low molecular weight heparin (LMWH), corticosteroids, intubation and mechanical ventilation; and mortality.

---

## RESULTS

---

One hundred patients were studied prospectively in our case series. All the patients had stage II to stage IV COPD. Their median age was 71 years (range between 36 to 84 years). The AE-COPD was found to be three times more common among males, than in females. The median stay in the hospital was nine days, (range 5 to 12 days). At initial presentation 28% patients were admitted directly to the ICU and 72% were admitted in the wards.

Overall 9% patients had DVT, out of which 7% had isolated calf veins thrombosis and 2% had an extension of the thrombus to the femoral veins. Unilateral DVT was observed in eight of the nine patients, while only one patient had bilateral disease. Two patients developed PE. Of these nine patients, seven had DVT at admission and two patients developed DVT during hospital stay.

Deep vein thrombosis prophylaxis with LMWH or a synthetic pentasaccharide (Fondaparinux) was administered to 26 patients who had severe functional disability and restricted physical activity due to the severity of COPD.

Thirty-six percent cases were smokers; 28% were ex-smokers and 36% were non-smokers. The comorbidities present in these patients included diabetes mellitus (40%), ischaemic heart disease (28%), hypertension (21%) and other diseases like hypothyroidism and cerebrovascular accidents (6%). Repeated admissions (range 2 to 4 times per year) were required in 21% patients. Both the patients with PE (2%) died.

---

## DISCUSSION

---

Chronic obstructive pulmonary disease represents a huge medical and economical burden for the healthcare system. Clinical presentation of AE-COPD includes worsening of dyspnoea, increased quantity of sputum production and increased purulence of sputum. Although this clinical criteria, i.e.

Anthonisen's classification have been used to determine which patient should be treated with antibiotics,<sup>2</sup> these criteria are neither sensitive nor specific enough to exclude other causes of dyspnoea in this population. Other frequent clinical conditions may mimic the symptoms of AE-COPD, including congestive heart failure (CHF), pneumonia, pneumothorax, pleural effusion and PE.

In patients with COPD, PE can have important pathophysiological implications, including decompensated right ventricular failure. Both acute PE and COPD can cause cor-pulmonale.

Chronic obstructive pulmonary disease is often cited among the risk factors for acute VTE and was recently identified as an independent predictor of PE.<sup>9</sup> Poulsen<sup>10</sup> showed that COPD is an independent risk factor for PE. In another study,<sup>11</sup> it was observed that PE was an absolute predictor of death and/or re-hospitalisation at three months in patients with CHF; in this study population, COPD was significantly more common in patients with CHF and PE than those with CHF and no PE.<sup>10</sup>

Our prospective study was aimed to determine the prevalence of VTE in patients getting admitted with AE-COPD, using a validated diagnostic strategy based on the venous Doppler of bilateral lower limbs. We found the prevalence of VTE was 9%. A thorough Medline search revealed a paucity of data from the Indian subcontinent on this subject. *To the best of our knowledge*, this was the only study from India, evaluating the prevalence of VTE in patients presenting with AE-COPD.

In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study,<sup>7</sup> the prevalence of PE in patients with COPD was 19%. The Advances in New Technologies Evaluating the Localisation of Pulmonary Embolism (ANTELOPE) study<sup>12</sup> showed a 29% prevalence of PE among patients with COPD. The PIOPED,<sup>13</sup> ANTELOPE,<sup>12</sup> studies were not designed to specifically look at all patients with COPD. Thus, their observations regarding the prevalence of PE does not resolve the dilemma that the primary care and the emergency doctors face when taking care of AE-COPD.

Autopsy studies have shown a 28% to 51% prevalence of PE in patients with COPD.<sup>13,14</sup>

More recently, Shone *et al* in their study (n=341) showed that the prevalence of PE in patients with COPD was 18%.<sup>16</sup> In another study,<sup>17</sup> the prevalence of PE in a cohort of patients with severe AE-COPD with unexplained dyspnoea was found to be 25%. This was the first prospective analysis of patients with severe AE-COPD. This result differed from the observations reported by Rutschmann *et al*<sup>18</sup> who found the prevalence of PE among 123 patients with AE-COPD evaluated in an emergency department to be only 3%.<sup>17</sup> There could be several explanations for these differences.

First, the imaging method used for diagnosing PE is a crucial factor. Ventilation-perfusion scintigraphy was used in previous studies.<sup>12</sup> Although scintigraphy is an acceptable tool for the diagnosis of PE in patients without underlying lung diseases, the interpretation of lung scintigraphy is difficult in patients with COPD, which might have led to an over-estimation of the true prevalence of PE in that population.<sup>12</sup> We used a validated algorithm based on the findings of the lower limb venous Doppler which should have minimised the risk of false-positive findings.

Secondly, most studies exploring the relationship between AE-COPD and DVT or PE were retrospective studies or were based on autopsy findings,<sup>11-15</sup> while the present study was a prospective, observational and epidemiological study.

Nevertheless, none of these explanations account for the difference between our findings (9%) and the 25% prevalence of PE recently reported in another study.<sup>17</sup> However, it is indeed important to identify PE in COPD patients because PE when present, increases the morbidity and mortality of patients with COPD. In another report,<sup>18</sup> a higher (53%) 1-year mortality rate was observed among patients with COPD and PE, as compared with the figure of a 29% observed among those with COPD alone.<sup>19</sup>

---

## CONCLUSIONS

---

Our results show a lower prevalence of unsuspected DVT/PE in Indian patients admitted for an AE-COPD. Future prospective, randomised studies are needed to confirm our findings in similar group of patients and to determine whether a systematic evaluation for VTE is justified in these patients, and hence, be recommended.

---

## REFERENCES

---

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;349:1269-76.
2. Sapey E, Stockley RA. COPD exacerbations: 2. Aetiology. *Thorax* 2006;61:250-8.
3. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *J Am Med Assoc* 1995;274:1852-7.
4. Sidney S, Sorel M, Lanes S, Deluise C, Lanes S, Eisner MD. COPD and Incident Cardiovascular Disease Hospitalizations and Mortality: Kaiser Permanente Medical Care Program. *Chest* 2005;128:2068-75.
5. Tapson VF. Acute pulmonary embolism. *N Engl J Med* 2008;358:1037-52.
6. Hull Russell D, Raskob Gary E, Brant Rollin F, Pineo GF, Valentine KA. The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy: the emerging theme of delayed recurrence. *Arch Intern Med* 1997;157:2317-21.

7. Lesser BA, Leeper KV Jr, Stein PD, Saltzman HA, Chen J, Thompson BT. The diagnosis of acute pulmonary embolism in patients with chronic obstructive pulmonary disease. *Chest* 1992;102:17-22.
8. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (updated 2010). Available from URL: <http://www.goldcopd.org>.
9. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D. Excluding pulmonary embolism a bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med* 2001;135:98-107.
10. Poulsen SH, Noer I, Moller JE, Knudsen TE, Frandsen JL. Clinical outcome of patients with suspected pulmonary embolism: a follow-up study of 588 consecutive patients. *J Inter Med* 2001;250:137-43.
11. Darze ES, Latado AL, Guimaraes AG, Guedes RAV, Santos AB, Moura Simone S, *et al.* Acute pulmonary embolism is an independent predictor of adverse events in severe decompensated heart failure patients. *Chest* 2007; 131:1838-43.
12. Hartmann IJC, Hagen PJ, Melissant CF, Postmus PE, Prins MH, on behalf of the ANTELOPE Study group. Diagnosing acute pulmonary embolism: effect of chronic obstructive pulmonary disease on the performance of D-dimer testing, ventilation/perfusion scintigraphy, spiral computed tomographic angiography, and conventional angiography. *Am J Respir Crit Care Med* 2000;162:2232-7.
13. Worsley DF, Alavi A. Comprehensive analysis of the results of the PIOPED Study. Prospective Investigation of Pulmonary Embolism Diagnosis Study. *J Nucl Med* 1995;36:2380-7.
14. Mitchell RS, Silvers GW, Dart GA, Maisel JC. Clinical and morphologic correlations in chronic airway obstruction. *Am Rev Respir Dis* 1968;97:54-62.
15. Baum-Gerald L, Fisher FD. The relationship of fatal pulmonary insufficiency with cor pulmonale, right sided mural thrombi and pulmonary emboli: a preliminary report. *Am J Med Sci* 1960;240:111-4.
16. Sohne M, Kruip MJHA, Nijkeuter M, Tick L, Kwakkel H, Halkes S J M, *et al.* Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure in older patients with suspected pulmonary embolism. *J Thromb Haemost* 2006;4:1042-6.
17. Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB, *et al.* Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006;144:390-6.
18. Rutschmann OT, Cornuz J, Poletti PA, Bridevaux PO, Hugli OW, Qanadli SD, *et al.* Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax* 2007;62:121-5.
19. Carson JL, Terrin ML, Duff A, Kelly MA. Pulmonary embolism and mortality in patients with COPD. *Chest* 1996;110:5 1212-9.

## 66<sup>th</sup> National Conference

on

### Tuberculosis and Chest Diseases (NATCON 2011)

Jointly with

### Tuberculosis Association of India

and

### Uttarakhand State Tuberculosis Association

from

November 18-20, 2011

at

### Dehradun [Uttarakhand], India

For further information and details, please contact: Dr Rohit Sarin, Vice-Chairman, E-mail: [drsarin\\_tai@yahoo.com](mailto:drsarin_tai@yahoo.com); Mobile: 9999971557; and Shri Tajinder Ahluwalia, Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi - 110 001; Mobile: 9810550888; Phone: 91-11-23715217; Fax: 91-11-23711303; E-mail: [tbassnindia@yahoo.co.in](mailto:tbassnindia@yahoo.co.in); Website: [www.tbassnindia.org](http://www.tbassnindia.org)

# Assessment of Severity of Methaemoglobinemia Following Fibreoptic Bronchoscopy with Lidocaine

Sajal De

Department of Tuberculosis and Respiratory Diseases, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha (Maharashtra), India

---

## ABSTRACT

---

**Background.** Lidocaine is commonly used for topical anaesthesia during fibreoptic bronchoscopy (FOB) and it can cause methaemoglobinemia. The present study was undertaken to evaluate the severity of post-bronchoscopy methaemoglobinemia while using lidocaine as a topical anaesthetic agent.

**Methods.** We prospectively studied consecutive adult patients who underwent diagnostic FOB in our institution. Blood methaemoglobin levels were estimated by co-oximetry before bronchoscopy and one hour after first instillation of lidocaine. Occurrence of symptoms suggestive of mild methaemoglobinemia (*i.e.*, fatigue, palpitation, dizziness, nausea and headache) were recorded in a severity scale before collection of post-bronchoscopy blood samples.

**Results.** A total of 48 adult patients were enrolled in this study. The mean amount of lidocaine used for bronchoscopy during this study was  $7.4 \pm 1.4$  mg/kg body weight. The mean pre- and post-bronchoscopy methaemoglobin levels were 0.44 mg/mL and 0.80 mg/mL, respectively. After bronchoscopy, severe and very severe symptoms were reported by 2.1% to 10.4% patients. However, severities of the symptoms were unrelated to post-bronchoscopy methaemoglobin level or the amount of lidocaine used during the FOB.

**Conclusions.** Blood methaemoglobin levels following FOB remained within the physiological limits when British Thoracic Society recommended dose of lidocaine was used. However, few patients had symptoms similar to mild methaemoglobinemia after FOB. [Indian J Chest Dis Allied Sci 2011;53:211-214]

**Key words:** Methemoglobin, Lidocaine, Bronchoscopy.

---

## INTRODUCTION

---

Local anaesthetic agents are used during fiberoptic bronchoscopy (FOB) for topical anaesthesia of the upper and lower respiratory tracts. These agents increase the comfort of patient and decrease cough during the procedure. Benzocaine is a potent oxidising agent and its use for FOB was associated with infrequent but fatal complications of methaemoglobinemia. Hence, lidocaine has replaced benzocaine as the local anaesthetic agent of choice for FOB.<sup>1</sup> Lidocaine is administered as gel and 1% to 4% solution. It is rapidly absorbed following intra-tracheal and endobronchial administration and can cause methaemoglobinemia during FOB.<sup>2</sup> Lidocaine-induced methaemoglobinemia especially when used with benzocaine have been documented earlier.<sup>1,3-5</sup>

Therefore, we planned a study to evaluate the severity of methaemoglobinemia after FOB when lidocaine is used as a topical anaesthetic agent.

---

## MATERIAL AND METHODS

---

We prospectively studied consecutive adult patients who underwent diagnostic FOB without sedation in our institution from July 2009 to February 2010. Patients taking medications known to cause methaemoglobinemia were excluded from the study. A written informed consent was taken from all the patients.

The patients were instructed to remain in the fasting state for at least six hours prior to the procedure. No pre-medication or sedation were administered during FOB. Before instillation of lidocaine, venous blood samples were collected and co-oximetry was performed with Avoximeter 4000® (A-Vox Systems Inc, Texas USA).

During FOB, oropharynx and hypo-pharynx were sprayed with 15% lidocaine and 4% lidocaine was instilled inside the nostril. The tip of bronchoscope was lubricated by 2% lidocaine jelly and vocal cords

---

[Received: February 10, 2011; accepted after revision: May 2, 2011]

**Correspondence and reprint requests:** Dr Sajal De, Qr No. 8, Vivekananda Block, MGIMS Campus, Sevagram-442 102 (Maharashtra), India; Phone: 91-9404086815; E-mail: sajalde@yahoo.com

were anaesthetised by 4% lidocaine. Carina and tracheobronchial tree were anaesthetised by spraying 2% lidocaine through the working channel. If required, additional 2% lidocaine was instilled in the peripheral airways during the procedure. Supplemental oxygen was administered during the bronchoscopy as and when required basis. After bronchoscopy, blood samples were collected one hour after the first instillation of lidocaine spray and coximetry was performed. The percentages of methaemoglobin levels were expressed in absolute values to calculate the absolute increase in methaemoglobin levels.

Demographic profiles of the patients, indication for FOB and amount of lidocaine used during FOB were recorded. Occurrence of symptoms suggestive of mild methaemoglobinemia (*i.e.*, fatigue, palpitation, dizziness, nausea and headache) were recorded before collection of post-bronchoscopy blood samples. The bronchoscopy technician recorded the severity of these symptoms using a severity scale (none, mild, moderate, severe and very severe). Hindi translations of this questionnaire were used during this study.

### Statistical Analysis

Normally distributed data were presented as mean±standard deviation and non-normally distributed data were presented with mean and standard error of mean (SEM). Chi-square test was used to compare methaemoglobin level and severity of symptom score. Pearson's rank correlation coefficient was used to assess the univariate relationship between blood methaemoglobin level and lidocaine. A value of  $p < 0.05$  was considered significant. The statistical analysis was done using Statistical Package for the Social Sciences (SPSS)-version 9.0 (USA).

## RESULTS

Forty-eight consecutive adult patients were enrolled in this study. Their mean age was  $52.3 \pm 12.5$  years; there were 39 males (81%). The average haemoglobin level of study population was  $11.2 \pm 1.7$  g/dL%. The mean±SEM methaemoglobin level in the blood before FOB was  $0.44 \pm 0.05$  mg/mL (range 0 to 1.32). Corresponding value for post-bronchoscopy was  $0.80 \pm 0.07$  mg/mL (range 0.135 to 1.97). The increase of methaemoglobin level in blood one hour after instillation of first dose of lidocaine was  $0.36 \pm 0.04$  mg/mL. The mean time interval between the collections of two blood sample was  $59.3 \pm 3.8$  minutes.

The mean amount of lidocaine used for FOB during this study was  $7.4 \pm 1.4$  mg/kg of body weight. No statistically significant positive correlation was found between post-bronchoscopy increase in blood methaemoglobin and the amount of lidocaine used

(Figure 1). One hour after first instillation of lidocaine, 45.8% to 72.9% subjects reported no symptoms (fatigue 54.2%, palpitation 45.8%, dizziness 79.2%, nausea 45.8% and headache 72.9%). The incidences of mild and moderate symptoms were varied from 16.7% to 50% (fatigue 37.5%, palpitation 43.8%, dizziness 16.7%, nausea 50% and headache 25%). Severe and very severe symptoms were reported by 2.1% to 10.4% (fatigue 8.3%, palpitation 10.4%, dizziness 4.2%, nausea 4.2% and headache 2.1%) subjects. Symptom severity scores for fatigue, palpitation, dizziness, nausea and headache are shown in figure 2. No additional treatment was required for any of these post-bronchoscopy symptoms.

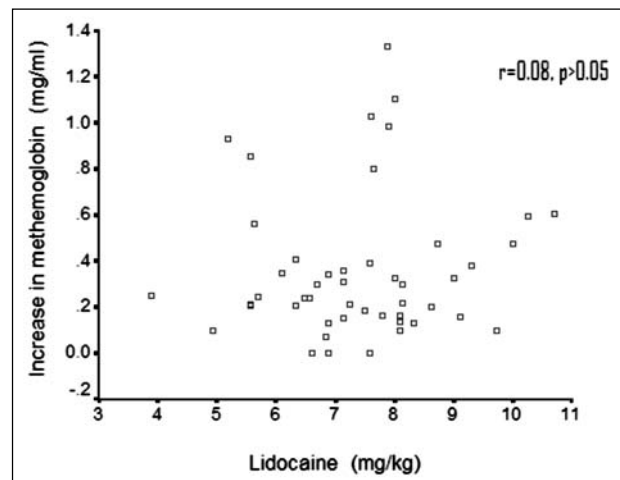


Figure 1. Scatter plot of lidocaine used during bronchoscopy and absolute rise of methaemoglobin level.

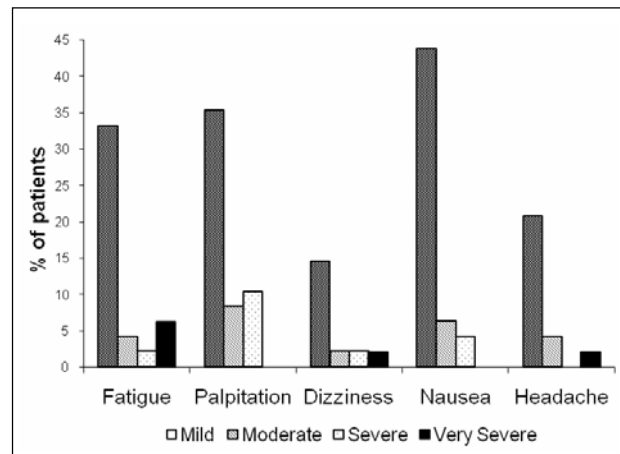


Figure 2. Symptoms severity scores one hour after the first dose of lidocaine instillation.

There was no significant difference in symptom severity scores between the amounts of lidocaine used or post bronchoscopy methaemoglobin to normal haemoglobin ratio was observed. Gender of the subjects also had no relationship with the severity of symptom scores.

---

## DISCUSSION

---

In this study, we evaluated the severity of post-bronchoscopy methaemoglobinemia with lidocaine as a topical anaesthetic agent. Methaemoglobinemia is an uncommon, but potentially fatal haemoglobinopathy. It results from oxidation of haeme iron moieties of the haemoglobin tetramer from ferrous ( $\text{Fe}^{2+}$ ) to the ferric ( $\text{Fe}^{3+}$ ) state. This auto-oxidation of haemoglobin occurs in normal physiological process. But reductive metabolic pathways, *i.e.* nicotinamide adenine dinucleotide (NAD)-dependent cytochrome b5 reductase enzyme system, methaemoglobin reductase and nicotinamide adenine dinucleotide phosphate (NADPH) directly reduce the ferric haemoglobin to ferrous haemoglobin. The causes of methaemoglobinemia are either hereditary or acquired. Hereditary methaemoglobinemia is rare and is caused by either a homozygous deficiency of NADH-methaemoglobin reductase or the presence of haemoglobin variant, such as haemoglobin M. The acquired forms of methaemoglobinemia are due to exposure to oxidising agents in a quantity that overwhelms the reductive metabolic processes. A wide variety of agents including drugs, *i.e.* acetaminophen, sulfonamide, chloroquine, phenytoin, nitrate etc induce methaemoglobinemia.<sup>1</sup> Lidocaine occasionally causes methaemoglobinemia in unusually susceptible individuals. But, the mechanism of increased individual susceptibility to lidocaine is not clear and probably most common cause is heterozygous form of NADH-methaemoglobin reductase deficiency.<sup>6</sup>

The methaemoglobin can not bind with oxygen and in addition it shifts the oxygen dissociation curve towards left and further decrease tissue oxygen delivery by the remaining normal haemoglobin. Normal methaemoglobin in blood is less than 1.5% of the total haemoglobin (<2.4mg/mL).<sup>7</sup> Depending upon reductase activity, excessive nitrate concentration in drinking water can cause severe methaemoglobinemia (7%-27%) in healthy individuals.<sup>8</sup> Methaemoglobin level in Indian population may be variable due to variable nitrate content of drinking water and adaption of cytochrome b5 reductase activity. Smoking can cause methaemoglobinemia, but the effects of smoking on blood methaemoglobin levels are variable across the studies.<sup>9,10</sup>

Clinical symptoms and signs of methaemoglobinemia depend on the ratio of methaemoglobin to total haemoglobin. Central cyanosis usually occurs with methaemoglobin concentrations greater than 15%, though it can occur with level as low as 2.5% in anaemic individuals.<sup>1</sup> When methaemoglobin level reaches to 20% to 30%, patients develop fatigue, anxiety, light headache, dizziness, nausea, vomiting

and tachycardia.<sup>11</sup> These symptoms are due to decreased tissue oxygenation. Higher blood methaemoglobin level may cause generalised seizures, coma, arrhythmias, haemodynamic instability and the level of 70% is usually fatal. In the absence of serious underlying illness, when the offending agent is removed and oxygen is administered, methaemoglobinemia less than 30% usually resolve spontaneously over 15 to 20 hours. The treatment of acute methaemoglobinemia is determined by the level of methaemoglobin and the presence or absence of symptoms.

Lidocaine is a tertiary amide derivative of diethylaminoacetic acid. Plasma level of lidocaine reaches peak within 15 minutes of application to larynx and trachea and within five minutes when instilled in distal airways.<sup>11</sup> Plasma half-life of lidocaine varies from 70 to 110 minutes in healthy adults. During the bronchoscopy, variable amount of lidocaine is either aspirated or cough out by the patients, and thus, all the administered lidocaine does not reaches into systemic circulation. Absorption of lidocaine gel is limited, and thus, lidocaine gel used during bronchoscopy have little influence on peak serum concentration.<sup>12</sup> Systemic adverse effects of lidocaine are due to involvement of central nervous system (CNS), cardiovascular system and gastrointestinal (GI) tract. Except for GI system, the adverse effects are dosing related.<sup>11</sup> At low serum concentration, CNS toxicity symptoms, *i.e.* nervousness, tingling sensation, tremor, dizziness, nausea appear and these symptoms may mimic the symptoms of mild methaemoglobinemia.

British Thoracic Society (BTS) guidelines<sup>13</sup> recommend that total dose of lidocaine during bronchoscopy in adults should be limited to 8.2 mg/kg. However, Frey *et al*<sup>14</sup> reported that use of lidocaine at a dosage higher than the BTS recommended dose (>12mg/kg) during FOB does not cause toxic serum lidocaine level or toxicity symptoms and methaemoglobinemia. Ameer *et al*<sup>15</sup> failed to observe any serious lidocaine toxicity symptoms during bronchoscopy with toxic serum levels of lidocaine (>5 $\mu\text{g}/\text{mL}$ ). The amount of lidocaine used in our study was  $7.4 \pm 1.4 \text{ mg/kg}$  and this was within the BTS recommended dose for bronchoscopy. Post-bronchoscopy symptoms scores in our study were not related to the amount of lidocaine used during the procedure. In a retrospective cohort study, post-operative methaemoglobinemia (2.2%-18%) was observed with subcutaneous administration of lidocaine ( $13 \pm 3.1 \text{ mg/kg}$ ) in 20% infants.<sup>16</sup> Whereas, in a study where intravenous lidocaine was used in 40 patients with arrhythmias failed to show clinically significant elevated level of methaemoglobin.<sup>17</sup> *To the best of our knowledge*, no study has evaluated the severity of methaemoglobinemia after FOB while

using lidocaine in BTS recommended dose. In the present study, pre-bronchoscopy methaemoglobin was undetectable in five cases (10.4%) and post-bronchoscopy methaemoglobinemia varied from 0.1% to 1.5%, except in one case. We failed to observe any significant correlation with the amount of lidocaine used for bronchoscopy and increment of methaemoglobin level after FOB. This is possibly due to variable absorption of lidocaine from mucous membrane and individual susceptibility to lidocaine induced methaemo-globinemia.

In the present study, 2.1% to 10.4% patients reported severe and very severe symptoms after FOB with palpitations being the most common symptom. However, symptoms severity scores were unrelated to post-bronchoscopy methaemoglobin level or the amount of lidocaine used during the bronchoscopy. If FOB is performed under sedation, 35 to 60 minutes wake up time is necessary to make the patient alert enough to assess their discomfort and these discomforts are often masked by the sedatives used.<sup>17</sup> Frey *et al*<sup>14</sup> administered questionnaire two hours after bronchoscopy with conscious sedation and observed mild dizziness and headache in 11.8% and 1% cases, respectively. We performed FOB without any pre-medication or sedation and apparently high incidence of severe post-bronchoscopy symptoms were possibly due to the absence of amnestic effects of sedatives and early administration of questionnaire.

The BTS guidelines recommend<sup>15</sup> that all patients should have pulse oximetry during bronchoscopy and supplemental oxygen should be administered to maintain the arterial oxygen saturation at or above 90%. Pulse oximeter uses only two different wavelengths of light and it cannot distinguish deoxyhaemoglobin from methaemoglobin. In presence of methaemoglobin, pulse oximeter gives erroneous result, and thus, pulse oximeter is not useful to detect methaemoglobinemia during bronchoscopy. The co-oximeter measure the relative absorbance at four different wavelengths of light and thus able to differentiate methaemoglobin from carboxyhaemoglobin, oxyhaemoglobin, and deoxyhaemoglobin. Methaemoglobinemia during FOB can be suspected in presence of cyanosis with low oxygen saturation on pulse oximetry and a normal partial pressure of oxygen and saturation in arterial blood gas analysis. However, before initiating the treatment, diagnosis of methaemoglobinemia must be confirmed by co-oximetry.

In conclusion, our study showed that post-bronchoscopy methaemoglobin level remained within the normal level while using lidocaine in BTS recommended dose. If no sedatives are used during the bronchoscopy, patient may have complaints similar to mild methaemoglobinemia after the procedure. These symptoms are unlikely due to methaemoglobinemia or lidocaine toxicity unless the

patient was receiving any oxidising medicines or the use of lidocaine exceeded the recommended dose.

---

## ACKNOWLEDGEMENT

---

The author is thankful to Mrs Rijwana Zulfequar, Bronchoscopy Technician, Bhopal Memorial Hospital and Research Centre for her help in data collection.

---

## REFERENCES

---

1. Kurapati S, Mehta AC, Jain P. Benzocaine-induced methaemoglobinemia. *J Bronchol* 2007;14:41-4.
2. Karim A, Ahmed S, Siddiqui R, Mattana J. Methaemoglobinemia complicating topical lidocaine used during endoscopic procedures. *Am J Med* 2001;111:150-3.
3. Nguyen ST, Cabrales RE, Bashour CA, Rosenberger TE, Michener JA, Yared JP, *et al*. Benzocaine-induced methaemoglobinemia. *Anesth Analg* 2000;90:369-71.
4. Clary B, Skaryak L, Tedder M, Hilton A, Botz G, Harpole D. Methaemoglobinemia complicating topical anesthesia during bronchoscopic procedures. *J Thorac Cardiovasc Surg* 1997;114:293-5.
5. Kwok S, Fischer JL, Rogers JD. Benzocaine and lidocaine induced methaemoglobinemia after bronchoscopy: a case report. *J Med Case Reports* 2008;2:16.
6. Kotler RL, Hansen-Flaschen J, Casey MP. Severe methaemoglobinaemia after flexible fiberoptic bronchoscopy. *Thorax* 1989;44:234-5.
7. Vajpae N, Graham S, Bem S. Basic examination of blood and bone marrow. In: Mepherson RA, Pincus MR, editors *Henry's Clinical Diagnosis and Management by Laboratory Methods*; 21<sup>st</sup> edition. New Delhi: W.B. Saunders; 2007: p.457.
8. Gupta SK, Gupta RC, Seth AK, Gupta AB, Bassin JK, Gupta A. Methaemoglobinaemia in areas with high nitrate concentration in drinking water. *Natl Med J India* 2000; 13:58-61.
9. Imbriani M, Melotti A, Ghittori S. Methaemoglobin and carboxyhaemoglobin levels in smokers and non smokers. *G Ital Med Lav* 1987;9:11-14.
10. Borland C, Harnes K, Cracknell N, Mack D, Higenbottam T. Methaemoglobin levels in smokers and non-smokers. *Arch Environ Health* 1985;40:330-3.
11. Bose AA, Colt HG. Lidocaine in bronchoscopy practical use and allergic reactions. *J Bronchol* 2008;15:163-6.
12. Loukides S, Katsoulis K, Tsarpalis K, Panagou P, Kalogeropoulos N. Serum concentrations of lignocaine before, during and after fiberoptic bronchoscopy. *Respiration* 2000;67:13-7.
13. British Thoracic Society. Guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001;56:i1-i21.
14. Frey WC, Emmons EE, Morris MJ. Safety of high dose lidocaine in flexible bronchoscopy. *J Bronchol* 2008;15:33-7.
15. Ameer B, Burlingame MB, Harman EM. Systemic absorption of topical lidocaine in elderly and young adults undergoing bronchoscopy. *Pharmacotherapy* 1989;9:74-81.
16. Neuhaeuser C, Weigand N, Schaaf H, Mann V, Christophis P, Howaldt HP, *et al*. Postoperative methaemoglobinemia following infiltrative lidocaine administration for combined anesthesia in pediatric craniofacial surgery. *Pediatr Anesth* 2007;18:125-31.
17. Weiss LD, Generalovinch T, Heller MB, Paris PM, Stewart RD, Kaplan RM, *et al*. Methaemoglobin levels following intravenous lidocaine administration. *Ann Emerg Med* 1987;16:323-5.
18. Hadzri HM, Azarisman SMS, Fauzi ARM, Roslan H, Roslina AM, Adina ATN, *et al*. Can a bronchoscopist reliably assess a patient's experience of bronchoscopy? *J R Soc Med Sh Rep* 2010;1:35.

# Breath Carbon Monoxide Level of Non-Smokers Exposed to Environmental Tobacco Smoke

Raj Kumar, Gopal C. Mahakud, Jitendra K. Nagar, S.P. Singh, N. Raj, K. Gopal and V.K. Vijayan

Department of Respiratory Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

---

## ABSTRACT

---

**Background.** Environmental tobacco smoke (ETS) exposure is a health hazard for non-smokers.

**Objective.** To measure breath carbon monoxide (CO) levels of non-smoking subjects exposed to ETS and of non-smoking subjects not exposed to ETS.

**Results.** The study was conducted with the help of a pre-designed questionnaire. One hundred male subjects were selected for the study; group I consisted of 50 non-smokers (waiters in hotels/restaurants/bars) exposed to ETS and group II consisted of 50 non-smokers not exposed to ETS. All subjects underwent clinical examination. Breath CO levels of both the groups were measured by the Mini Smoklyzer. The mean breath CO level (ppm) was higher in group I compared to group II ( $9.18 \pm 2.84$  versus  $4.56 \pm 1.62$ ;  $p < 0.001$ ). The mean breath CO level was also significantly higher in ETS exposed subjects who worked for more than nine hours a day in bars, restaurants and hotels ( $p = 0.018$ ) and in subjects suffering from respiratory diseases ( $p < 0.001$ ) compared to normal subjects.

**Conclusion.** The abnormally high level of breath CO observed in passive smokers exposed to ETS may suggest that these subjects may be prone to develop the tobacco related diseases. [Indian J Chest Dis Allied Sci 2011;53:215-219]

**Key words:** Carbon monoxide, Passive smoking, Non-smoker, Environmental tobacco smoke.

---

## INTRODUCTION

---

Smoking or use of tobacco may be considered a curse to a healthy society. People who are in the vicinity with smokers inhale the smoke emitted by the smokers and are considered to be "secondary smokers" or "passive smokers". The passive smokers also suffer from diseases related to smoking similar to active smokers. Tobacco smoking by patrons is common in hotels and restaurants in metropolitan cities like Delhi. The waiters serving in such hotels and restaurants work for 8 to 10 hours a day, inhale the smoke emitted by active smokers in closed environment of the establishment and suffer harmful effects of smoking.

Smoking is considered a prime cause of carbon monoxide (CO) exposure, though small amount of exposure can also occur due to vehicular smoke emission, occupational exposure, etc.<sup>1</sup> Various studies<sup>2-4</sup> have been done to correlate the number of cigarettes smoked per day and levels of CO in breath. The CO when inhaled from tobacco smoke is absorbed through lungs and enters into the blood stream and combines with haemoglobin to form

carboxyhaemoglobin (COHb), which can be measured in the blood and is a useful marker of tobacco smoke absorption.<sup>5-10</sup> The CO remains in the blood for about 24 hours after inhalation of tobacco smoke depending on various factors such as gender, physical activity, and ventilation rate.<sup>11-13</sup> It then re-enters the alveoli because of concentration gradient at the alveoli. This CO that is present in expired air can be measured using portable CO analysers. The breath CO concentration has been found to be a reliable indicator of COHb level in the blood.<sup>1,14</sup> Therefore, indirect measurement of COHb through breath analysis is preferred over direct measuring of blood COHb levels because of its non-invasive nature, easy procedure and better compliance.<sup>1,15</sup>

Most of the studies based on smoking and its relation with CO levels were done on normal people and active smokers. This study is focused on passive smokers working in the hotels, bars and restaurants.

---

## MATERIAL AND METHODS

---

This study was sponsored by Ministry of Health and Family Welfare, Government of India and World

---

[Received: September 9, 2010; accepted after revision: May 25, 2011]

**Correspondence and reprint requests:** Dr Raj Kumar, Professor and Head, Department of Respiratory Allergy and Applied Immunology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110 007, India; Phone: 91-11-27667102, 27667667, Extn 144; Fax: 91-11-27667420; E-mail: rajkumar\_27563@yahoo.co.in

Health Organization. Informed consent was obtained from all participants of the study. A questionnaire was prepared which consisted general profile of smokers, duration of work, exposure to passive smoking, respiratory problems etc. A total of 100 male subjects were studied. This included passive smokers exposed to environmental tobacco smoke (ETS) working as waiters in hotels, restaurants and bars (n=50; group I); and 50 age-matched non-smokers not exposed to ETS (n=50; group II), were studied. Group II subjects were selected from the caretakers and relatives of the patients visiting the V.P. Chest Institute, University of Delhi, Delhi. All subjects underwent clinical examination. Exhaled CO levels were measured using a portable CO monitor (Mini-Smokerlyzer, Bedfont, England) in both the groups. The smokerlyzer measures breath CO levels in parts per million (ppm) based on the conversion of CO to carbon dioxide (CO<sub>2</sub>) over a catalytically active electrode. Exhaled CO levels were measured following the method described by Jervis and Co-workers,<sup>15</sup> according to which, the participants were asked to exhale fully, inhale deeply and hold their

breath for 20 seconds before exhaling rapidly into a disposable mouth-piece. During the procedure, the nose of the subjects was clamped. This was done to remove any contribution from the paranasal sinuses to the exhaled CO levels. The procedure was repeated for three times with one minute of normal breathing between each repetition, and the mean value was considered for analysis.

## RESULTS

### Comparison of Demographic Parameters, Type and Duration of Occupation, Smoke-less Tobacco Use, Knowledge Regarding Smoking and Other Parameters Between Passive Smokers and Non-smokers

Comparison of demographic parameters, type and duration of occupation, smoke-less tobacco (SLT) use, knowledge regarding smoking and other parameters between passive smokers and non-smokers is shown in table 1.

**Table 1: Comparison of demographic parameters, type and duration of occupation, smoke-less tobacco use, knowledge regarding smoking and other parameters between passive smokers and non-smokers\***

Characteristic	Passive Smokers (n=50)	Non-smokers (n=50)
Age (years) (mean±SD)		
Age group (years)	38.56±8.65	32.36±9.25
22-30 [No. (%) ]	10 (20)	26 (52)
31-40 [No. (%) ]	15 (30)	14 (28)
41-50 [No. (%) ]	25 (50)	10 (20)
Sex [No.(%)]		
Male	50 (100)	50 (100)
Occupation	All are hotel, restaurant and bar waiters	Professionals (n=4, 8%); business (n=16, 32%); student (n=5, 10%); skilled (n=23, 46%); unemployed (n=2, 4%)
SLT user [No. (%)]	<b>15 (30)</b>	<b>15 (30)</b>
<i>Khaini</i>	7 (14)	10 (20)
<i>Gutka</i>	1 (2)	4 (8)
<i>Pan</i>	7 (14)	1 (2)
Hours of working [No. (%)]		
8	5 (10)	
9	24 (48)	
10	16 (32)	-----
11	4 (8)	
12	1(2)	
Years of working [No. (%)]		
≤5	12 (24)	
5-10	19 (38)	
10-20	8 (16)	-----
20-25	7 (14)	
>25	4 (8)	

*Cont.*

Table 1 Cont.

Feeling of change in outer and inner environment due to ETS [No. (%)]		
Yes	41 (82)	-----
No	9 (18)	
Serving smoker customer [No. (%)]		
<10	41 (82)	-----
>10	9 (18)	
Liking of the work place [No. (%)]		
Yes	44 (88)	-----
No	6 (12)	
Knowledge of harmful effect of passive smoking [No. (%)]		
Yes	47 (94)	-----
No	3 (6)	
Respiratory problems [No. (%)]		
Yes	8 (16) [rhinitis (n=6), asthma (n=2)]	-----
No	42 (84)	
Smokers in family [No. (%)]		
Yes	3 (6)	-----
No	47 (94)	
Respiratory patients in family [No. (%)]		
Yes	3 (6)	-----
No	47 (94)	
Feeling of health problem before and after joining [No. (%)]		
Yes	2 (4)	-----
No	48 (96)	
Job satisfaction [No. (%)]		
Yes	44 (88)	-----
No	6 (12)	
Support laws to ban smoking in hotels, restaurants and bars [No. (%)]		
Yes	3 (6)	-----
No	47 (94)	
CO level (ppm) [No. (%)]		
0-6	1 (2)	46 (92)
7-10	37 (74)	4 (8)
>10	12 (24)	0 (0)

\*All the parameters of the passive smokers exposed to ETS were not taken in non-smokers, (not exposed to ETS) as the aim of this study was to compare the breath CO level of passive smokers, exposed to ETS and non-smokers not exposed to ETS  
SLT=Smoke-less tobacco; ETS=Environmental tobacco smoke; CO=Carbon monoxide; ppm=parts per million.

### Passive Smokers (Non-smokers Exposed to ETS)

The average age of passive smokers (non-smokers exposed to ETS) was 38.6 years (range 22 to 50 years). All subjects, by nature of their work, were exposed to ETS for 8 to 12 hours daily. Majority (n=25, 50%) of subjects were between 41 to 50 years of age. Of these, 15 (30%) subjects used smoke-less type of tobacco. Maximum number of subjects (n=19, 38%) had worked in that environment for 5 to 10 years. The

mean breath CO levels were higher in passive smokers who had worked for more than six years compared to those who worked for less than six years in the same environment (Table 2).

Most of the subjects (n=24, 48%) used to work for nine hours daily. The breath CO level was significantly higher (p=0.018) in subjects working for more than nine hour a day (Table 2). Forty-nine (98%) of the subjects were working in the evening or night shift. Forty-two (84%) subjects, who were exposed to

**Table 2: Significance of breath carbon monoxide (CO) level in passive smokers**

Category		No. of Subjects	Mean Level of CO (ppm)	p-Value
Hours of working	≥9 hours	21	10.38±3.39	p=0.018
	<9 hours	29	8.31±2.00	
Years of working	≥6	38	9.26±2.63	p=0.758
	<6	12	8.91±3.52	
Serving smoker customer daily	≥10	23	10.17±3.51	p=0.030
	<10	27	8.33±1.77	
Respiratory diseases	Yes	2	11.00±0.00	p<0.001
	No	48	9.10±2.87	

ppm=parts per million

ETS used to feel stuffy in front of the smoking customer or in the smokey environment. Forty-one (82%) of the subjects felt drastic change in the environment outside and inside their working place due to ETS, while other (9, 18%) of subjects did not complain; 41 (82%) subjects were serving 5 to 10 smoker customers daily whereas the rest of the subjects (n=9, 18%) were serving 10 to 20 smoker customers daily. Breath CO level was significantly high (p=0.030) in subjects who served 10 or more smoker customers daily compared to the subjects those used to serve less than 10 smoker customers daily (Table 2). Only six (12%) subjects detested the location of their hotel, restaurant and bars while the remaining 44 (88%) liked their working place. Forty-seven (94%) subjects had no knowledge about the harmful effects produced by passive smoking or ETS and even they did not know that they are inhaling the smoke indirectly. Among the passive smokers it was found that 16% of subjects had respiratory problems (Table 1).

During the study, two (4%) subjects reported that they experienced cough, sneezes and breathlessness during the time they were serving the smoker customer. Only two (4%) of subjects stated that their health has deteriorated physically after joining the job. Only three (6%) subjects had family history smoking. When enquired whether smoking should be banned in restaurants, hotels and bars, 47 (94%) of subjects did not agree for the same while three (6%) of subjects agreed.

In most of the subjects (74%), breath CO levels ranged from 7-10 parts per million (ppm). In 12 of them (24%) breath CO levels ranged from 10-20 ppm which could be considered as the dangerous levels (Table 1).

### Non-smokers (Not Exposed to ETS)

Their mean age was 32.4 years (range 22 to 50 years); most of them (n=26, 52%) were between 22 to 30 years of age. These subjects were from different

occupations. Maximum number of subjects (n=16, 32%) were from businessmen group (Table 1). Maximum number of the subjects (n=46, 92%) had breath CO levels between 0-6 ppm. In four subjects (8%), breath CO levels between 7 and 10 ppm were observed. Of four subjects, one was the worker of polymer company, two were drivers and one was working in Delhi Transport Corporation.

### Comparison of Breath Carbon Monoxide Between the Passive Smokers and the Non-smokers

The mean breath CO levels were significantly high in the passive smokers who worked more than nine hours per day (p=0.018) (Table 2). The mean breath CO levels were also higher in the subjects working for a period of more than six years but this difference was not statistically significant (p=0.758). The breath CO level was significantly (p=0.030) high in the waiters who were serving more than 10 smoker customers daily and spending more time with the smokers (Table 2). Breath CO was significantly higher in the subjects who were suffering from respiratory diseases compared to normal subjects (p<0.001). There was no significant correlation between CO level in passive smokers and ventilation system in bars, restaurants and hotels. The mean breath CO level of 9.18±2.84 ppm was significantly higher in the passive smokers who were exposed to ETS compared to non-smokers (4.56±1.62 ppm) who were not exposed to ETS (p<0.001).

## DISCUSSION

Smoking is not injurious only for the smoker himself but for his family members and the society also. This study was conducted in Delhi city, India where many of the small restaurants and hotels are starved of space and located in congested and suffocating market places with poor ventilation facilities. Most of

the waiters worked 8 to 10 hours in that environment and inhale the smoke; hence they are a vulnerable group. In this study, the mean breath CO level of passive smokers and non-smokers was  $9.18 \pm 2.84$  ppm and  $4.56 \pm 1.62$  ppm, respectively. These findings are similar to the observations reported by Devecia *et al.*,<sup>16</sup> where the mean exhaled CO level was  $17.13 \pm 8.50$  ppm for healthy smokers,  $3.61 \pm 2.15$  ppm in healthy non-smokers and  $5.20 \pm 3.38$  ppm in passive smokers.

In the present study, breath CO levels among passive smokers who serve 10 or more smoker customers daily was significantly higher ( $p=0.030$ ). Passive smokers who worked for more than nine hours a day had a breath CO levels that were significantly higher ( $p=0.018$ ). Breath CO level was higher in passive smokers working for more than six years compared to the passive smokers working less than six year although the difference was not statistically significant ( $p=0.758$ ). Passive smokers having respiratory diseases had breath CO level significantly high ( $p<0.001$ ) compared to the passive smokers who did not have any respiratory diseases. In another study,<sup>17</sup> it was found that 74% and 77% of the workers in taverns and bars reported respiratory symptoms and mucosa irritation symptoms, respectively due to the effect of ETS exposure. In this study<sup>17</sup> spirometric assessment included measurement of forced expiratory volume in one second ( $FEV_1$ ) and forced vital capacity (FVC). After prohibition of work place smoking they observed improvement in mean FVC and to a lesser extent in mean  $FEV_1$  (0.039). Complete cessation of workplace ETS exposure was also associated with improved mean FVC and mean  $FEV_1$ . From these findings it is clear that the respiratory symptoms and sensory irritation symptoms (eye, nose, and throat) occur more frequently due to the ETS exposure in the work place. It was also found in a study<sup>18</sup> that passive smoking airborne nicotine level was high compared to the non-smoking areas. Few studies have<sup>17,18</sup> compared breath CO levels between smokers and passive smokers but sparse published literature is available regarding the comparison of the breath CO level between passive smokers and non-smokers. More studies are required in this area.

In conclusion, compared to non-smokers passive smokers are more prone to respiratory diseases and other harmful effect of smoking. Smokers should be conscious about the harmful effect of smoking not only for themselves but for others and should stop smoking in public places, hotels, restaurant and bars.

#### ACKNOWLEDGEMENT

Authors are thankful to the Ministry of Health and Family Welfare, Government of India and World Health Organization

(WHO) for providing the financial assistance for the successful completion of the project.

#### REFERENCES

- Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Biochemical markers of smoke absorption and self reported exposure to passive smoking. *J Epidemiol Community Health* 1984;38:335-9.
- Wald N, Idle M, Bailey A. Carboxyhaemoglobin levels and inhaling habits in cigarette smokers. *Thorax* 1978;33:201-6.
- Middleton ET, Morice AH. Breath carbon monoxide as an indication of smoking habit. *Chest* 2000;117:758-63.
- Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. *Am J Public Health* 1987;77:1435-8.
- Ohlin P, Lundh B, Westling H. Carbon monoxide blood levels and reported cessation of smoking. *Psychopharmacology* 1976;46:263-5.
- Jamrozik K, Vessey M, Fowler G, Wald N, Parker G, Van Vunakis H. Controlled trial of three different antismoking interventions in general practice. *Br Med J* 1984;288:1499-502.
- Ringold A, Goldsmith JR, Helwig HI, Finn R, Schuette F. Estimating recent carbon monoxide exposures. *Arch Environ Health* 1962;5:308-18.
- Cohen SL, Perkins NM, Ury HK, Goldsmith JH. Carbon monoxide uptake in cigarette smoking. *Arch Environ Health* 1971;22:55-60.
- Rea JN, Tyrer PJ, Kasap HS, Beresford SAA. Expired air carbon monoxide, smoking, and other variables. *Br J Prev Soc Med* 1973;27:114-20.
- Goldsmith JR, Aronow WS. Carbon monoxide and coronary heart disease: a review. *Environ Res* 1975;10:236-48.
- Wald N, Howard S, Smith PG, Bailey A. Use of carboxyhaemoglobin levels to predict the development of diseases associated with cigarette smoking. *Thorax* 1975;30:133-40.
- Mellvaine PM, Nelson WC, Bartlett D. Temporal variation of carboxyhaemoglobin concentrations. *Arch Environ Health* 1969;19:83-91.
- Deller A, Stenz R, Forstner K, Konrad F. The elimination of carboxyhaemoglobin: gender specific and circadian effects. *In: Further Transfusmed* 1992;19:121-6.
- Joumard R, Chiron M, Vidon R, Maurin M, Rouzioux JM. Mathematical models of the uptake of carbon monoxide on haemoglobin at low carbon monoxide levels. *Environ Health Perspect* 1981;41:277-89.
- Jarvis MJ, Russel MAH, Saloojee Y. Expired air carbon monoxide: a sample Breathe test of tobacco smoke intake. *BMJ* 1980;281:484-5.
- Devecia SE, Devecib F, Acika Y, Ozana AT. Measurement of exhaled carbon monoxide in healthy smokers and non-smokers. *J Respir Med* 2004;98:551-6.
- Eisner MD, Smith AK, Blanc PD. Bartenders' respiratory health after establishment of smoke-free bars and taverns. *JAMA* 1998;280:1909-14.
- Lenko C, Pisaniello D, Esterman A. A study of environmental tobacco smoke in South Australian pubs, clubs and cafes. *Int J Environ Health Res* 2004;14:3-11.

### **RADIOLOGY FORUM**

It is proposed to extend the scope of the Radiology Forum of our Journal by inviting our readers as well as other workers in the field of Respiratory Medicine to submit brief report of patients with interesting clinical and radiological features for publication. These will be published, provided that:

1. The condition is of sufficient clinical and radiological interest;
2. Photographs (10cm×8cm) are of excellent quality for printing (Maximum: 4 photographs);
3. The diagnosis in each case has been confirmed; and
4. The chest radiograph is accompanied by brief clinical account, not exceeding two page typescript (with sub-head: Clinical Summary, Investigations, Diagnosis, Discussion and References)

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

*Editor-in-Chief*

# **Bone Scintigraphy in Pulmonary Alveolar Microlithiasis**

Mehul Shah and J.M. Joshi

Department of Pulmonary Medicine, T.N. Medical College and B.Y.L. Nair Hospital, Mumbai, India

[Indian J Chest Dis Allied Sci 2011;53:221-223]

---

## **CLINICAL SUMMARY**

---

A 33-year-old woman, recently diagnosed to have cholelithiasis and advised cholecystectomy, was referred for evaluation of chest radiograph abnormality detected during pre-operative evaluation. She had no present or past history of any major respiratory illness. Physical examination revealed bilateral basal crackles on auscultation.

---

## **INVESTIGATIONS**

---

Haemogram parameters and serum biochemistry, including calcium, phosphorous and alkaline phosphatase levels were within normal limits. The chest radiograph (Figure 1) showed bilateral middle-zone and lower-zone dense reticulonodular opacities. High resolution computed tomography (HRCT) of the chest (Figures 2 and 3) showed bilateral intra-lobular interstitial and septal thickening with a perivascular distribution pattern and dense calcification along with the presence of small subpleural cysts on both sides.

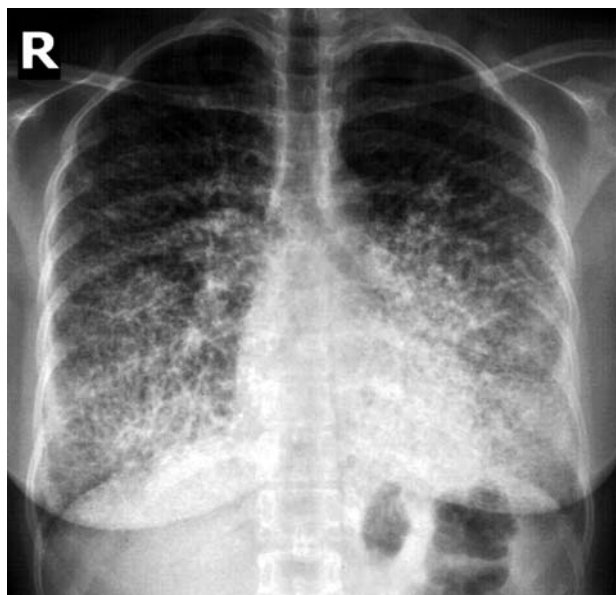


Figure 1. Chest radiograph (postero-anterior view) showing bilateral dense reticulonodular opacities.

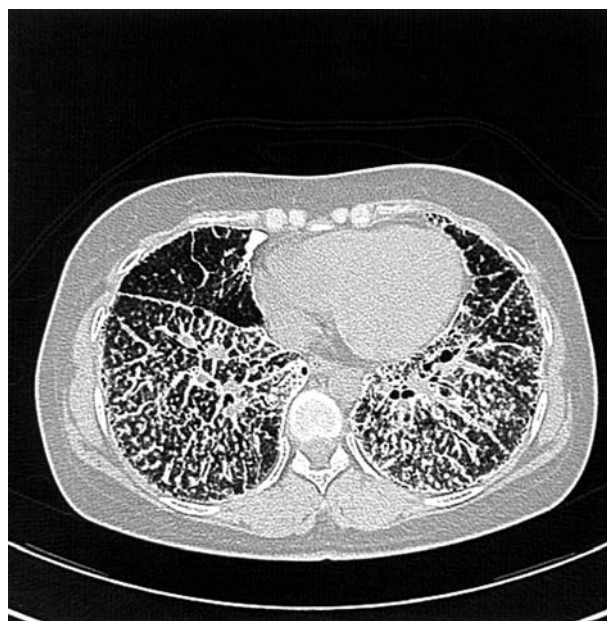


Figure 2. Coronal section of high resolution computed tomography of chest showing bilateral intra-lobular interstitial and septal thickening with dense calcification. Also note small subpleural cysts on both sides.

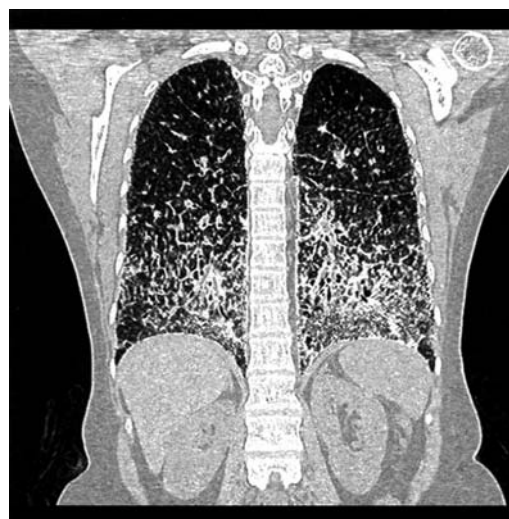


Figure 3. Axial section of high resolution computed tomography of chest showing the predominant involvement of lower portions of the lungs with extensive calcification.

[Received: February 21, 2011; accepted after revision: April 29, 2011]

**Correspondence and reprint requests:** Dr J.M. Joshi, Professor and Head, Department of Pulmonary Medicine, T.N. Medical College and B.Y.L. Nair Hospital, Mumbai - 400 008, India; Phone: 91-22-23027642/43; E-mail: drjoshijm@gmail.com

Technetium-99m methylene diphosphonate (Tc-99m MDP) whole body bone scintigraphy (Figure 4) showed diffusely increased radiotracer uptake in both the lungs. Whole body 18-fluorodeoxyglucose positron emission tomography (FDG-PET) did not show any significant uptake in the lungs. Microscopic examination of sputum and bronchial washings did not show presence of "calcospherites".

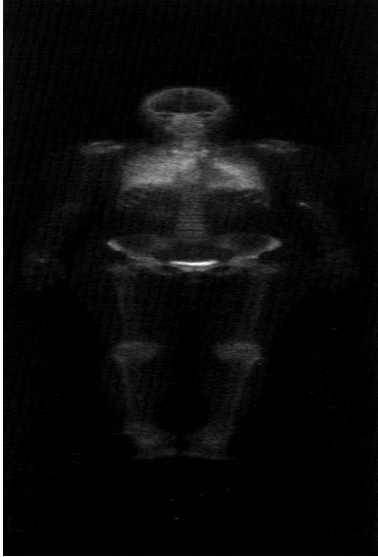


Figure 4. Technetium-99m methylene diphosphonate whole body bone scintigraphy showing diffusely increased radiotracer uptake in both lungs.

Arterial blood gas analysis showed a mild increase in the alveolar-arterial gradient. Lung function testing showed a mild restrictive ventilatory defect with a forced vital capacity (FVC) of 64% (1.99L) and a forced expiratory volume in one second ( $FEV_1$ ) of 65% (1.76L) and a decrease in the diffusion capacity of lung for carbon monoxide DLCO (56%).

---

### DIAGNOSIS

---

Pulmonary alveolar microlithiasis confirmed by bone scintigraphy.

---

### DISCUSSION

---

Pulmonary alveolar microlithiasis (PAM) is a rare idiopathic disorder characterised by intra-alveolar accumulation of spherical calcified concretions which are known as calcospherites or microliths. Most patients are asymptomatic at the time of diagnosis and the disease is found incidentally, as was the case with our patient. The disorder may affect people of any age ranging from early childhood to elderly. However, they usually become symptomatic between the third and fourth decades of life.<sup>1-3</sup> The occurrence may be sporadic or hereditary with an autosomal recessive inheritance.<sup>1</sup>

The hallmark of this disorder is a clinico-radiological dissociation, *i.e.* there is paucity of symptoms in contrast to imaging findings. The predominant symptom is dyspnoea followed by cough and occasionally chest pain. Though various hypotheses for the pathogenesis of this disorder have been proposed, it is now believed that a mutation in the type IIb sodium-phosphate cotransporter gene (SLC34A2 gene), that is involved in phosphate homeostasis in various organs including lungs and prevents excessive phosphate accumulation that may later act as a *nidus* for formation of microliths, is responsible for the pathology.<sup>4</sup>

The chest radiographs usually show diffuse, bilateral areas of micronodular calcifications, resembling a "sandstorm", that predominate in the middle and lower zones of lungs.<sup>1,2,5</sup> The calcification may be so dense that it may obliterate the heart borders and the diaphragm. A black pleural line is another typical finding that appears as an area of hyperlucency, caused by the water density of pleura, between the calcified lung parenchyma and the ribs.<sup>5</sup> The characteristic HRCT chest findings include ground-glass opacities probably due to small calculi in alveoli, subpleural linear calcifications, confluent and diffuse calcified nodules, calcification along bronchovascular bundles and small thin-walled subpleural cysts.<sup>5</sup> The inter-lobular septa are of calcium density due to the deposition of calcospherites within the peripheral lobular parenchyma adjacent to the septa.<sup>5</sup> Rarely, multiple calcified plaques may be seen along the costal pleura.<sup>6</sup>

Bone scintigraphy using technetium-99m labelled diphosphonate compounds, that have a natural affinity for calcification foci at soft tissue level, may detect early pulmonary calcification in PAM.<sup>7</sup> Some cases may also show a high FDG uptake in both lungs on FDG-PET examination.<sup>8</sup> Other investigations include demonstration of microliths in sputum and fluid of bronchoalveolar lavage or on histological examination of lung biopsies.<sup>3</sup>

The disease may progress with chronic alveolar calcification causing interstitial inflammation and fibrosis leading to decreased lung volumes and eventually right heart failure.<sup>9</sup> Currently, the only effective therapy is lung transplantation especially when it is performed before the disease progresses to an advanced stage.<sup>3</sup> Disodium etidronate, which acts by inhibiting microcrystal growth of hydroxyapatite, and thus, presenting ectopic calcification, has been used to treat PAM with mixed results. Some reports have shown little or no benefit while a recent study<sup>10</sup> has demonstrated an improvement in lung functions and radiological changes.

In our patient, though the FDG-PET examination did not show any significant uptake in the lungs, the characteristic CT and bone scintigraphy findings were

consistent with the diagnosis of PAM. The parenchymal calcification was not extensive enough to give rise to the black pleural line. Since she had no respiratory symptoms and her spirometry showed only a mild restrictive abnormality, a decision was made to keep her under observation with periodic reassessments. She remains stable over a six-month follow-up period.

---

### ACKNOWLEDGEMENTS

---

The authors would like to thank Dr Bhavin Jankharia, Consultant Radiologist, Piramal Diagnostic Jankharia Imaging, Mumbai, India for the computed tomographic images and Dr Bhairavi Bhat, Radio Isotope Center, T.N. Medical College and B.Y.L. Nair Hospital, Mumbai for the bone scintigraphy images.

---

### REFERENCES

---

- Hoshino H, Koba H, Inomata S, Kurokawa K, Morita Y, Yoshida K, *et al.* Pulmonary alveolar microlithiasis: high-resolution CT and MR findings. *J Comput Assist Tomogr* 1998;22:245-8.
- Helbich TH, Wojnarovsky C, Wunderbaldinger P, Heinz-Peer G, Eichler I, Herold CJ. Pulmonary alveolar microlithiasis in children: radiographic and high-resolution CT findings. *Am J Roentgenol* 1997;168:63-5.
- Mariotta S, Ricci A, Papale M, De Clementi F, Sposato B, Guidi L, *et al.* Pulmonary alveolar microlithiasis: report on 576 cases published in the literature. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21:173-81.
- Huqun Izumi S, Miyazawa H, Ishii K, Uchiyama B, Ishida T, Tanaka S, *et al.* Mutations in the SLC34A2 gene are associated with pulmonary alveolar microlithiasis. *Am J Respir Crit Care Med* 2007;175:263-8.
- Marchiori E, Goncalves CM, Escuissato DL, Teixeira KI, Rodrigues R, Barreto MM, *et al.* Pulmonary alveolar microlithiasis: high-resolution computed tomography findings in 10 patients. *J Bras Pneumol* 2007;33:552-7.
- Malhotra B, Sabharwal R, Singh M, Singh A. Pulmonary alveolar microlithiasis with calcified pleural plaques. *Lung India* 2010;27:250-2.
- Chan ED, Morales DV, Welsh CH, McDermott MT, Schwarz MI. Calcium deposition with or without bone formation in the lung. *Am J Respir Crit Care Med* 2002;165:1654-69.
- Ito K, Kubota K, Yukihiro M, Izumi S, Miyano S, Kudo K, *et al.* FDG-PET/CT finding of high uptake in pulmonary alveolar microlithiasis. *Ann Nucl Med* 2007;21:415-8.
- Tachibana T, Hagiwara K, Johkoh T. Pulmonary alveolar microlithiasis: review and management. *Curr Opin Pulm Med* 2009;15:486-90.
- Ozcelik D, Yalcin E, Ariyurek M, Ersoz DD, Cinel G, Gulhan B, *et al.* Long-term results of disodium etidronate treatment in pulmonary alveolar microlithiasis. *Pediatr Pulmonol* 2010;45:514-7.

## 4<sup>th</sup> Asian Pacific Congress

on

## Bronchology and Interventional Pulmonology

Jointly with

## 17<sup>th</sup> Annual Conference of Indian Association for Bronchology (IAB)

from

January 19-22, 2012

at

**Jaipur [Rajasthan], India**

*For further information and details, please contact:* Dr S.K. Sarkar, Organising President, 4<sup>th</sup> APCB 2012, C-24, Vaishali Marg, Vaishali Nagar, Jaipur - 302 021[Rajasthan]; Phone: 91-141-2357660; Fax: 91-141-2355660; E-mail: [info@apcb2012.com](mailto:info@apcb2012.com); Website: [www.apcb2012.com](http://www.apcb2012.com)

**Full text articles published in IJCDAS from July-September 2003 onwards can be accessed online on Internet through the following sites**

V.P. Chest Institute's site: <http://www.vpci.org.in>

Indmed's site: <http://medind.nic.in>

*Guidance for Authors appears in every issue.*

*Authors' Index appears in the last issue of the year*

### **Clinical Trials Registry-India**

A Clinical Trials Registry-India has been set up jointly by the Department of Science and Technology (DST), World Health Organisation (WHO) and Indian Council of Medical Research at the National Institute of Medical Statistics (NIMS), New Delhi. This Registry will provide a platform for registration of all clinical trials. The objective of the Registry is to establish a public record system by registering all prospective clinical trials of any intervention (drug, surgical procedure, preventive measures, lifestyle modifications, devices, educational or behavioural treatment, rehabilitation strategies and complementary therapies) conducted in India involving human participants. The Registry will be made publicly available on the internet at no cost. The website of the Indian Registry is [www.ctri.in](http://www.ctri.in).

# Mediastinal Haematoma: A Rare Complication Following Insertion of Central Venous Catheter

Pankaj Gupta<sup>1</sup>, Sandeep Guleria<sup>1</sup> and Sanjay Sharma<sup>2</sup>

Departments of Surgical Disciplines<sup>1</sup> and Radiodiagnosis<sup>2</sup>, All India Institute of Medical Sciences (AIIMS), New Delhi, India

---

## ABSTRACT

---

Mediastinal haematoma is a rare complication following insertion of central venous catheter, with few cases reported in the literature. We report a case of mediastinal haematoma in a 33-year-old male patient with end-stage renal disease. In this patient central venous catheter insertion through the right subclavian vein was attempted on the operation table for renal transplantation but the procedure was abandoned as the attempt was unsuccessful. Post-procedure chest radiograph showed a large mediastinal haematoma occupying right hemithorax that developed as a result of injury to the subclavian vein. Patient was managed conservatively and haematoma completely resolved in four weeks time. This case is being reported to signify the importance of routine obtaining a post-procedure chest radiograph and to state that even large mediastinal haematoma can be managed conservatively in asymptomatic patients.

[Indian J Chest Dis Allied Sci 2011;53:225-228]

**Key words:** Central venous catheter, Complications, Mediastinal haematoma, Conservative management.

---

## INTRODUCTION

---

Central venous catheters are placed everyday in patients admitted to intensive care units, dialysis units and operation theaters, both for therapeutic and diagnostic indications. As with all other invasive procedures, central venous catheter placement is associated with number of recognised complications and strategies have been developed to minimise them. Complications due to the procedure may occur either during insertion of the catheter (e.g., arterial puncture resulting in bleeding, pneumothorax, cardiovascular side effects); and/or during maintenance of the line (e.g., infection, thrombosis or other mechanical risks). The use of post-procedure chest radiograph to confirm correct position of catheter and to detect other complications, such as, pneumothorax and haemothorax is routine practice.

We report a case of inadvertent mediastinal haematoma following insertion of a central venous catheter in a patient undergoing live-related renal transplantation and outcome of conservative management. *To the best of our knowledge this is an uncommon complication with few reports in the published literature.*<sup>1-5</sup>

---

## CASE REPORT

---

A 33-year-old male patient with end-stage renal disease, hypertension, on maintenance haemodialysis was taken up for live-related renal transplantation with his mother as the donor. Placement of a triple-lumen central venous catheter through the right subclavian vein was planned, to monitor intra-operative and post-operative central venous pressure and to guide the fluid therapy. The catheter was inserted with Seldinger technique under ultrasound guidance and guided over a guide wire after dilating the tract with a dilator. However, blood could not be aspirated through the catheter, so that procedure was abandoned. Instead, the catheter was inserted through left external jugular vein.

The surgical procedure of renal transplantation was uneventful and patient was haemodynamically stable and comfortable in post-operative period with a heart rate of 84 beats per minute, blood pressure of 138/84 mmHg, respiratory rate of 14 per minute, central venous pressure of 7cm of water, maintaining saturation of 100% on room air and good graft function and urine output.

As per our institutional protocol, the patient underwent a routine chest radiograph in post-operative period. To our surprise, there was a radio-

---

[Received: January 19, 2011; accepted after revision: June 2, 2011]

**Correspondence and reprint requests:** Dr Sandeep Guleria, Professor, Department of Surgical Disciplines, 5th Floor Teaching Block, All India Institute of Medical Sciences (AIIMS), Ansari Nagar, New Delhi - 110 029, India; Phone: 9891640002; E-mail: sandeepguleria@hotmail.com

opaque shadow in right hemithorax displacing right lung laterally (Figure 1).

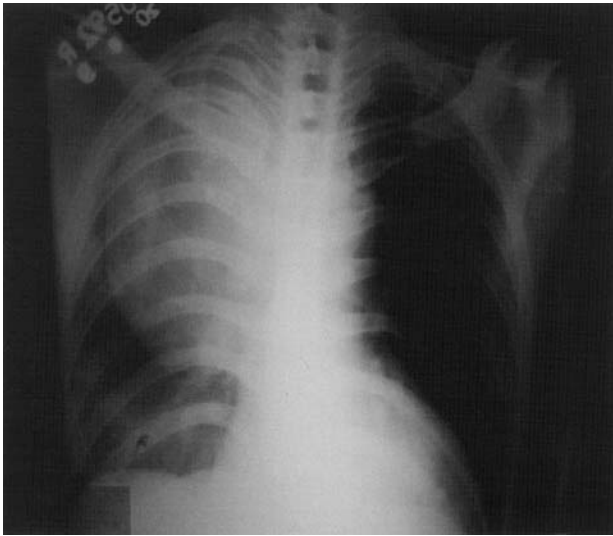


Figure 1. Chest radiograph (postero-anterior view) showing large radio-opaque shadow in the right hemithorax displacing right lung laterally.

Subsequently patient underwent contrast enhanced computed tomography (CECT) chest on which there was non-opacification of right subclavian vein with reflux of contrast into chest wall collaterals with 9cm×9cm×14cm sized well-defined heterogeneous lesion having the CT density ranging from 61 HU in the centre to 72 HU in the periphery in right para-vertebral region with collapse of adjacent lung parenchyma, suggestive of right mediastinal haematoma with injury to right subclavian vein (Figures 2 and 3).



Figure 2. CECT chest showing heterogeneous density measuring 9cm×9cm×14cm in the right para-vertebral region with collapse of adjacent lung parenchyma suggestive of right mediastinal haematoma.

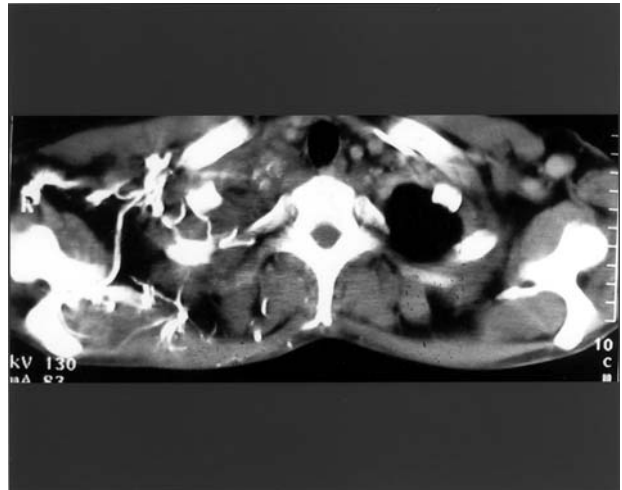


Figure 3. CECT chest showing non-opacification of the right subclavian vein and reflux of contrast into chest wall collaterals, suggesting right subclavian vein injury.

As the patient was immunosuppressed and was receiving triple immunosuppression with tacrolimus, prednisolone, and mycophenolate mofetil, and was asymptomatic, we kept a close vigil and managed the patient conservatively with repeated clinical examinations and chest radiography.

His stay at hospital was uneventful and was discharged as per protocol for discharge of renal transplant patients on 10<sup>th</sup> post-operative day. The patient was on follow-up and had undergone weekly chest radiographs, in addition to bi-weekly kidney function test and haemogram. Haematoma completely resolved in four weeks (Figure 4). He continues to be on regular follow up with us and is maintaining a serum creatinine level of 1.1mg/dL.

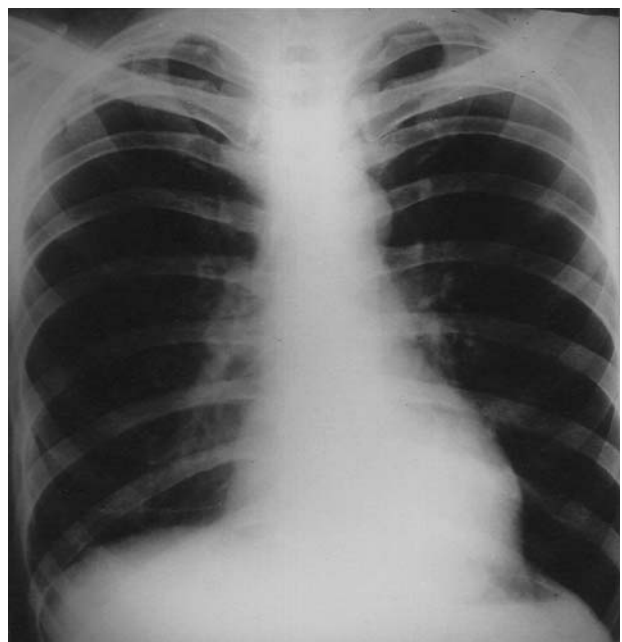


Figure 4. Chest radiograph (postero-anterior view) obtained four weeks later showing resolution of haematoma.

## DISCUSSION

Since the introduction of central venous catheterisation to clinical practice in 1945, the technique has been widely used. Central venous catheters allow measurement of haemodynamic variables that cannot be measured accurately by non-invasive means and allow delivery of medications and nutritional support that cannot be given safely through peripheral venous catheters. Unfortunately, the use of central venous catheters is associated with adverse events that are both hazardous to patients and expensive to treat. More than 15% of patients who receive these catheters have complications.<sup>6</sup> Mechanical complications are reported to occur in 5% to 19% of patients,<sup>6</sup> infectious complications in 5% to 26%, and thrombotic complications have been observed in 2% to 26%.<sup>6</sup>

Vascular complications are most often related to the injury of the subclavian vein. Perforation of the subclavian artery occurs in less than 1% of cases,<sup>7</sup> leading to haemothorax (1%) and rarely quadriplegia. Perforation of the aorta and cardiac tamponade can occur if the cannula-site perforation is within the pericardial reflection. This complication is associated with a 90% death rate.<sup>8</sup> Pseudo-aneurysms, arterio-

venous fistulas and vertebral artery injuries are rare complications (0.2%).<sup>9</sup> The fact that the right subclavian-jugular venous junction overlies the subclavian artery and the right subclavian vein enters the innominate artery at a sharper angle makes these vessels more vulnerable to perforation if a firm dilator is inserted too deeply.

Vascular complication during insertion of central line can be attributed to the unsafe manipulation of the dilators, some times even causing ventricular perforations. Other possible mechanism of injury include kinking of the guide wire, resulting in misdirection of the dilator and perhaps insertion of the guide wire outside the vessel.<sup>10</sup> All these complications result from inexperience, the number of needle passes made, the use of relatively larger gauge needle, severe dehydration, morbid obesity and coagulopathy.

There are few reports in the literature (Table) documenting the occurrence of mediastinal haematoma following central venous line insertion. Development of hydromediastinum and bilateral hydrothorax after a subclavian line insertion has been described.<sup>1</sup> The patient became tachypnoeic, tachycardiac and hypotensive after central line insertion. The chest radiograph showed widening of

**Table. Occurrence of mediastinal haematoma following central venous line insertion**

Case No. <sup>ref.</sup>	Age (in years) and Gender (M/F)	Site	Clinical Features	Method of Diagnosis	Diagnostic Modality	Management	Outcome
1 <sup>1</sup>	28 M	Left subclavian vein	Tachycardia, hypotension, tachypnoea	Bilateral hydrothorax and hydromediastinum	Chest radiograph, Dye injection through central line	Insertion of bilateral intercostals drains for hydrothorax Hydromediastinum managed conservatively	Recovered
2 <sup>2</sup>	51 M	Left subclavian vein	Dyspnoea, hypotension	Hydromediastinum and left hemothorax	Chest radiograph, CT chest	Conservative management	Death
3 <sup>3</sup>	78 M	Right subclavian vein	Pain in shoulder, bradycardia	Pleural effusion and hydromediastinum	Fluoroscopy, CT chest, Angiography	Coil embolisation of IMA	Recovered
4 <sup>3</sup>	75 M	Right subclavian vein	Tachycardia, hypotension, tachypnoea	Right sided pleural effusion Hydromediastinum	Angiography	Coil embolisation of IMA	Recovered
5 <sup>3</sup>	22 M	Left subclavian vein	Asymptomatic	Hydromediastinum	Chest radiography	Coil embolisation of IMA	Recovered
6 <sup>4</sup>	0.5 F	Left subclavian vein	Tachycardia, hypotension	Bilateral hydrothorax and hydromediastinum	Transoesophageal echocardiography, Chest radiograph	Insertion of bilateral intercostals drains for hydrothorax Hydromediastinum managed conservatively	Recovered
7 <sup>5</sup>	55 M	Left subclavian vein	Hypotension	Hydromediastinum	CT chest, Angiography, Chest radiograph	Thoracotomy	Recovered
8 (Present case)	33 M	Right subclavian vein	Asymptomatic	Mediastinal haematoma	Chest radiograph, CT chest	Conservative	Recovered

IMA=Internal mammary artery

mediastinum and bilateral hydrothorax. Extravasation of radio-opaque dye inserted through the line into the mediastinum confirmed the diagnosis. The authors believed that injury of vein during cannulation by the dilator was the cause of hydromediastinum, as occurred in our case and shift of fluid from the mediastinum into the pleural cavities caused bilateral hydrothorax. Insertion of intercostal drains relieved the patient. In another report,<sup>2</sup> occurrence of mediastinal haematoma following insertion of left subclavian vein catheter for haemodialysis in patients with end-stage renal failure was documented.<sup>2</sup> The patient developed dyspnoea and hypotension, chest radiograph revealed large opacity covering the mediastinum and left hemithorax, as occurred in our case. Computed tomography (CT) of the chest confirmed the diagnosis of mediastinal haematoma and the patient died of hypovolaemic shock. The authors<sup>2</sup> suggested that guide wire penetrated the vein and caused the haematoma. Three cases of mediastinal haematoma following central venous line insertion through subclavian vein has also been reported.<sup>3</sup> Haematoma was caused by iatrogenic injury of the internal mammary artery. Microcoil embolisation of the internal mammary artery was done to treat the patients. In another report,<sup>4</sup> hydromediastinum in a 6-month-old girl following insertion of left subclavian vein catheter.<sup>4</sup> The condition was diagnosed by transoesophageal echocardiography and was caused by dislocation of the central line. It was managed conservatively by removing the cannula. Posterior mediastinal haematoma causing tracheal obstruction after internal jugular cannulation has also been reported.<sup>5</sup> Central venous and pulmonary artery (PA) catheters were inserted via the right internal jugular vein in a patient undergoing coronary artery bypass surgery. The patient began to experience progressive dyspnoea, orthopnoea and stridor on the second post-operative day. Chest CT revealed a posterior mediastinal haematoma behind the oesophagus that compressed the trachea and oesophagus. At thoracotomy there was no significant bleeding in the anterior mediastinum. A haematoma was found in the posterior mediastinum behind the oesophagus which was evacuated and the patient recovered. The authors assumed that haematoma was caused by malpositioning of the internal jugular catheter or guide wire into the azygos venous system.

We believe that hydromediastinum in our case was caused by the dilator, used to dilate the tract. Guide wire must have kinked, so when the dilator was

inserted it perforated the subclavian vein, which is the reason when cannula was inserted blood could not be aspirated, as the tip of the cannula was outside the subclavian vein. The complication was detected on the post-procedure chest radiograph. As patient was asymptomatic and immunocompromised, we decided not to intervene and had kept close vigil; the patient improved with this conservative approach.

In conclusion, meticulous surgical technique, awareness of the complications and close observation of the patient are necessary in the management of a central venous line. Routine post-procedure chest radiographs should be done. Mediastinal haematoma can be managed conservatively in asymptomatic patients.

---

## REFERENCES

---

1. Naguib M, Farag H, Joshi RN. Bilateral hydrothorax and hydromediastinum after a subclavian line insertion. *Canadian Anaesth Soc J* 1985;32:412-4.
2. Arik N, Akpolat T, Demirkan F, Demirkazik F, Yasavul U, Turgan T, *et al.* Mediastinal hematoma: a rare complication of subclavian catheterization for haemodialysis. *Nephron* 1993;63:354.
3. Chemelli AP, Chemelli-Steingruber IE, Bonaros N, Luckner G, Millonig G, Seppi K, *et al.* Coil embolization of internal mammary artery injured during central vein catheter and cardiac pacemaker lead insertion. *Eur J Radiol* 2009;71:269-74.
4. Hohlrieder M, Oberhammer R, Lorenz IH, Margreiter J, Kühbacher G, Keller C. Life-threatening mediastinal hematoma caused by extravascular infusion through a triple-lumen central venous catheter. *Anesth Analg* 2004; 99:31-5.
5. Doi A, Iida H, Saitoh Y, Sunazawa T, Tajika Y. A posterior mediastinal hematoma causing tracheal obstruction after internal jugular cannulation for cardiac surgery. *J Cardiothorac Vasc Anesth* 2009;23:682-3.
6. Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E, *et al.* Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001;286:700-7.
7. Oliver WC Jr, Nuttall GA, Beynen FM, Raimundo HS, Abenstein JP, Arnold JJ. The incidence of artery puncture with central venous cannulation using a modified technique for detection and prevention of arterial cannulation. *J Cardiothorac Vasc Anesth* 1997;11:851-5.
8. Carr M, Jagannath A. Hemopericardium resulting from attempted internal jugular vein catheterization: a case report and review of complications of central venous catheterization. *Cardiovasc Intervent Radiol* 1986;9:214-8.
9. Sato O, Tada Y, Sudo K, Ueno A, Nobori M, Idezuki Y. Arteriovenous fistula following central venous catheterization. *Arch Surg* 1986;121:729-31.
10. Schummer W, Schummer C, Fröber R. Internal jugular vein and anatomic relationship at the root of the neck. *Anesth Analg* 2003;96:1540.

# Polymyositis Presenting with Respiratory Failure

Jerryl Maclean<sup>1</sup>, Raj B. Singh<sup>1</sup> and Zaheer Ahmed Sayeed<sup>2</sup>

Departments of Respiratory Medicine<sup>1</sup>and Neurology<sup>2</sup>, Apollo Hospitals, Chennai, India

---

## ABSTRACT

---

Polymyositis is a systemic autoimmune disorder characterised by inflammatory myopathy of the skeletal muscles predominantly affecting the proximal muscles and associated with extra-muscular manifestations like dysphagia and skin involvement. In this case report, we describe the occurrence of diaphragmatic weakness and respiratory failure due to polymyositis with relatively well preserved power in limb muscles. [Indian J Chest Dis Allied Sci 2011;53:229-231]

**Key words:** Polymyositis, Myopathy, Diaphragmatic weakness, Respiratory failure.

---

## INTRODUCTION

---

Polymyositis is a type of idiopathic inflammatory myopathy (IIM) which is characterised by proximal muscle weakness and non-suppurative inflammation of skeletal muscle, often accompanied by extra-muscular manifestations. We present a patient with polymyositis who unusually had profound respiratory muscle weakness with relatively well preserved power in limb muscle.

---

## CASE REPORT

---

A 70-year-old female was admitted with complaints of intermittent fever and cough with scanty sputum for four days. She did not report any other symptom. She was known to have systemic hypertension for the preceding two years and blood pressure was well controlled by medication. In 2008, she had experienced some generalised muscle weakness transiently but had not been investigated. She had been empirically started on oral corticosteroids with which she had apparently improved. The dose of oral prednisolone was gradually tapered and she was receiving 5mg prednisolone per day at the time of her present evaluation. On examination, she was febrile (temperature 102 °F). Her blood pressure was 140/90 mmHg. There were a few crackles in the left infra-scapular region. Central nervous system examination revealed power of 4/5 in all four limbs with no sensory deficit. Other systems were normal. Chest radiograph showed consolidation of the left lower lobe. Laboratory examination revealed neutrophilic leukocytosis. Sputum examination was negative for any pathogens. Urine showed no *Legionella* antigen.

She was diagnosed to have a community-acquired pneumonia and was treated with co-amoxiclav and azithromycin. As the fever settled and chest radiograph done after seven days showed partial clearing of the pneumonia, she was discharged.

Four days after discharge she was re-admitted with breathlessness on lying down and difficulty in swallowing. Power in her arm and leg was 4/5. Her neck muscles were weak but she was able to lift her neck off the bed. Bedside observation revealed hypoxaemia only on lying down. Diaphragmatic weakness was considered likely. This was confirmed by ultrasound examination which showed severely restricted diaphragmatic movements on both sides. Arterial blood gas (ABG) analysis on room air showed partial pressure of oxygen (PaO<sub>2</sub>) – 52mmHg; partial pressure of carbon dioxide (PCO<sub>2</sub>) – 48mmHg, pH 7.38. Echocardiogram showed normal left ventricular function. Computed tomography (CT) of the chest showed that she still had a consolidation in the left lower lobe (Figures 1 and 2). Neurologist's advice was obtained. Rheumatoid factor, antinuclear antibody (ANA), anti-double stranded deoxy-ribonucleic acid (anti-ds DNA) antibody and anti-smooth muscle antibody were negative. Nerve conduction studies in both upper and lower limbs were normal. Electromyogram was not done. Creatinine phosphokinase (CPK) level was 24,300 IU/L. Her hypoxia worsened. The ABG analysis showed PaO<sub>2</sub> – 58 mmHg, PCO<sub>2</sub> – 78mmHg, pH 7.28 indicating type II respiratory failure. Non-invasive ventilation was tried but due to persistent hypoxia, she was intubated and ventilated. She was started on high dose intravenous methyl prednisolone 1g once daily for three days. Her respiratory effort and diaphragmatic movement improved and she was

---

[Received: October 5, 2010; accepted after revision: March 7, 2011]

**Correspondence and reprint requests:** Dr Raj B. Singh, Z-232A, 6th Street, Anna Nagar, Chennai - 600 040, India; Phone: 91-44-26288735 Fax: 91-044-26193009; E-mail: rajbsingh@hotmail.com

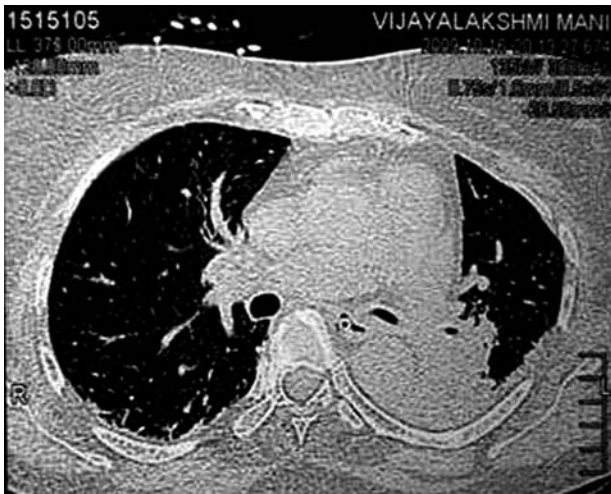


Figure 1. Computed tomography of chest (lung window) showing left lower lobe consolidation.



Figure 2. Computed tomography of chest (mediastinal window) showing left lower lobe consolidation.

weaned off the ventilator and extubated. The ABG analysis reverted back to normal. The CPK level came down to 239IU/L. Intercostal and deltoid muscle biopsies were done. Histo-pathological examination showed degeneration of muscle fibers by inflammatory cells and increase in fibrous tissue which was suggestive of polymyositis (Figures 3 and 4). Along with corticosteroids she was also started on intravenous cyclophosphamide pulse therapy (750mg once every 45 days for 6 doses). The patient was discharged while still on bi-level positive airway pressure (BiPAP) at night. Three weeks later the respiratory effort had improved considerably and BiPAP was discontinued.

## DISCUSSION

Polymyositis from a clinicopathological perspective is classified under idiopathic inflammatory myopathies

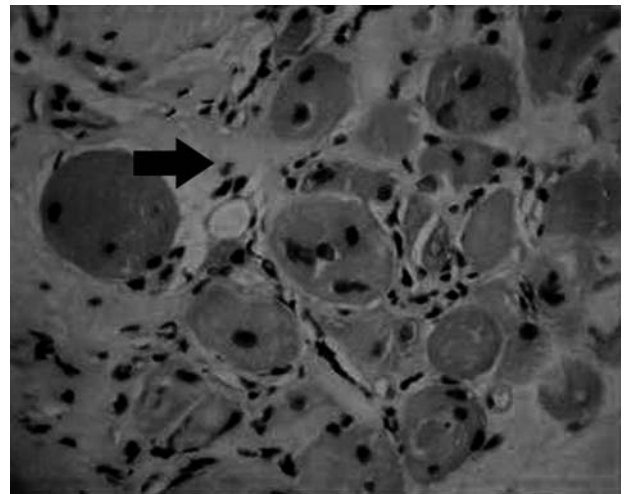


Figure 3. Photomicrograph showing degeneration of muscle fibres by inflammatory cells (black arrow) and increase in fibrous tissue (Haematoxylin-eosin stain).

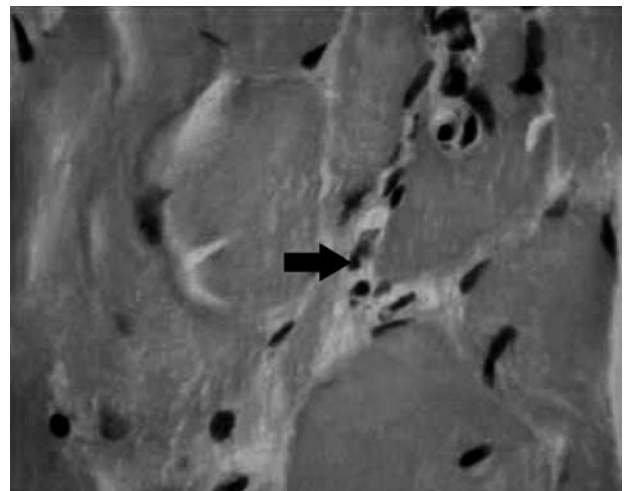


Figure 4. High power view of the same as in figure 3.

which is a heterogeneous group of immune mediated disorders that may present in an isolated form or in association with another autoimmune or connective tissue disease,<sup>1</sup> a malignancy or rarely an infection. Polymyositis is presumed to be an autoimmune-mediated disease secondary to defective cellular immunity. The antibodies being implicated in the pathogenesis are the anti-Jo-1, anti-Mi-2 and anti-signal recognition particle antibodies.<sup>2</sup> The other pathogenic mechanism proposed is T-cell mediated cytotoxic process directed against unidentified muscle antigens. Supporting this mechanism is the presence of CD8+ T-cells, which along with macrophages, initially surround healthy non-necrotic muscle fibers and eventually invade and destroy them.<sup>3,4</sup> The average overall annual incidence rates for inflammatory myopathy<sup>1</sup> vary from  $2.18 \times 10^{-6}$  to  $7.7 \times 10^{-6}$ . In general, the incidence rates of polymyositis are higher in women. Annual incidence

rates of idiopathic inflammatory myopathies increased with age, ranging from  $2.5 \times 10^{-6}$  in people under 15 years of age to  $10.5 \times 10^{-6}$  in people over 65 years of age.<sup>5</sup> The characteristic clinical features include non-selective painless proximal muscle weakness which may be of subacute onset in early adult life; associated systemic dysphagia and interstitial lung disease. Muscle usually occurs in the following descending order: pelvic girdle is usually the earliest to be involved, followed by, shoulder, neck muscles (flexors), distal muscle (in severe cases) and pharyngeal muscles. Diaphragm is rarely involved.<sup>6</sup> The characteristic laboratory features include elevated serum CPK levels, electromyography showing the features of myopathic motor unit potentials with or without spontaneous discharges and muscle biopsy evidence of a necrotising inflammatory myopathy.<sup>6</sup> Corticosteroids remain the agents of choice for the initial empiric treatment of inflammatory myopathy.<sup>7</sup> A regimen of oral prednisolone (60mg per day) which is tapered over a period of four weeks until a maintenance dose of 5mg is reached is often used.<sup>7</sup> Immunosuppressive agents are considered in patients with polymyositis who show a partial response to corticosteroid treatment. These agents control myositis or the extra-muscular features of this disease and are effective as steroid-sparing drugs.<sup>7</sup> In case of refractory myositis combination of immunosuppressive agents is used. Prognosis for polymyositis is usually good. A 20-year follow-up study of a 46-patient cohort seen from 1978 to 1999 revealed 5- and 10-year survival rates of 95%

and 84%, respectively.<sup>8</sup> In this case report, we document the rare occurrence of early diaphragmatic paralysis and the consequent respiratory failure in one patient with polymyositis.

---

## REFERENCES

---

1. Dalakas MC. Retrovirus and inflammatory myopathies in humans and primates. *Baillieres Clin Neurol* 1993;2:659-91.
2. Nishikai M, Ohya K, Kosaka M, Akiya K, Tojo T. Anti-Jo-1 antibodies in polymyositis or dermatomyositis: evaluation by ELISA using recombinant fusion protein Jo-1 AS antigen. *Br Rheumatol* 1998;37:357-61.
3. Engel AG, Arahata K. Monoclonal antibody analysis of mononuclear cells in myopathies. II: phenotypes of autoinvasive cells in polymyositis and inclusion body myositis. *Ann Neurol* 1984;16:209-15.
4. Engel AG, Arahata K, Emslie-Smith A. Immune effector mechanisms in inflammatory myopathies. *Res Publ Assoc Res Nerv Ment Dis* 1990;68:141-57.
5. Oddis CV, Conte CG, Steen VD. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963-1982. *J Rheumatol* 1990;17:1329-34.
6. Mastaglia FL, Phillips BA. Idiopathic inflammatory myopathies: epidemiology, classification, and diagnostic criteria. *Rheum Dis Clin North Am* 2002;28:723-41.
7. Oddis CV. Idiopathic inflammatory myopathy: management and prognosis. *Rheum Dis Clin North Am* 2002;28:979-1001.
8. Sultan SM, Ioannou Y, Moss K, Isenberg DA. Outcome in patients with idiopathic inflammatory myositis: morbidity and mortality. *Rheumatology* (Oxford) 2002;41:22-6.

**NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)***Fellowship/Membership Fee*

Membership (Annual)	:	₹ 500.00
Membership (Life)	:	₹ 5000.00
Fellowship	:	₹ 5000.00
Enrolement (new members only)	:	₹ 1000.00

*Payments should be made by Cheque/Demand Draft, drawn in favour of the Secretary, National College of Chest Physicians (I). Please add ₹75/- to all out-station cheques.*

**Annual membership is valid for one financial year (April-March) only.**

*Sd/-  
Secretary*

**NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)**

Fellows and Members of the College are requested to mention their old address also while informing for change of address alongwith their Fellowship/ Membership number to the Secretary, NCCP (I) and/or to Publication Department, IJCDAS to avoid any mistake/delay in mailing the Journal's copy as well as College's information.

*Sd/-  
Secretary*

# Type A Thymoma with Generalised *Myasthenia Gravis*

Manjiri Karandikar and R.M. Swami

Department of Pathology, Bharati Vidyapeeth Medical College, Pune (Maharashtra), India

## ABSTRACT

Thymoma is a very rare tumour arising from thymus in the anterior mediastinum. A case of a spindle cell thymoma with *Myasthenia gravis* in a 34-year-old female who presented with difficulty in breathing and swallowing with shortness of breath is reported. [Indian J Chest Dis Allied Sci 2011;53:233-235]

**Key words:** Thymus, Mediastinum, Tumour.

## INTRODUCTION

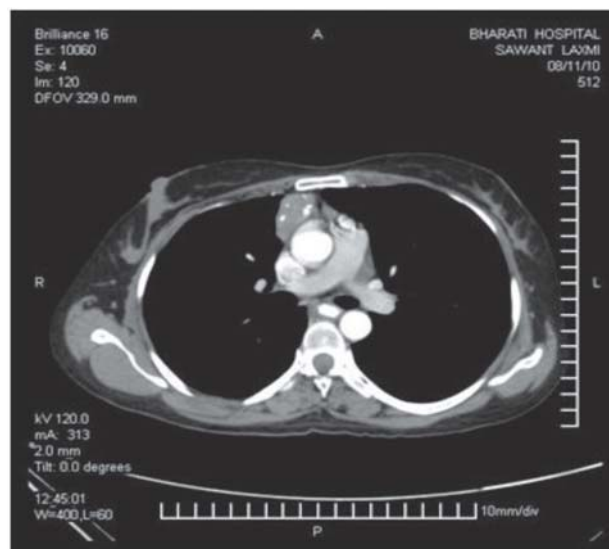
Thymoma is the most common neoplasm of anterior mediastinum and originates within the epithelial cells of thymus. It accounts for 20% to 25% of all mediastinal tumours and 50% of anterior mediastinal masses.<sup>1</sup> It has an incidence of 0.15 per 100,000 and 30% to 40% of patients with thymoma experience symptoms suggestive of *Myasthenia gravis*. An additional 5% of patients have other systemic syndromes, including pure red cell aplasia, dermatomyositis, systemic lupus erythematosus, Cushing's syndrome, and syndrome of inappropriate antidiuretic hormone secretion.<sup>1</sup>

A thymoma is an uncommon tumour, best known for its association with the neuromuscular disorder *Myasthenia gravis*.<sup>2</sup> About 10% to 15% of patients with *M. gravis* have a thymoma and, conversely, 30% to 45% of patients with thymomas have *M. gravis*.<sup>3</sup> Production of autoantibodies against the acetylcholine receptor results from an antigen-driven immune reaction that starts inside the thymus but spreads to extra-thymic sites during the early phase of *M. gravis*. Para-neoplastic *M. gravis* occurs only in type A, AB and B1-3 thymomas.<sup>4</sup> Abnormal micro-environment triggers non-tolerogenic T-cell selection by neoplastic epithelial cells. After transport of substantial number of naïve, potentially autoreactive T-cells to extra-tumorous sites, T-cell activation outside the thymoma initiate the autoimmune process.<sup>4</sup>

## CASE REPORT

A 34-year-old female presented with a mass in the anterior mediastinum. She was apparently well two years back when she developed sudden ptosis of the

left eyelid with dysphagia and dyspnoea. The muscles of face, eyes and jaws were involved. She had diplopia and difficulty in speech. There was a progressive bulbar and neck muscle weakness. She was diagnosed as a case of *M. gravis* and was treated with intravenous corticosteroids and neostigmine. Computed tomography (CT) of the chest done because of respiratory symptoms showed a well-defined heterogeneously enhancing mass (4.8cm×2.0cm×1.9cm) in the anterior mediastinum (Figure 1) with peripheral calcification. The lungs, bronchi and trachea were normal with a radiological diagnosis of thymoma, the patient was admitted for excision of the mass and after controlling symptoms of *M. gravis*, she underwent thymectomy.



**Figure 1.** Computed tomography of the chest showing a well-defined mass (arrow) in the anterior mediastinum with peripheral calcification.

[Received: November 30, 2010; accepted after revision: February 18, 2011]

**Correspondence and reprint requests:** Dr Ravi Swami, B 2, First Floor, Vrundeshwar Society, Bibwevadi, Near Bhagali Orthopedic Hospital, Pune - 411 037 (Maharashtra), India; E-mail: ravimswami@rediffmail.com

Grossly it was a single nodular, encapsulated firm mass measuring 6.5cmx3cmx1.5cm. The external surface appeared yellowish grey. On cut-section, the tumour appeared lobulated with yellowish and grey areas. Few dark brownish and black areas of haemorrhage/congestion were also noted (Figure 2).

Microscopic examination showed a tumour mass surrounded by a thick fibrous capsule showing dystrophic calcification (Figure 3). The tumour had infiltrated the capsule but was not found traversing across the capsule. The tumour cells were epithelial, present in sheets and short fascicles of spindled tumour cells with elongated nuclei and dense chromatin (Figure 4). Majority of the tumour cells were polygonal with pale cytoplasm and indistinct

cytoplasmic borders giving them a syncytial appearance. The nuclei were round to oval, vesicular and had indistinct nucleoli. Mitotic figures were sparse. Activated lymphocytes with convoluted nuclei were distributed throughout the tumour. Perivascular spaces with oedema fluid and lymphoid infiltrate, pseudoglandular formations were few and seen mainly at the periphery of the lobule. A diagnosis of type A thymoma (World Health Organization [WHO] classification) with stage I (modified Masaoka staging system) was made. Immunohistochemistry (IHC) showed tumour cells positive for pancytokeratin proving its epithelial origin (Figure 5).

The tumour was negative for CD5, CD 117 and p53 that ruled out a thymic carcinoma.



Figure 2. Specimen of thymoma showing external and cut-surface

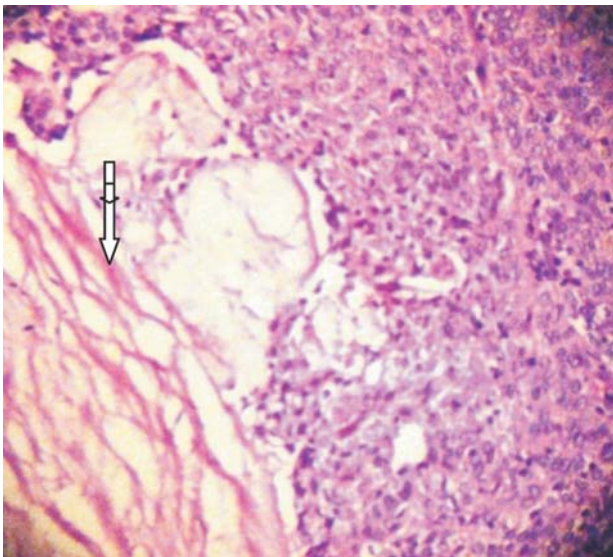


Figure 3. Microscopic photograph of the tumour mass showing thick capsule, pseudoglandular spaces and epithelial component (Haematoxylin-eosin×100).

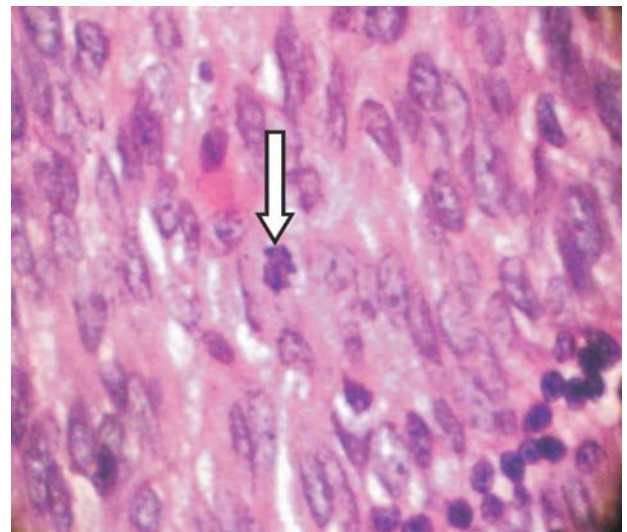


Figure 4. Histopathological picture showing spindle cell component and occasional mitotic figure (Haematoxylin-eosin×100).

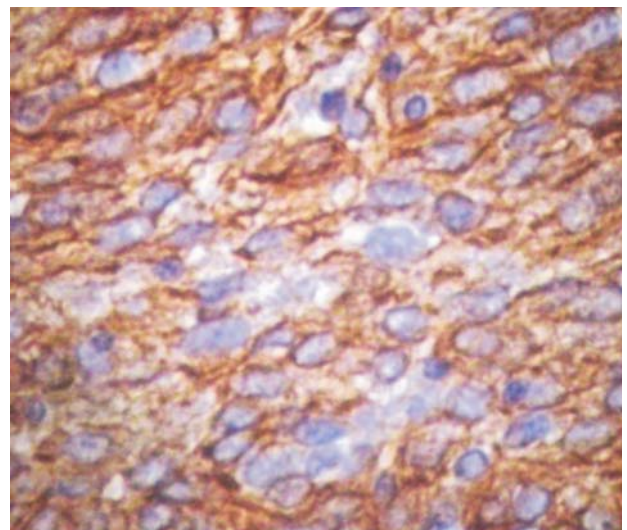


Figure 5. Photomicrograph showing strong pancytokeratin positivity (IHC×400).

---

## DISCUSSION

---

A thymoma is a thymic epithelial neoplasm exhibiting some organotypic features, accompanied by variable number of reactive lymphoid cells. Organotypic features include lobulation, medullary differentiation, perivascular spaces and the presence of immature T-lymphocytes. The peak incidence is in the 5<sup>th</sup> and 6<sup>th</sup> decades of life with a male preponderance.<sup>5</sup> One-third of the patients present with symptoms attributed to mediastinal mass such as dyspnoea and hoarseness. A type A or B thymoma can be associated with *M. gravis* (15% for type A, 40% for type B1 and 50% for type B2 and B3 thymomas). There are no known aetiological factors for a thymoma in humans. The single most important prognostic factor for a thymoma is its tumour stage (modified Masaoka staging system).<sup>5</sup> Apart from that, the completeness of excision and tumour size (>11 cm carrying a bad prognosis) are other important prognostic factors.<sup>5</sup> *Myasthenia gravis* was previously thought to be an adverse prognostic factor but recent studies have not substantiated this.<sup>5</sup>

On electron microscopy, thymoma cells possess multiple inter-digitating elongated cell processes connected by desmosomes. Intra-cytoplasmic tonofilaments are often prominent.<sup>5</sup> Type A thymomas show few genetic alterations with 6p deletion being a recurrent alteration.<sup>5</sup>

The main differential diagnosis in this case was a thymic carcinoma, but was excluded by a negative CD5, CD117 and p53 markers.

On IHC, the epithelial component of a thymoma stains for cytokeratin (CK) and the epithelial membrane antigen (EMA) and variably with CD57.<sup>5</sup> In type A thymoma, interspersed glandular structures show stronger staining for cytokeratin than the spindled tumour cells. Neoplastic epithelial cells of type A thymoma may stain with B cell markers, such as CD20. The lymphoid component is made-up of immature T lymphocytes positive for TdT, CD 1a, CD3 and CD 99a. The differential diagnosis includes neuroendocrine tumours, Hodgkin's lymphoma and non-Hodgkin's lymphoma and thymic carcinoma.

A thymoma is an uncommon tumour with a largely indolent growth pattern. It has malignant

potential as a result of its ability to invade locally and metastasise regionally and is often associated with a number of immune- and non-immune-mediated paraneoplastic syndromes. Surgery is the mainstay of treatment, with adjuvant radiotherapy recommended for an invasive thymoma. In incompletely resected and inoperable patients, chemotherapy may be added.<sup>6</sup>

The WHO classification of thymic epithelial tumours reflects their oncological behaviour. Type A, AB and B1 tumours have better prognosis than types B2 and B3 tumours, suggesting the significance of this classification in the clinical practice of thymomas. Type B tumours are more invasive than type A and AB tumours. Type B1 and B2 tumours are frequently associated with *M. gravis* while type A and AB tumours are not. On CT imaging type A and AB tumours tend to be round and have a smooth surface while type B1, B2 and B3 tumours are often flat and have irregular surfaces. Type AB, B1 and B2 tumours possess a significant number of CD4+CD8+ double positive T cells in the tumour.<sup>8</sup>

---

## REFERENCES

---

1. Quddus MA, Rahman MM, Ali ZI, *et al.* Treatment of myasthenia gravis: a surgical profile. *Mymensingh Med J* 2009;18:203-7.
2. Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. *J Clin Oncol* 1999;17:2280-9.
3. Aster JC. The hematopoietic and lymphoid systems. In: Mitchell, Kumar, Robbins, Abbas, Fausto, editors *Robbins Basic Pathology*; 8<sup>th</sup> edn. Elsevier: Philadelphia; 2007: p.476.
4. Blalock A, Mason MF, Morgan HJ, Riven SS. Myasthenia gravis and tumours of the thymic region: report of a case in which the tumour was removed. *Ann Surg* 1939; 110:544-61.
5. Fletcher DM. *Diagnostic Histopathology of Tumors*; Vol. 2; 3<sup>rd</sup> edn. Elsevier; 2007:pp1315-36.
6. Suster S. Diagnosis of thymoma. *J Clin Pathol* 2006; 59:1238-44.
7. Rosai J, Levine GD. Tumours of the thymus. In: *Atlas of Tumour Pathology*; 2<sup>nd</sup> series, Fascicle 13. Washington DC: Armed Forces Institute of Pathology;1976.
8. Okumura M, Ohta M, Tomiyama N, Minami M, Hirabayashi H, Matsuda H. WHO classification in thymoma. *Kyobu Geka* 2002;55:916-20.

With best compliments

from

## ELDER PHARMACEUTICALS LTD.,

SHELCAL 250/500MG  
 SHELCAL HD/SHELCAL - K  
 SHELCAL OS, SHELCAL - M  
 SHELCAL CT/SHELCAL SYRUP  
 CARNISURE TAB & INJ  
 SOMAZINA TAB & INJ.  
 AMIFRU/AMIFRU-S  
 ELMECOB/OD TAB & INJ  
 FLAVOSPAS  
 HORMORIN100/200MG  
 B-LONG TAB./B-LONG -F  
 DEVIRY 10MG  
 EPRIN 75/150MG  
 SAMPURE /SAMPLUS  
 PHYTOMEGA  
 CLOTAN CAP.

AUGPOD 325MG/162.5MG ( Cefpodoxime + Clavulanic Acid)

TAZOMUST 4.5 GM ( Piperacilline 4gm + Tazobactam 0.5gm)

OFVISTA (Ofloxacin) ELVOX (Levofloxacin) ELDOCORT (Deflazacort)

CLAVACTUM (Amoxicillin + Clavulanic Acid) ELZEE (Azithromycin)

CHYMORAL FORTE/DS

CHYMORAL PLUS

ELDERVIT PLUS TAB. & INJ.

FORMIC TABS & INJ.(Cefixime)

WIDCEF TABS & INJ.(Cefuroxime)

HIBOUR INJ.(Bemiparin Sod.)

KEFBACTUM INJ 1GM & 2GM

TOBRANEG 20/60/80MG

ENZAR FORTE/LIQUID/ENZAR HS

REPRAL & REPRAL-D

TANTUM ORAL RINSE/ TANTUM GEL

ONTAC GEL

XPLOCEF 1.5GM


ESLITE CREAM/ PROTOCREAM/





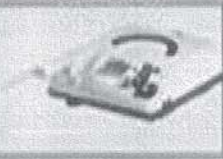
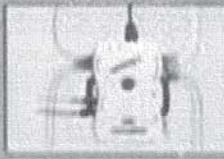

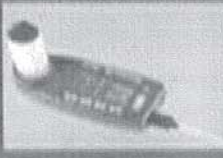



STEROMOM CREAM


ELPOD 100/200 (Cefpodoxime Proxetil)

Tired of Sleepiness ?  
Tired of Snoring ?

The best automatic treatments  
for your sleep apnea



<b>CPAP</b> 	<b>AUTO CPAP</b> 	<b>BIPAP AUTO S</b> 	
<b>BIPAP AUTO ST</b> 	<b>NON INVASIVE VENTILATOR</b> 	<b>POLYSOMNOGRAPHY SYSTEM (SLEEP LAB)</b> 	<b>POLYGRAPHY SYSTEM (RESPIRATORY SLEEP LAB)</b> 
<b>HANDHELD SPIROMETER</b> 	<b>TABLETOP SPIROMETER</b> 	<b>PATIENT MONITOR</b> 	<b>PULSE OXIMETER</b> 



**Elder**  
Instruments Pvt. Ltd.  
(Medical Electronics Division)

604, Morya Landmark - II, Opp. Infinity Mall,  
New Link Road, Andheri (West), Mumbai - 400 053.  
Telfax : 022-40147330 | Tollfree No.: 18002090777  
Email: medequip@elderindia.com | www.elderindia.com

# Intrapulmonary Teratoma Presenting with Trichoptysis: A Case Report and Review of the Literature

Jagdish Rawat<sup>1</sup>, Sunil Saini<sup>2</sup>, Sailendera Raghuvanshi<sup>3</sup>, Girish Sindhwani<sup>1</sup> and Vikas Kesarwani<sup>1</sup>

Departments of Pulmonary Medicine<sup>1</sup>, Oncosurgery<sup>2</sup> and Radiology<sup>3</sup>, Himalayan Institute of Medical Sciences, Dehradun (Uttarakhand), India

## ABSTRACT

Intrathoracic teratoma usually occurs in the mediastinum but rarely, these may originate from the lung. We report a case of an intrapulmonary teratoma in a 34-year-old male. [Indian J Chest Dis Allied Sci 2011;53:237-239]

**Key words:** Intrapulmonary teratoma, Trichoptysis, Germ cell neoplasm.

## INTRODUCTION

A teratoma is defined as a neoplasm that consists of one or more types of tissues that usually derived from more than one germ cell layer. A germ cell tumour arises as a result of the proliferation of primitive extra-gonadal germ cells that have the potential to differentiate into various cell types. The anterior mediastinum is the most common extra-gonadal site in adults for this tumour and these rarely arise within the lung parenchyma. The most common germ cell neoplasm is mature cystic teratoma or a dermoid cyst. This tumour is benign in nature and accounts for approximately 80% of the germ cell neoplasms.<sup>1</sup>

Clinically, while patients with intrathoracic teratoma present with chest pain, haemoptysis, cough with expectoration but pathognomonic symptom that clinches the diagnosis of an intrapulmonary teratoma with trichoptysis (expectoration of hairs). Trichoptysis is seen in 15% of cases.<sup>2</sup> We present here a case of this rare tumour.

## CASE REPORT

A 34-year-old male, labourer by occupation, non-smoker, and tea-totaller presented with a seven-year history of dull aching chest pain and cough with expectoration. Expectoration was intermittent, 30-40 mL in 24 hours, mucopurulent and non-foul smelling and often contained thin brown silky hairs. The quantity increased in the supine and left lateral position. There was no history of haemoptysis, fever and loss of weight. The patient received anti-

tuberculosis treatment (ATT) three times during this duration without any clinico-radiological improvement. Finally, the treating physician referred the patient to us for further evaluation.

On examination, he was afebrile. The vital signs were within normal limits. The patient had grade III clubbing. Auscultation revealed reduced breath sounds and crepitations over the right mammary and axillary area. The rest of the physical examination was unremarkable.

The patient's laboratory findings were: haemoglobin 9.5 g/dL, haematocrit 34%, random glucose 110 g/dL, serum sodium 130 mmol/L. The rest of the laboratory results were unremarkable.

Chest radiograph (postero-anterior view) showed a well-defined homogeneous opacity in the right middle and lower zones (Figure 1).

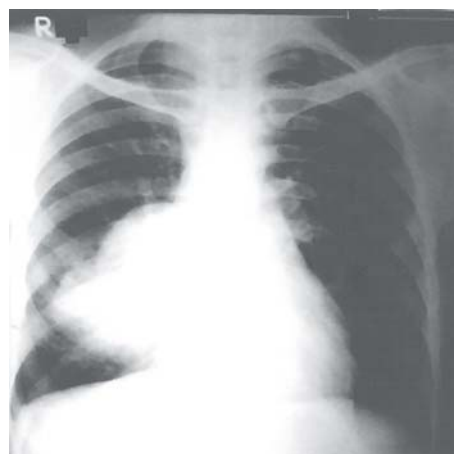


Figure 1. Chest radiograph (postero-anterior view) showing a well-defined mass in the right middle and lower zones.

[Received: March 3, 2011; accepted after revision: June 16, 2011]

**Correspondence and reprint requests:** Dr Jagdish Rawat, Assistant Professor, Department of Pulmonary Medicine, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Jolly Grant, Dehradun - 248 140 (Uttarakhand), India; Phone: 91-135-2471362; 9639212630; Fax: 91-135-2471317; E-mail: drjagdishrawat@yahoo.com

Contrast enhanced computed tomography (CECT) of the chest showed a heterogeneous cystic lesion measuring 6.8cmx5.6cmx5.4cm in the right middle lobe (Figure 2). The lesion showed a heterogeneous density containing soft tissue elements, fat, cystic areas and foci of calcification. This is the classical computed tomographic appearance of mature cystic teratoma (Figure 2). The mass appeared to be adherent to the mediastinal pleura medially and the sub-costal pleura antero-laterally. No endobronchial lesion was visualised on bronchoscopy. However, thick secretions were seen coming from the right upper lobe bronchus. The bronchoalveolar lavage (BAL) did not reveal any malignant cells on pathogenic organisms on Gram's stain, acid-fast stain and KOH mount for fungal element. A CT-guided fine needle aspiration was suggestive of inflammatory pathology with negative malignant cells. Two sputum smears were negative for acid-fast bacilli.

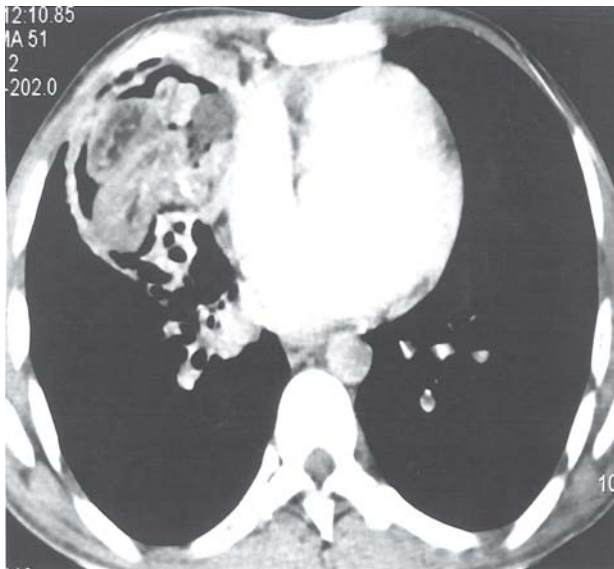


Figure 2. Computed tomography of thorax showing a heterogeneous mass in the right lung with areas of fat attenuation, calcification and solid components with air-lucent rim around the mass.

A diagnosis of an intrapulmonary mature cystic teratoma was made on the basis of the clinical and radiological findings. A right-sided thoracotomy for excision of the lesion with resection of the right middle lobe was undertaken. Figure 3 showed the excised mass (7.1cmx5.4cmx5.2cm) with solid areas of sebaceous material and white silky hairs as well as solid ill-defined structure. On histopathological examination, sections showed tissue bits lined by stratified squamous epithelium, many sebaceous glands, mature pancreatic tissue, cartilage, lymphoid tissue, blood vessels and smooth muscle bundles (Figure 4 A,B,C). No immediate complication was observed during the intra- and post-operation period.

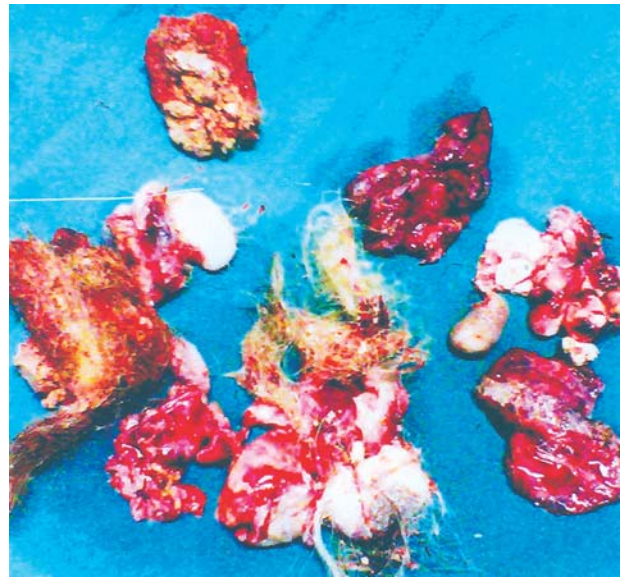


Figure 3. Gross surgical specimen showing multiple irregular tissue pieces, partially cystic, filled with hairs and sebaceous material.

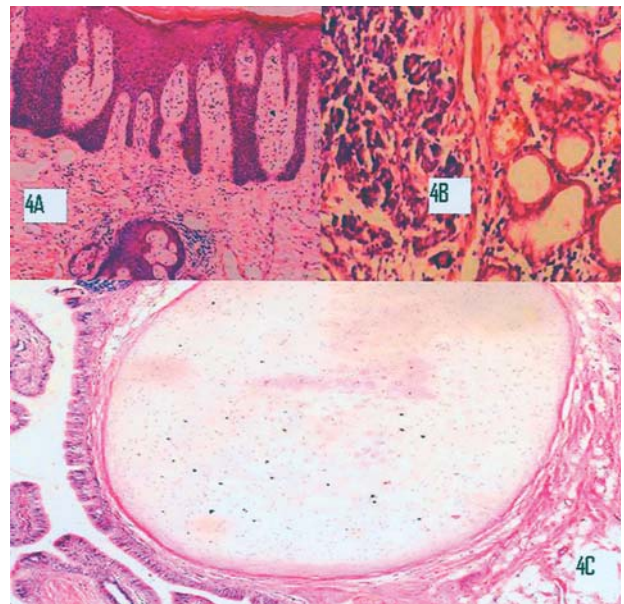


Figure 4. Microscopic examination showing a variety of cell lines; (A) stratified squamous epithelium and sebaceous glands, (B) pancreatic tissue, (C) cartilage and adipose tissue.

## DISCUSSION

The anterior mediastinum is the most common extra-gonadal site for a teratoma in adults whereas in children, the sacrococcegal area is more common. Lungs are a rare site for origin of these tumours. Germ cell tumour may be benign or malignant. The most common intrathoracic germ cell tumour is the mature cystic teratoma or dermoid cyst. The most common

site for an intrapulmonary teratoma is the left upper lobe. However, in our case, the tumour was found in the right middle lobe. This tumour is benign and accounts for 80% of all germ cell neoplasms. Intrapulmonary teratoma is very rare with only 65 cases reported in the world literature between 1839 to 1996. A teratoma occurs equally in both sexes and is usually diagnosed in the 2<sup>nd</sup> to 4<sup>th</sup> decade of life.

Mature teratomas usually do not produced symptoms and are discovered during screening by chest radiography. A large teratoma may produce cough, shortness of breath and chest pain. Occasionally, it may rupture and spill its contents into the pleural cavity or the mediastinum resulting in mediastinitis and empyema formation. Rarely, the cyst ruptures into the bronchus producing haemoptysis and recurrent cough with expectoration.<sup>4,5</sup> The cyst rupture due to erosion caused by locally produced pancreatic enzyme. Our patient presented with trichoptysis, a specific symptom of an intrapulmonary teratoma and seen in only 15 % of cases.<sup>2</sup> Radiological signs of a mature cystic teratoma include a lobulated opacity within the affected lobe, calcification<sup>6</sup> within the lesion, cavitations<sup>7</sup> or a rim of air around the opacity.<sup>8</sup> In our case, peripheral translucency area was seen that indicates communication of cyst with bronchus.

Clinico-radiological features of a teratoma may occasionally simulate pulmonary tuberculosis. Our patient had received many courses of ATT. A lack of response to ATT should alert the physician to other possibilities.

On CT of the chest, a teratoma presents as a mass with a smooth wall that contains soft tissue, fluid density, fat density, calcification, or any combination of these.<sup>9</sup> These features were also observed in the CT of our patient.

Complications of a teratoma that may be evident on either a chest radiograph or a CT include; atelectasis, obstructive pneumonitis, pneumonia with formation of multiple cavity (cyst rupture into the lung parenchyma) and effusion (secondary to rupture of cyst into the pleural space).<sup>9</sup>

Histopathologically, an intrapulmonary teratoma is similar to other teratomas being composed of an

epithelial lining and may contain any tissue originating from one of the three germinal layers.

Excision of the tumour is the treatment of choice for a mature teratoma. Patients who do not undergo surgery can present with complications, such as massive haemoptysis, recurrent infection and accidentally cyst rupture into nearby organs and these may be fatal.<sup>10</sup> Benign teratoma also has the potential to transform into a malignancy.

In conclusion, an intrapulmonary teratoma is a rare tumour. Trichoptysis is the only clinical feature that can clinch the diagnosis of an intrapulmonary teratoma. Surgical resection is curative.

---

## REFERENCES

---

1. Roberts JR, Kaiser LR. Acquired lesions of the mediastinum: benign and malignant. In: Fishman AF, editor *Fishman's Pulmonary Diseases and Disorders*; 3 edn. New York: McGraw-Hill; 1998:pp1511-37.
2. Ustun MO, Demircan A, Paksoy N, Ozkaynak C, Tuzuner S. A case of intrapulmonary teratoma presenting with hair expectoration. *J Thorac Cardiovasc Surg* 1996; 44:271-3.
3. Asano S, Hoshikawa Y, Yamane Y, Ikeda M, Wakasa H. An intrapulmonary teratoma associated with bronchiectasis containing various kinds of primordium: a case report and review of the literature. *Virchows Arch* 2000;436:384-8.
4. Cobb CJ, Wynn J, Cobb SR, Duane GB. Cytological finding in an effusion caused by rupture of a benign cystic teratoma of the mediastinum into a serous cavity. *Acta Cytol* 1985;29:1015-20.
5. Southgate J, Slade PR. Teratodermoid cyst of the mediastinum with pancreatic enzyme secretion. *Thorax* 1982;37:476-7.
6. Trivedi SA, Mehta KN, Nanavaty JM. Teratoma of the lung: report of a case. *Br J Dis Chest* 1966;60:156-9.
7. Bateson EM, Hayes JA, Woo MM. Endobronchial teratoma associated with bronchiectasis and bronchiolectasis. *Thorax* 1968;23:69-76.
8. Collier FC, Dowling EA, Plott D, Schneider H. Teratoma of the lung. *AMA Arch Pathol* 1959;68:138-42.
9. Moeller KH, Rosado-Dechristenson M, Tempelton PA. Mediastinal mature teratoma: imaging feature. *AJR Am J Roentgenol* 1997;170:985-90.
10. Medeiros CWL, Kondo W, Dyckyj MT, Suzuki N. Teratoma intrapulmonary. *J Pneumol* 2001;27:272-4.



HINDUJA HOSPITAL

## 5<sup>th</sup> National Update in Respiratory Medicine

9<sup>th</sup> - 11<sup>th</sup> December, 2011

The 5<sup>th</sup> course in this annual series of Updates in Respiratory Medicine will be held at the P.D. Hinduja National Hospital & Medical Research Centre from 9<sup>th</sup> - 11<sup>th</sup> December, 2011. This 3-day course is designed for respiratory physicians, chest registrars and PG's in internal medicine with a special interest in respiratory medicine. An expert National and International Faculty will discuss various topics at the cutting edge of respiratory medicine. **A Special highlight of this course will be a full day dedicated to Updates in TB.**

*The last course was over subscribed; please register early to avoid disappointment. Limited seats*

**Hinduja Hospital is recognized by MMC for CME points**

**Course Directors : Dr Zarir F. Udwardia & Dr Ashok A. Mahashur**

**Registration fees : Rs. 3000/- (Consultants), Rs. 1500/- (PG's)**

### REGISTRATION FORM

**Name** : Dr \_\_\_\_\_

**Designation** : \_\_\_\_\_

**MCI / State Medical Council Regn. No.:** \_\_\_\_\_

**Address** : \_\_\_\_\_

**Tel. Nos.** : **Clinic/ Hospital:** \_\_\_\_\_ **Resi.:** \_\_\_\_\_

**Mobile:** \_\_\_\_\_

**E-mail** : \_\_\_\_\_

**Course Fees** : **Amount: Rs.** \_\_\_\_\_

**D.D. /Cheque (local only) should be in favour of  
"P.D. Hinduja National Hospital & Medical Research Centre"**

**Ch./D.D. No.** \_\_\_\_\_ **Dated** \_\_\_\_\_

**Drawn on** \_\_\_\_\_

**Address to: MARKETING DEPARTMENT**

P. D. Hinduja National Hospital & Medical Research Centre  
Veer Savarkar Marg, Mahim, Mumbai - 400 016 (Maharashtra)  
**Tel:** 022-24447704; **E-mail:** events.hindujahospital@gmail.com

**Kindly visit our website [www.hindujahospital.com](http://www.hindujahospital.com) to register online for the course (Mandatory)**

*\* Delegates have to arrange their own accommodation*

**Brief Communication**

# Difference in the Outcome of Patients with Different Grades of Initial Sputum Positivity under the Revised National Tuberculosis Control Programme

Abhijit Mukherjee<sup>1</sup>, Rupak Singla<sup>2</sup>, Indranil Saha<sup>3</sup>, Anirban Sarkar<sup>4</sup> and Parthasarathi Bhattacharyya<sup>5</sup>

Department of Community Medicine, R.G. Kar Medical College<sup>1</sup>, Kolkata; Department of Tuberculosis and Respiratory Diseases, LRS Institute of Tuberculosis and Respiratory Diseases<sup>2</sup>, New Delhi; Department of Community Medicine, Burdwan Medical College, Burdwan<sup>3</sup>; Department of Tuberculosis and Respiratory Diseases, Medical College and Hospital<sup>4</sup>, Kolkata and Institute of Pulmocare and Research<sup>5</sup>, Kolkata, India

Under the Revised National Tuberculosis Control Programme (RNTCP) positive sputum smears are graded and reported based on the number of acid-fast bacilli per oil immersion field. However, these grades signifying different levels of the bacillary load are not taken into account while instituting therapy. The present study was undertaken to examine the association between the initial sputum positivity and treatment outcomes.

This record-based study was carried out at the Bagula Tuberculosis Unit, West Bengal, having five designated microscopy centres that are attached to five peripheral health institutions (PHIs). Collection, preparation of sputum smears, examination and grading were done according to the RNTCP guidelines. Patients were categorised by the Medical Officers and treatment was initiated. Adherence and action for missed doses was ensured. For the present study, a favourable outcome was defined as cured and treatment completed taken together, while default, died, failure and transfer out clubbed together were classified as an unfavourable outcome. Scanty, 1+ and 2+ smears were considered low grade, while 3+ smear was considered as high grade of sputum positivity.

A total of 1414 patients were studied. Cure rate was found to be the highest in scanty (90.4%) and 1+ (90.7%), decreasing to 89.2% and 82.7% in the 2+ and 3+ grades, respectively. Unfavourable outcomes increased with increasing grades of sputum positivity (Table 1).

Sputum positivity was highest (94%) in 1+ grade, followed by 93.3% in scanty. It was least (84%) in 3+ grade (Table 2). A significantly greater number of patients with higher sputum grades needed prolongation of the intensive phase (12.1% *versus* 22.6%) (Table 3).

With increasing grades of sputum positivity, there was a decrease in the favourable outcomes and an increase in the adverse events. Similar observations were also reported by Singla *et al*<sup>1</sup> and Gopi *et al*.<sup>2</sup> Rajpal *et al*<sup>3</sup> from Delhi observed an increase in death and default rates in patients with higher grades of sputum positivity.

Rates of sputum conversion at three months decreases with higher grades of sputum positivity.<sup>2,4</sup> In agreement with studies conducted at the Tuberculosis Research Centre, Chennai<sup>2</sup> and New Delhi,<sup>1</sup> we found that a greater number of patients

**Table 1. Distribution of different treatment outcome of newly diagnosed sputum positive patients**

Treatment Outcomes	Sputum Grading				Total (n=1414)
	Scanty (n=165)	1+ (n=321)	2+ (n=314)	3+ (n=614)	
<b>Favourable outcome</b>					
Cured	149 (90.4)	291 (90.7)	280 (89.2)	508 (82.7)	1228 (86.8)
Treatment completed	1 (0.6)	3 (0.9)	4 (1.3)	12 (2.0)	20 (1.4)
<b>Unfavourable outcome</b>					
Death	6 (3.6)	9 (2.8)	8 (2.4)	30 (4.9)	53 (3.7)
Failure	4 (2.4)	4 (1.2)	9 (2.9)	15 (2.4)	32 (2.3)
Default	4 (2.4)	9 (2.8)	9 (2.9)	37 (6.0)	59 (4.2)
Others	1 (0.6)	5 (1.6)	4 (1.3)	12 (2.0)	22 (1.6)

Figures in parenthesis indicate percentages

[Received: March 8, 2011; accepted after revision: April 1, 2011]

**Correspondence and reprint requests:** Dr Abhijit Mukherjee, 34, S.N. Banerjee Road, New Barrackpore, Kolkata - 700 131 (West Bengal), India; Phone: 91-9433187412; E-mail: drabhijit71@gmail.com

**Table 2. Sputum conversion rate at two months in different grades of sputum smear grading (N=1414)**

Pre-treatment Sputum Grading	Patients No. (%)	Sputum Conversion No. (%)
Scanty	165 (11.7)	154 (93.3%)
1+	321 (22.7)	302 (94.0%)
2+	314 (22.2)	287 (91.4%)
3+	614 (43.4)	516 (84.0%)
<b>Total</b>	<b>1414 (100)</b>	<b>1259 (89.0%)</b>

will improve the final outcome in patients with higher grades of sputum positivity needs to be evaluated in larger studies.

### REFERENCES

1. Singla R, Singla N, Sarin R, Arora VK. Influence of pretreatment bacillary load on treatment outcome of pulmonary tuberculosis patients receiving DOTS under the Revised National Tuberculosis Control Programme. *Indian J Chest Dis and Allied Sci* 2005;47:19-23.

**Table 3. Distribution of different treatment outcome among low and high grade sputum positive patients**

Treatment Outcomes	Low Grade (Scanty, 1+ & 2+) (n=800) No. (%)	High Grade (3+) (n=614) No. (%)	z Test for Proportion	Exact p Value
Favourable outcome (Cured + Treatment Completed)	728 (91.0)	520 (84.7)	3.57	0.00*
Death	23 (2.9)	30 (4.9)	1.82	0.03*
Failure	17 (2.1)	15 (2.5)	0.32	0.37
Default	22 (2.8)	37 (6.0)	2.84	0.00*
Others	10 (1.2)	12 (1.9)	0.85	0.19
Unfavourable outcome ( Total)	72 (9.0)	94 (15.3)	3.57	0.00*
Sputum conversion at 3 months	92.9%	84.0%	5.22	0.00*
Patients needing prolongation of the intensive phase	97 (12.1)	139 (22.6)	5.18	0.00*

\*=Statistically significant,  $p < 0.05$

with higher initial sputum positivity needed prolongation of the intensive phase.

Sputum conversion at the end of two months of the intensive phase is considered the most important predictor of the outcome in sputum-smear-positive patients. Persistent sputum positivity is more likely to have a less favourable outcome compared to those with sputum conversion to negative.<sup>5</sup> Since human immunodeficiency virus seropositivity and primary drug resistance is low in this geographical area, their impact on the outcomes were not taken into account in the study.

The present study reveals that there is a difference in the outcomes of patients in relation to their pre-treatment sputum grades. We suggest that the grades of initial sputum positivity be considered in the treatment regimen under the RNTCP. Whether adding another antituberculosis drug to the current regimen or a more prolonged duration of treatment

2. Gopi PG, Chandrasekaran V, Subramani R, Santha T, Thomas A, Selvakumar N, *et al.* Association of conversion and cure with initial smear grading among new smear positive pulmonary tuberculosis patients treated with Category I regimen. Tuberculosis Research Centre (ICMR), Chennai, India. *Indian J Med Res* 2006;123:807-14.
3. Rajpal S, Dhingra VK, Aggarwal JK. Sputum grading as a predictor of treatment outcome in pulmonary tuberculosis. *Indian J Tuberc* 2002;49:139-41.
4. Singla R, Osman MM, Khan N, Al Sharif N, Al Sayegh MO, Shaikh MA. Factors predicting persistently sputum smear positivity among pulmonary tuberculosis patients two months after treatment. *Int J Tuberc Lung Dis* 2003; 7:58-64.
5. Lienhardt C, Manneh K, Bouchier V, Lahai G, Milligan PJM, Mc Adam KPWJ. Factors determining the outcome of treatment of adult smear positive tuberculosis cases in The Gambia. *Int J Tuberc Lung Dis* 1998;2:712-8.

## **NCCP Textbook of Respiratory Medicine**

*Editor-in-Chief: D. Behera; Associate Editors: S.N. Gaur, S.K. Katiyar, Bharat Gopal and S.K. Luhadia; Published by: Jaypee Brothers Medical Publishers (P) Ltd, New Delhi; 2011; Hard Cover; Pages: 980+XIV+18 pages of colour photographs; First Edition; ISBN: 978-93-5025-212-3*

The textbook has been published under the aegis of National College of Chest Physicians and edited by D. Behera, an eminent chest physician of our country. He has been assisted by four associate editors in compiling this multi-authored textbook. It contains 41 chapters contributed by noted authors in the field, both from India and abroad. This single volume textbook sets out to provide comprehensive yet concise information on the ever expanding field of respiratory medicine, with special emphasis on the disease conditions commonly encountered in our country. One of the explicitly stated goals for the book is to address the needs of a gamut of audience, including undergraduates and postgraduates, the future of the speciality.

The selection of the topics for the chapters is judicious, covering all the diseases relevant in our setting, and overall the text is very lucid and well organised. The book begins with a brief review of respiratory system examination, the common symptomatology of chest diseases, and a chapter on physiology; which is beautifully illustrated, informative, and clear. The chapter on diagnostic methods gives an account of emerging modalities like positron emission tomography (PET) scan and endoscopic ultrasound (EUS), and a separate chapter is dedicated to electromagnetic navigation bronchoscopy (ENB), intending to keep readers abreast with the latest advances in diagnostic technology. The inclusion of a discussion on pulmonary function test (PFT) as a tool of evaluation in pulmonary medicine would have been useful, particularly for the undergraduates and postgraduates. The text is well supported by figures and tables, as evident from chapters on fungal pneumonia, hydatid disease, pathogenesis of asthma, pulmonary embolism, and lung cancer diagnosis.

The chapters on tuberculosis, bronchial asthma and lung cancer have been covered extensively. The in-depth description of diagnostic methods, pathology and treatment strategies in tuberculosis is befitting for our setting. We would have welcomed a separate section for discussion on various recommendations of "Treatment of tuberculosis: guidelines" (4<sup>th</sup> edition) by The World Health

Organization, and its applicability in India in the light of the available evidence. The appendices following the chapter on tuberculosis present the *Revised National TB Control Programme* (RNTCP) guidelines, a must know for the undergraduates and postgraduates. The case based approach adapted in the chapter on treatment of tuberculosis in special conditions is appreciable, and another example of effort to connect with its readers in the medical school. Immunotherapy in bronchial asthma has been exhaustively covered including the relevant Indian data. Other major diseases like chronic obstructive pulmonary disease (COPD), pneumonia, acute respiratory distress syndrome (ARDS), pulmonary embolism, cor-pulmonale, interstitial lung disease (ILD), pleural diseases and human immunodeficiency virus (HIV) and respiratory diseases are discussed appropriately. Smoking and air pollution related respiratory disorders have been given the due importance consistent with their relevance in the clinical practice.

The textbook is an excellent compilation of relevant topics in the field of pulmonary medicine presented in a lucid and flowing language. The book cogently summarises the current knowledge in the field. The major strength of the book is being comprehensive yet concise. It should be useful to undergraduates and postgraduates students of pulmonary medicine and internal medicine, as well as serve as quick referral for the busy practitioners and respiratory physicians. We recommend this book as a valuable addition to any medical library.

**Prof. S.K. Sharma**

*Editor, IJCDAS  
and*

**Dr Manish Soneja**

*Department of Medicine*

*All India Institute of Medical Sciences*

*New Delhi-110 029, India*

*Telephone: 91-11-26593303 (O), 91-11-26594415 (O)*

*Fax: 91-11-26589898*

*E-mail: sksharma.aiims@gmail.com,*

*sksharma.aiims@yahoo.com*

Correspondence

## ***Burkholderia pseudomallei*: An Uncommon Cause of Bacteraemic Pneumonia in a Diabetic**

**To the Editor:** A recent report by Subbalaxmi *et al*<sup>1</sup> on melioidosis pneumonia, *Burkholderia pseudomallei* lung infection, is very interesting. Subbalaxmi *et al* noted that this is an uncommon infection.<sup>1</sup> Indeed, this conclusion is correct for Indian situation but it might not be generalised for all other settings. For the endemic areas, East and Southeast Asia, this problem is common and can be more common in the immunocompromised host as diabetic patients. In the recent report from Taiwan, it is well demonstrated that the problem was common in diabetic patients.<sup>2</sup> In addition, a similar report from Malaysia can also be seen.<sup>3</sup> It should be concluded that the melioidosis pneumonia can be an important differential diagnosis for any cases with clinical presentations concordant with pneumonia and live or have history entering into endemic areas.

**Somsri Wiwanitkit**

Professor

Wiwanitkit House, Bangkhuae

Bangkok, Thailand 10160;

Phone: 66870970933

E-mail: somsriwiwan@hotmail.com

---

### REFERENCES

1. Subbalaxmi MV, Chandra N, Rao MN, Vemu L, Raju YS. *Burkholderia pseudomallei*: an uncommon cause of bacteraemic pneumonia in a diabetic. *Indian J Chest Dis Allied Sci* 2011;53:185-7.
2. Kung CT, Li CJ, Hung SC, Ko SF, Chen MC, Lee CH, *et al*. Acute melioid community-acquired pneumonia. *Int J Infect Dis* 2011 Jun 20. [Epub ahead of print]
3. Deris ZZ, Hasan H, Siti Suraiya MN. Clinical characteristics and outcomes of bacteraemic melioidosis in a teaching hospital in a northeastern state of Malaysia: a five-year review. *J Infect Dev Ctries* 2010;4:430-5.

**The Authors' reply:** We appreciate the interest of Somsri Wiwanitkit and Viroj Wiwanitkit on our case report. We agree to the comment that *Burkholderia pseudomallei* is endemic to East and Southeast Asia

*albeit* uncommon.<sup>1</sup> However, at our tertiary care medical institute this is the 4th case of melioidosis in the last eight years. The first case was a case of septicemic melioidosis,<sup>2</sup> followed by a case of calvarial abscess,<sup>3</sup> and third case is a case of septicemia with septic arthritis with prostatic abscess.<sup>4</sup> Unlike other aetiologies, we would like to emphasise that pneumonia due to *Burkholderia pseudomallei* needs a special attention as the antimicrobial therapy is specific and requires a prolonged period of treatment. Lack of awareness among the clinicians about the infection and the laboratories not capable of isolating and identifying *B. pseudomallei* may be responsible for the under-reporting of melioidosis in India. The magnitude of this infection may still remain unknown, unless large scale epidemiological studies are undertaken in India.

**M.V.S. Subbalaxmi**

Assistant Professor

Department of General Medicine

Nizam's Institute of Medical Sciences

Hyderabad-500 082 (Andhra Pradesh), India

Phone: 91-949-0457909

E-mail: subbalaxmimvs@yahoo.com

---

### REFERENCES

1. Kung CT, Li CJ, Hung SC, Ko SF, Chen MC, Lee CH, *et al*. Acute melioid community-acquired pneumonia. *Int J Infect Dis* 2011 Jun 20. [Epub ahead of print]
2. Anuradha K, Meena AK, Lakshmi V. Isolation of *Burkholderia pseudomallei* from a case of septicaemia: a case report. *Indian J Med Microbiol* 2003;21:129-32.
3. Bommakanti K, Ankathi P, Uma P, Malladi S, Laxmi V. Cerebral abscess and calvarial osteomyelitis due to *Burkholderia pseudomallei*. *Neurol India* 2010;58:801-2.
4. Thomas J, Jayachandran NV, Shenoy Chandrasekhara PK, Lakshmi V, Narsimulu G. Melioidosis: an unusual cause of septic arthritis. *Clin Rheumatol* 2008;27 (Suppl. 2):S59-S61.

Abstracts' Service

## Hospital Mortality, Length of Stay, and Preventable Complications Among Critically Ill Patients Before and After Tele-ICU Reengineering of Critical Care Processes

Craig M. Lilly, Shawn Cody, Huifang Zhao, Karen Landry, Stephen P. Baker, John McIlwaine, M. Willis Chandler, Richard S. Irwin, for the University of Massachusetts Memorial Critical Care Operations Group

*JAMA* 2011;305:1777-1785

**Context.** The association of an adult tele-intensive care unit (ICU) intervention with hospital mortality, length of stay, best practice adherence, and preventable complications for an academic medical center has not been reported.

**Objective.** To quantify the association of a tele-ICU intervention with hospital mortality, length of stay, and complications that are preventable by adherence to best practices.

**Design, Setting, and Patients.** Prospective stepped-wedge clinical practice study of 6290 adults admitted to any of 7 ICUs (3 medical, 3 surgical, and 1 mixed cardiovascular) on 2 campuses of an 834-bed academic medical center that was performed from April 26, 2005, through September 30, 2007. Electronically supported and monitored processes for best practice adherence, care plan creation, and clinician response times to alarms were evaluated.

**Main Outcome Measures.** Case-mix and severity-adjusted hospital mortality. Other outcomes included hospital and ICU length of stay, best practice adherence, and complication rates.

**Results.** The hospital mortality rate was 13.6% (95% confidence interval [CI], 11.9%-15.4%) during the preintervention period compared with 11.8% (95% CI, 10.9%-12.8 %) during the tele-ICU intervention period

(adjusted odds ratio [OR], 0.40 [95 % CI, 0.31-0.52]). The tele-ICU intervention period compared with the preintervention period was associated with higher rates of best clinical practice adherence for the prevention of deep vein thrombosis (99% vs 85%, respectively; OR, 15.4 [95% CI, 11.3-21.1]) and prevention of stress ulcers (96% vs 83%, respectively; OR, 4.57 [95% CI, 3.91-5.77]), best practice adherence for cardiovascular protection (99% vs 80%, respectively; OR, 30.7 [95% CI, 19.3-49.2]), prevention of ventilator-associated pneumonia (52% vs 33%, respectively; OR, 2.20 [95% CI, 1.79-2.70]), lower rates of preventable complications (1.6% vs 13%, respectively, for ventilator-associated pneumonia [OR, 0.15; 95% CI, 0.09-0.23] and 0.6% vs 1.0%, respectively, for catheter-related bloodstream infection [OR, 0.50; 95% CI, 0.27-0.93]), and shorter hospital length of stay (9.8 vs 13.3 days, respectively; hazard ratio for discharge, 1.44 [95 % CI, 1.33-1.56]). The results for medical, surgical, and cardiovascular ICUs were similar.

**Conclusion.** In a single academic medical center study, implementation of a tele-ICU intervention was associated with reduced adjusted odds of mortality and reduced hospital length of stay, as well as with changes in best practice adherence and lower rates of preventable complications.

## Comparison of Effect Sizes Associated With Biomarkers Reported in Highly Cited Individual Articles and in Subsequent Meta-analyses

John P.A. Ioannidis, Orestis A. Panagiotou

*JAMA* 2011;305:2200-2210

**Context.** Many biomarkers are proposed in highly cited studies as determinants of disease risk, prognosis, or response to treatment, but few eventually transform clinical practice.

**Objective.** To examine whether the magnitude of the effect sizes of biomarkers proposed in highly cited studies is accurate or overestimated.

**Data Sources.** We searched ISI Web of Science and MEDLINE until December 2010.

**Study Selection.** We included biomarker studies that had a relative risk presented in their abstract. Eligible articles were those that had received more than 400 citations in the ISI Web of Science and that had been published in any of 24 highly cited biomedical journals. We also searched MEDLINE for subsequent meta-analyses on the same associations (same biomarker and same outcome).

**Data Extraction.** In the highly cited studies, data extraction was focused on the disease/outcome, biomarker under study, and first reported relative risk in the abstract. From each meta-analysis, we extracted the overall relative risk and the relative risk in the largest study. Data extraction was performed independently by 2 investigators.

**Results.** We evaluated 35 highly cited associations. For 30 of the 35 (86%), the highly cited studies had a stronger effect estimate than the largest study; for 3 the largest study was also the highly cited study; and only

twice was the effect size estimate stronger in the largest than in the highly cited study. For 29 of the 35 (83%) highly cited studies, the corresponding meta-analysis found a smaller effect estimate. Only 15 of the associations were nominally statistically significant based on the largest studies, and of those only 7 had a relative risk point estimate greater than 1.37.

**Conclusion.** Highly cited biomarker studies often report larger effect estimates for postulated associations than are reported in subsequent meta-analyses evaluating the same associations.

## Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer

Aaron S. Kesselheim, Jessica A. Myers, Jerry Avorn

*JAMA* 2011;305:2320-2326

**Context.** The Orphan Drug Act incentivizes medication development for rare diseases, offering substantial financial benefits to the manufacturer. Orphan products constitute most new drug approvals in oncology, but safety and efficacy questions have emerged about some of these agents.

**Objectives.** To define characteristics of orphan cancer drugs and their pivotal clinical trials and to compare these with nonorphan drugs.

**Design and Setting.** We identified all new orphan and nonorphan drugs approved between 2004 and 2010 to treat cancer. We then collected data on key development variables from publicly available information on the US Food and Drug Administration's Web site and in the Code of Federal Regulations.

**Main Outcome Measures.** We assessed clinical testing dates, approved indications, and regulatory characteristics (regular vs accelerated review, advisory committee review, postmarketing commitments). We then compared design features (randomization, blinding, primary end point) of pivotal trials supporting approval of orphan and nonorphan drugs and rates of adverse safety outcomes (deaths not attributed to disease

progression, serious adverse events, dropouts) in pivotal trials.

**Results.** Fifteen orphan and 12 nonorphan drugs were approved between January 1, 2004, and December 31, 2010. Pivotal trials of orphan drugs had smaller participant numbers (median, 96 [interquartile range {IQR}, 66-152] vs 290 [IQR, 185-394] patients exposed to the drug;  $P < .001$ ) and were less likely to be randomized (30% vs 80%;  $P = .007$ ). Orphan and nonorphan pivotal trials varied in their blinding ( $P = .04$ ), with orphan trials less likely to be double-blind (4% vs 33%). Primary study outcomes also varied ( $P = .04$ ), with orphan trials more likely to assess disease response (68% vs 27%) rather than overall survival (8% vs 27%). More treated patients had serious adverse events in trials of orphan drugs vs trials of nonorphan drugs (48% vs 36%; odds ratio, 1.72; 95% confidence interval, 1.02-2.92;  $P = .04$ ).

**Conclusion.** Compared with pivotal trials used to approve nonorphan cancer drugs, pivotal trials for recently approved orphan drugs for cancer were more likely to be smaller and to use nonrandomized, unblinded trial designs and surrogate end points to assess efficacy.

## Television Viewing and Risk of Type 2 Diabetes, Cardiovascular Disease, and All-Cause Mortality

Anders Grøntved, Frank B. Hu

*JAMA* 2011;305:2448-2455

**Context.** Prolonged television (TV) viewing is the most prevalent and pervasive sedentary behavior in industrialized countries and has been associated with morbidity and mortality. However, a systematic and

quantitative assessment of published studies is not available.

**Objective.** To perform a meta-analysis of all prospective cohort studies to determine the

association between TV viewing and risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality.

**Data Sources and Study Selection.** Relevant studies were identified by searches of the MEDLINE database from 1970 to March 2011 and the EMBASE database from 1974 to March 2011 without restrictions and by reviewing reference lists from retrieved articles. Cohort studies that reported relative risk estimates with 95% confidence intervals (CIs) for the associations of interest were included.

**Data Extraction.** Data were extracted independently by each author and summary estimates of association were obtained using a random-effects model.

**Data Synthesis.** Of the 8 studies included, 4 reported results on type 2 diabetes (175 938 individuals; 6428 incident cases during 1.1 million person-years of follow-up), 4 reported on fatal or nonfatal cardiovascular disease (34 253 individuals; 1052 incident cases), and 3 reported on all-cause

mortality (26 509 individuals; 1879 deaths during 202 353 person-years of follow-up). The pooled relative risks per 2 hours of TV viewing per day were 1.20 (95% CI, 1.14-1.27) for type 2 diabetes, 1.15 (95% CI, 1.06-1.23) for fatal or nonfatal cardiovascular disease, and 1.13 (95% CI, 1.07-1.18) for all-cause mortality. While the associations between time spent viewing TV and risk of type 2 diabetes and cardiovascular disease were linear, the risk of all-cause mortality appeared to increase with TV viewing duration of greater than 3 hours per day. The estimated absolute risk differences per every 2 hours of TV viewing per day were 176 cases of type 2 diabetes per 100 000 individuals per year, 38 cases of fatal cardiovascular disease per 100 000 individuals per year, and 104 deaths for all-cause mortality per 100 000 individuals per year.

**Conclusion.** Prolonged TV viewing was associated with increased risk of type 2 diabetes, cardiovascular disease, and all-cause mortality.

## Effect of Bronchoalveolar Lavage-Directed Therapy on *Pseudomonas aeruginosa* Infection and Structural Lung Injury in Children With Cystic Fibrosis: A Randomized Trial

Claire E. Wainwright, Suzanna Vidmar, David S. Armstrong, Catherine A. Byrnes, John B. Carlin, Joyce Cheney, Peter J. Cooper, Keith Grimwood, Marj Moodie, Colin F. Robertson, Harm A. Tiddens, for the ACFBAL Study Investigators

*JAMA* 2011;306:163-171

**Context.** Early pulmonary infection in children with cystic fibrosis leads to increased morbidity and mortality. Despite wide use of oropharyngeal cultures to identify pulmonary infection, concerns remain over their diagnostic accuracy. While bronchoalveolar lavage (BAL) is an alternative diagnostic tool, evidence for its clinical benefit is lacking.

**Objective.** To determine if BAL-directed therapy for pulmonary exacerbations during the first 5 years of life provides better outcomes than current standard practice relying on clinical features and oropharyngeal cultures.

**Design, Setting, and Participants.** The Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) randomized controlled trial, recruiting infants diagnosed with cystic fibrosis through newborn screening programs in 8 Australasian cystic fibrosis centers. Recruitment occurred between June 1, 1999, and April 30, 2005, with the study ending on December 31, 2009.

**Interventions.** BAL-directed (n=84) or standard (n=86) therapy until age 5 years. The BAL-directed therapy group underwent BAL before age 6 months when well, when hospitalized for pulmonary exacerbations, if *Pseudomonas aeruginosa* was detected

in oropharyngeal specimens, and after *P aeruginosa* eradication therapy. Treatment was prescribed according to BAL or oropharyngeal culture results.

**Main Outcome Measures.** Primary outcomes at age 5 years were prevalence of *P aeruginosa* on BAL cultures and total cystic fibrosis computed tomography (CF-CT) score (as a percentage of the maximum score) on high-resolution chest CT scan.

**Results.** Of 267 infants diagnosed with cystic fibrosis following newborn screening, 170 were enrolled and randomized, and 157 completed the study. At age 5 years, 8 of 79 children (10%) in the BAL-directed therapy group and 9 of 76 (12%) in the standard therapy group had *P aeruginosa* in final BAL cultures (risk difference, -1.7% [95% confidence interval, -11.6% to 8.1 %];  $P=.73$ ). Mean total (CF-CT scores for the BAL-directed therapy and standard therapy groups were 3.0% and 2.8%, respectively (mean difference, 0.19% [95% confidence interval, -0.94% to 1.33%];  $P=.74$ ).

**Conclusion.** Among infants diagnosed with cystic fibrosis, BAL-directed therapy did not result in a lower prevalence of *P aeruginosa* infection or lower total CF-CT score when compared with standard therapy at age 5 years.

## Authors' Index-2011 [Vol. 53, Nos. 1-4]

- Agarwal N and Agarwal Ritu. Fractured tracheostomy tube migrating into the tracheo-bronchial tree: a rare complication ..111
- Agarwal R. Allergic bronchopulmonary aspergillosis: lessons learnt from genetics ..137
- Agarwal R. *See under* Mootha, VK (21); Gupta, D (41)
- Agarwal R, Khan A, Aggarwal AN, Singh N, Bhagat H, Kumar B, Yaddanapudi LN, Sethi S, Khandelwal N and Gupta D. Initial experience of endobronchial silicon stents from a tertiary care centre in north India ..93
- Agarwal Ritu. *See under* Agarwal, N (111)
- Agarwal VV. *See under* Rao, RS (81)
- Aggarwal AN. *See under* Mootha, VK (21); Gupta, D (41); Agarwal, R (93)
- Anand Mani, Deshmukh SD, Naik A and Gaopande Vandana. Congenital cystic adenomatoid malformation in an adolescent: an unusual presentation with pleural effusion and pneumatocele ..173
- Bali Roseleen Kaur. *See under* Gupta, Shweta (117)
- Bardhan S. *See under* Bhattacharyya, P (51)
- Behera D and Sharma PP. A retrospective study of seasonal variation in the number of cases diagnosed at a tertiary care tuberculosis hospital ..145
- Bhagat H. *See under* Agarwal, R (93)
- Bhanja P. *See under* Chaudhuri, AD (181)
- Bhattacharyya P, Bardhan S, Nag S, Mukherjee S and Verma A. Transthoracic decompression of emphysematous bulla: a novel experience ..51
- Bhattacharyya P. *See under* Mukherjee, A (241)
- Bhuniya S. *See under* Chaudhuri, AD (181)
- Chandra N. *See under* Subbalaxmi, Malladi VS (185)
- Chaudhuri AD, Bhuniya S, Pandit Sudipta, Mukherjee S, Bhanja P, Karmakar Rupam, Dhua Aparup and Saha Mita (Dutta Choudhury). A rare case of concurrent multiple primary lung cancer of different histological types ..181
- Chaturvedi RK and Zidulka A. Continuous positive airway pressure *versus* continuous negative pressure around the chest for patients with acute exacerbation of chronic obstructive pulmonary disease in the intensive care unit: a pilot study ..141
- Dagaonkar Rucha S. *See under* Udwardia, ZF (79)
- Das K. *See under* Gupta, Shweta (117)
- De Sajal. Prevalence of depression in stable chronic obstructive pulmonary disease ..35  
— Assessment of severity of methaemoglobinemia following fiberoptic bronchoscopy with lidocaine ..211
- Deshmukh SD. *See under* Anand, Mani (173)
- Dewan RK. *See under* Gupta, Shweta (117)
- Dhua Aparup. *See under* Chaudhuri, AD (181)
- Dutt N. *See under* Mohapatra, PR (55)
- Dutt TS and Udwardia ZF. Prevalence of venous thromboembolism in acute exacerbations of chronic obstructive pulmonary disease: an Indian perspective ..207
- Epstein Marcia. *See under* Kumar, Toshita (99)
- Fuladi AB. *See under* Ganju, AA (87)
- Ganju AA, Fuladi AB, Tayade BO and Ganju NA. Cardiopulmonary exercise testing in evaluation of patients of chronic obstructive pulmonary disease ..87
- Ganju NA. *See under* Ganju, AA (87)
- Gaopande Vandana. *See under* Anand, Mani (173)
- Gaur SN. Allergen immunotherapy: the scientific facts ..205
- Ghosal AG. *See under* Mitra, Subhra (107)
- Gopal K. *See under* Kumar, R (215)
- Gopikrishna G, Reddy MS, Gowrinath K, Sasidhar P and Srinivas M. Fatal re-expansion pulmonary oedema in a mechanically ventilated patient ..177
- Gothi D and Joshi JM. Pulmonary rehabilitation in resource poor settings ..163
- Goyal V. *See under* Gupta, KB (113)
- Gowrinath K. *See under* Gopikrishna, G (177)
- Guleria S. *See under* Gupta, P (225)
- Gupta D. *See under* Mootha, VK (21); Agarwal, R (93)
- Gupta D, Aggarwal AN, Agarwal R and Verma Indu. Immune responses to mycobacterial antigens in sarcoidosis: a systematic review ..41
- Gupta KB, Kumar V, Goyal V, Gupta PP, Indu Kumari and Rana P. Chest wall metastasis of squamous cell carcinoma of larynx ..113
- Gupta P, Guleria S and Sharma S. Mediastinal haematoma: a rare complication following insertion of central venous catheter ..225
- Gupta PP. *See under* Gupta, KB (113)
- Gupta Shweta, Bali Roseleen Kaur, Das K, Sisodia Anula, Dewan RK and Singla R. Rare

- presentation of spontaneous acquired diaphragmatic hernia ..117
- Hirota J. *See under* Khalil, Diana (59)
- Indu Kumari. *See under* Gupta, KB (113)
- Janmeja AK. *See under* Mohapatra, PR (55)
- Jindal SK. *See under* Mootha, VK (21)
- Joshi JM. *See under* Gothi, D (163); Shah, Mehul (221)
- Karandikar Manjiri and Swami RM. Type A thymoma with generalised *Myasthenia gravis* ..233
- Karmakar Rupam. *See under* Chaudhuri, AD (181)
- Kesarwani V. *See under* Rawat, J (237)
- Khalil Diana, Hirota J and Nair P. Cholinergics, airway eosinophils and asthma exacerbation in the elderly ..59
- Khan A. *See under* Agarwal, R (93)
- Khandelwal N. *See under* Agarwal, R (93)
- Khanduri S. *See under* Mohapatra, PR (55)
- Kumar B. *See under* Agarwal, R (93)
- Kumar R, Mahakud GC, Nagar JK, Singh SP, Raj N, Gopal K and Vijayan VK. Breath carbon monoxide level of non-smokers exposed to environmental tobacco smoke ..215
- Kumar Toshita, Epstein Marcia, Markovskaya Yelena, Narasimhan Mangla, Rosen M and Talwar A. Bronchoscopy and endobronchial disease in patients with human immunodeficiency virus infection ...99
- Kumar V. *See under* Gupta, KB (113)
- Kundu S. *See under* Mitra, Subhra (107)
- Maclean J, Singh RB and Sayeed ZA. Poly-myositis presenting with respiratory failure ..229
- Madegedara D. *See under* Nishantha, KMC (189)
- Mahakud GC. *See under* Kumar, R (215)
- Markovskaya Yelena. *See under* Kumar, Toshita (99)
- Mitra Subhra, Kundu S, Pattari SK and Ghosal AG. Metastatic pleural effusion: a rare presentation of salivary gland adenoid cystic carcinoma ..107
- Mohapatra PR, Khanduri S, Dutt N, Sharma Preeti and Janmeja AK. Diagnostic dilemma of anti-neutrophil cytoplasmic antibody seropositivity in human immunodeficiency virus infection ..55
- Mittal V. *See under* Singh, S (25)
- Mootha VK, Agarwal A, Singh N, Aggarwal AN, Gupta D and Jindal SK. Medical thoracoscopy for undiagnosed pleural effusion: experience from a tertiary care hospital in North India ..21
- Mukherjee A, Singla R, Saha I, Sarkar A and Bhattacharyya P. Difference in the outcome of patients with different grades of initial sputum positivity under the revised national tuberculosis control programme ..241
- Mukherjee S. *See under* Bhattacharyya, P (51); Chaudhuri, AD (181)
- Nag S. *See under* Bhattacharyya, P (51)
- Nagar JK. *See under* Kumar, R (215)
- Naik A. *See under* Anand, Mani (173)
- Nair P. *See under* Khalil, Diana (59)
- Narasimhan S. *See under* Kumar, Toshita (99)
- Nishantha KMC and Madegedara D. *Myasthenia gravis*: a rare cause of orthopnoea due to bilateral diaphragmatic paralysis ..189
- Pandit Sudipta. *See under* Chaudhuri, AD (181)
- Patial K. *See under* Singh, TD (11); Sadasivam, K (153)
- Pattari SK. *See under* Mitra, Subhra (107)
- Pinto LM. *See under* Udwardia, ZF (9)
- Purwar B. *See under* Saxena, Y (29)
- Raghuvanshi S. *See under* Rawat, J (237)
- Raj N. *See under* Kumar, R (215)
- Raju YS. *See under* Subbalaxmi, Malladi VS (185)
- Rana P. *See under* Gupta, KB (113)
- Rao MN. *See under* Subbalaxmi, Malladi VS (185)
- Rao RS, Singh S, Sharma BB, Agarwal VV and Singh V. Sildenafil improves six-minute walk distance in chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial ..81
- Ravi K. *See under* Singh, TD (11); Sadasivam, K (153)
- Rawat J, Saini S, Raghuvanshi S, Sindhvani G and Kesarwani V. Intrapulmonary teratoma presenting with tricoptysis: a case report and review of the literature ..237
- Reddy MD. *See under* Gopikrishna, G (177)
- Rosen M. *See under* Kumar, Toshita (99)
- Sadasivam K, Patial K, Vijayan VK and Ravi K. Anti-oxidant treatment in obstructive sleep apnoea syndrome ..153
- Saha Mita (Dutta Chowdhury). *See under* Chaudhuri, AD (181)
- Saha I. *See under* Mukherjee, A (241)
- Saini A. *See under* Singh, S (25)
- Saini S. *See under* Rawat, J (237)
- Sarkar A. *See under* Mukherjee, A (241)
- Sasidhar P. *See under* Gopikrishna, G (177)
- Saxena Y, Purwar B and Upmanyu Rashi. Adiposity: determinant of peak expiratory flow rate in young Indian adults male ..29

- Sayeed ZA. *See under* Maclean, J (229)
- Sethi S. *See under* Agarwal, R (93)
- Shah Ashok. Nosing around in chronic obstructive pulmonary disease ..5
- Shah Mehul and Joshi JM. Bone scintigraphy in pulmonary alveolar microlithiasis ..221
- Sharma BB. *See under* Rao, RS (81)
- Sharma PP. *See under* Behera, D (145)
- Sharma Preeti. *See under* Mohapatra, PR (55)
- Sharma S. *See under* Gupta, P (225)
- Sindhwani G. *See under* Rawat, J (237)
- Singh N. *See under* Mootha, VK (21); Agarwal, R (93)
- Singh RB. *See under* Maclean, J (229)
- Singh S. *See under* Rao, RS (81)
- Singh S, Soumya M, Saini A, Mittal V, Singh UV and Singh V. Breath carbon monoxide levels in different forms of smoking ..25
- Singh SP. *See under* Kumar, R (215)
- Singh TD, Patial K, Vijayan VK and Ravi K. Role of nitric oxide in the diuresis and natriuresis occurring in patients with obstructive sleep apnoea syndrome ..11
- Singh UV. *See under* Singh, S (25)
- Singh V. *See under* Singh, S (25); Rao, RS (81)
- Singla R. *See under* Gupta, Shweta (117); Mukherjee, A (241)
- Sisodia Anula. *See under* Gupta, Shweta (117)
- Soumya M. *See under* Singh, S (25)
- Srinivas M. *See under* Gopikrishna, G (177)
- Subbalaxmi Malladi VS, Chandra N, Rao MN, Vemu Lakshmi and Raju YS. *Burkholderia pseudomallei*: an uncommon cause of bacteraemic pneumonia in a diabetic ..185
- Swami RM. *See under* Karandikar, Manjiri (233)
- Talwar A. *See under* Kumar, Toshita (99)
- Tayade BO. *See under* Ganju, AA (87)
- Udwadia ZF and Pinto LM. Why "STOP TB" is incomplete without "QUIT SMOKING" ..9
- Udwadia ZF and Dagaonkar Rucha S. Statins and the lung: hope or hype? ..79
- Udwadi ZF. *See under* Dutt, TS (207)
- Upmanyu Rashi. *See under* Saxena, Y (29)
- Vemu Lakshmi. *See under* Subbalaxmi, Malladi VS (185)
- Verma A. *See under* Bhattacharyya, P (51)
- Verma Indu. *See under* Gupta, D (41)
- Vijayan VK. *See under* Singh, TD (11); Sadasivam, K (153); Kumar, R (215)
- Yaddanapudi LN. *See under* Agarwal, R (93)
- Zidulka A. *See under* Chaturvedi, RK (141)

## Guidelines to Authors

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

**Submission of Manuscripts.** Manuscripts should be submitted in a CD in MS word (in addition to hard copies). Typescript including figures (in triplicate) should be sent to *The Editor-in-Chief, The Indian Journal of Chest Diseases and Allied Sciences, C/o Publication Division, V.P. Chest Institute, University of Delhi, Delhi-110007, Post Box No. 2101.*

Articles can also be submitted on our e-mail at: [ijcdas@yahoo.co.in](mailto:ijcdas@yahoo.co.in)

Manuscripts should be submitted with the undertaking that they are not under consideration elsewhere and have not been reported earlier partly/ totally. Submission of a manuscript indicates tacit acknowledgement that all authors have made significant contributions to the study and have read and approved the contents. Any change in authorship following the original submission must be justified and agreed to in writing by the affected author(s). Manuscripts are acknowledged upon receipt.

*When inquiring about a manuscript, please refer to the article accession number assigned to the manuscript by the Publication Office of the IJCDAS.*

Manuscripts are evaluated critically by the Editorial Board with the help of Experts. Acceptance of manuscripts for publication is based on: (a) originality of contribution; (b) proper analysis of scientific data; (c) clarity of presentation; and (d) ethically acceptable design of the study. **All accepted manuscripts are subject to manuscript editing.** Only one copy of rejected manuscripts will be returned.

### Preparation of Manuscript

Presentation of manuscripts should conform with the uniform requirements for manuscripts submitted to biomedical journals.

Authors are advised to see a recent issue of the Journal to get familiar with the format adopted on various elements of a paper. All the manuscripts should be submitted in the order set forth below. **Failure to follow these instructions may result in the manuscript being**

**returned to the author(s) for revision before it will be reviewed.**

**General.** Manuscripts must be typewritten, double-spaced with wide margin on A-4 size good quality bond paper. Each of these segments of the manuscript should begin on a new page: title page; abstract; introduction; references; legends; tables.

I. *Title Page.* This should be as concise and as informative as possible. List (i) title; (ii) the initials followed by the last name of each author; (iii) the name of the department(s) and institution(s) to which the work should be attributed; (iv) the name and address (**including e-mail**) of the author to whom queries, proofs and requests for reprints should be sent; and (v) a short running title (not exceeding 5-6 words).

II. *Abstract and Key Words.* The second page should carry a structured abstract of not more than 200 words with subheadings of Background and objectives, Methods, Results and Conclusions (unstructured abstract for case reports). It should be written for the readership of both clinicians and basic investigators and should state the hypothesis or central question of the study or investigation, the study subjects or experimental animals, observational and analytical methods, the main findings, and a final statement of the principal conclusions. **Three to six key words using, where possible terms of medical subjects headings list from Index Medicus.**

III. *Introduction.* It should commence on separate page and should briefly review the current state of knowledge strictly concerning the topic of the paper. It should also make a clear statement on the reasons for undertaking the study being reported and what it hoped to achieve. No mention should be made of the results obtained or conclusions drawn.

IV. *Material and Methods.* The material (patients, experimental animals, etc.) used for making observations must be described along with all other relevant information. The methods used in the study should be described, giving sufficient information to permit the work to be repeated. If a generally accepted technique has been used, only a reference to that is enough. If, however, such a technique has been modified by the workers, the manner in which this has been done should be clearly stated. **If statistical analysis of the data has been done, the methods used for analysis should be specified.**

V. *Results.* This section should not include materials suitable for inclusion in "Material and Methods" or "Discussion". The results should be presented in

logical sequence in the text, tables and illustrations. The data presented in the tables or figures should not be repeated in the text. Only important and significant observations should be included.

VI. *Discussion*. This should be limited to significance of results obtained and what can and what cannot be concluded and why. It should not be a repetition of the findings already given under 'Results'. Results should be discussed in the light of others' work in the field. Speculative and purely theoretical discussion to which results presented are not related will not be accepted.

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

VIII. *References*. References should be typed on a separate page after the text and these should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used in *Index Medicus*. Consult the *List of Journals Indexed in Index Medicus*, published annually as a separate publication by the library and as a list in the January issue of *Index Medicus*. The list can also be obtained through the library's web site (<http://www.nlm.nih.gov>). Unpublished work should not be cited in references, but may be cited fully parenthetically within the text. List all the authors when there are six or fewer; but when there are seven or more, list the first six, then 'et al'. Examples of correct form of references are given here :

### Articles in Journals

#### 1. Standard journal article

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

More than six authors:

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

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

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

#### 3. Volume with supplement

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

#### 4. Issue with supplement

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

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

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

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

#### 6. Volume with part

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

#### 7. Issue with part

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

#### 8. Issue with no volume

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

#### 9. No volume or issue

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

#### 10. Pagination in roman numerals

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

#### 11. Organization as author

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

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

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

13. *No author given*

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

14. *Article containing retraction*

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

15. *Article retracted*

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

16. *Article republished with corrections*

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

17. *Article with published erratum*

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

18. *Article not in English*

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

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

**Personal Communication**

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

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

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

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

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

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

21. *Conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. *Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming*; 2002 Apr 3-5; Kinsdale Ireland. Berlin: Springer. 2002; pp 182-91.

22. *Personal author(s)*

Murray PR, Rosenthal KS, Kobayashi GS, 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. Wiecek 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 Na-

tional 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/category/1736.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.

*Correctness of the reference list is the entire responsibility of the author (s).*

#### Figures and Tables

*Figures. Glossy print photographs (in triplicate) are required (usually 10 cm × 8 cm); good black and white contrast is essential for good reproduction.* All illustrations must be numbered and cited in the text. Legends should be provided for each illustration, listed on a separate page. All lettering must be done professionally. Freehand or typed lettering is not acceptable. All figures should bear author's name, short title and an arrow indicating top of the figure in pencil on the back of the photographs.

*Colour illustrations must be paid by the authors. Please ask rates/charges from the Publication Office of the IJCDAS.*

*Tables.* Each table should be typed double-spaced on a separate sheet. They should have an underlined title followed by a legend, if any. Explanatory matter should be in a footnote, not in the title. The approximate position of each table in the text should be indicated in the margin of the manuscript.

*Page Proofs and Reprints.* A galley proof will be sent to the corresponding author which should be returned within four days. Corrections should be limited to printers errors only and no substantial additions/deletions should be made. No change in the names of authors (by way of additions and/or deletions) is permissible at the proof stage. *Twenty-five reprints of the article will be sent free of cost to the corresponding author.*

*Papers which have been accepted/published become the property of the Indian Journal of Chest Diseases and Allied Sciences and permission to re-publish them must be obtained from the Editor.*

#### CHECKLIST FOR SUBMISSION OF MANUSCRIPT

- Covering letter including copy-right release
- Three copies of typescript of the article on A-4 size paper
- Name and address of author responsible for correspondence about the manuscript, including highest degree and affiliations of each author.
- Abstract (upto 150 words) along with 3-6 key words
- Running title (5-6 words)
- Three glossy prints for each illustration (10 cm × 8 cm), appropriately labelled and each illustration is cited in the text. Submit the legends on a separate sheet in the manuscript.
- Check all references for accuracy and completeness. Put references in proper format in numerical order, making sure each is cited in the text.

## The Indian Journal of Chest Diseases and Allied Sciences

*Publication Division  
V.P. Chest Institute  
University of Delhi  
Delhi - 110 007*

### UNDER TAKING BY AUTHORS

We, the undersigned, give an undertaking to the following effect with regard to our article entitled

---



---



---

submitted for publication in the *Indian Journal of Chest Diseases and Allied Sciences*:

1. The article mentioned above has not been published or submitted to or accepted for publication in any form, in any other journal;
2. We also vouchsafe that the authorship of this article will not be contested by anyone whose name(s) is/are not listed by use here; and
3. We also agree to the authorship of the article in following sequence:

Author's Name(s) (in sequence)	Signature of Author(s)
1. _____	_____
2. _____	_____
3. _____	_____
4. _____	_____
5. _____	_____
6. _____	_____
7. _____	_____
8. _____	_____

### IMPORTANT

1. All the authors are required to sign this form independently in the sequence given above.
2. Each author should have generated at least a part of the intellectual content of the paper.
3. Each author should be able to defend publicly in the scientific community, that intellectual content of the paper for which he/she can take responsibility.
4. No addition/deletion/or any change in the sequence of the authorship will be permissible at a later stage.

## THE INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES

Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110 007

- Editor-in-Chief & Publisher : **Prof. S.N. Gaur**  
Place of Publication : Delhi, India  
Web Address : <http://www.vpci.org.in>  
ISSN No. : 0377-9343  
Language : English  
Periodicity : Quarterly (Published in the months of January, April, July and October)  
Method of Printing : Offset Process  
Overall Size : 27.5 cm x 20.5 cm  
**Print Area** : **24.0 cm x 17.0 cm** (Advertisement materials required in Print Area size only)
- Spectrum of Readership : The readership comprises faculty members of medical colleges/research institutions, chest physicians, cardiologists, medical practitioners, postgraduate students, research scholars, biomedical scientists and libraries of medical colleges/hospitals; including 800 fellows/members of the National College of Chest Physicians (India)
- Countries where it is Circulated : India, USA, Canada, South American countries, USSR, UK, The Netherlands, Germany, Italy, African countries, Middle East, Japan, China, Australia and New Zealand
- International Standing : Abstracted and indexed in the globally reputed abstracting periodicals such as Index Medicus, Medline, IndMed, INSEAR, and Ulrich's Directory, etc

### ADVERTISEMENT RATES\*(w.e.f. 1<sup>st</sup> January 2011)

	<i>Per Issue</i>	<i>Per Volume (4 issues)</i>
Ordinary Full Page	₹ 8,000.00	₹ 25,000.00
Back Cover	₹ 15,000.00	₹ 55,000.00
Inside Cover	₹ 12,000.00	₹ 45,000.00
Facing Contents	₹ 15,000.00	₹ 55,000.00
<b>Colour Ads</b>	<b>50% extra on above rates</b>	

- \*Note:**
1. *The above rates are not subject to any Tax Deduction at Source.*
  2. *Advertisement materials (four positives in case of colour ads) are to be provided by the advertiser in a CD with a print out (hard copy) of the advertisement.*
  3. *A discount of 10% will be offered to Advertising Agencies only.*
  4. *Advertisement Payments (along with the space order and advertisement material) should be made in **advance** through **Banker's Cheque / Bank Drafts** only and should be drawn in favour of the **DIRECTOR, V. P. CHEST INSTITUTE, DELHI.***