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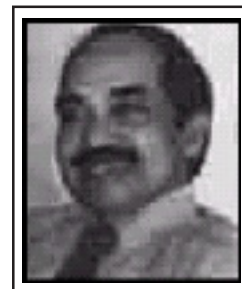
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## PRESIDENT WRITES

Dear Fellows and Members,

This part of the calendar year holds the door for many a young individual's career. The frantic scramble for application, facing entrance tests, interviews, awaiting with baited breath for admission cards and so forth occupies the waking hours for a sizable section of our youth. While entrance tests are getting computerised and objective with nuances of knowledge and intelligence being probed, aptitude is not often tested. This is a gap that must be covered. For a profession like ours, aptitude to the chosen field is very essential to sustain the young mind through the long gestation period of becoming competent in a very demanding call of service and knowledge. We must promote the cause of assessing aptitude also in the entrance test to the Medical Colleges.



The planners, Medical educationists and the Medical Council have a role in addressing this specific problem.

Dr. K. Jagadeesan,  
*President, IMSA*



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All fellows and members of IMSA can have **access** to the site and get information about its objectives, benefits to the fellows/members, chapters and their activities including seminars, refresher courses, rural CME's etc. and also IMSACON - a regular annual event of international standard; *application form for enrollment as fellow/member can also be downloaded.* Fellows - members and even non fellows - members can have access to full text in the quarterly journal - JIMSA from July-Sept. 2003 onwards by putting their E-mail address under '**user name**' and using the **password** '**UserJimsa**'.

Adv. Wockhart



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Dear Colleagues

Multi-disciplinary approach - a unique feature of JIMSA, has been adopted so that our readers cannot only educate themselves but also contribute to better understanding of the mechanism of disease. In today's world, one has to be very conscious of the new developments especially in terms of molecular biology, cell wall receptors, cell signalling processes, expression of genes etc. Our endeavour should be to get the latest information through newer modalities of communication like looking at the web spaces on the internet etc. JIMSA has been on website 'www.jimsaonline.com' for almost two years; our young and enthusiastic fellows and members should be visiting the website so as to look at the latest advances and pass on the information to other colleagues and readers of JIMSA by contributing original articles, up-dates etc.

In this issue of JIMSA, diagnostic approach to thyroid nodule has been brilliantly discussed by Prof. S.K. Agarwal; I am really grateful to him for his valuable contribution. Distinction between benign and malignant nodule has been made possible by a simple least invasive test - FNA as highlighted by Vikas Sinha & colleagues in their original paper. The authors of original articles, case reports published in the issue, have put in their best; the topics covered are of immense clinical importance; update contributed by Prof. J.K. Grover on 'erectile dysfunction' presents an overview of diagnosis and therapeutic profile of this common clinical entity amongst the male population. Other update by Dr. Medhi focuses on several emerging health problems included under 'Bio Terrorism'; the review provides useful information with regard to their diagnostic evaluation, treatment and control - strategies crucial for limiting the morbidity caused by these biological events. The therapy update on 'drug-induced hepatic injury' is an exhaustive and well written review by Prof. Kamlesh Kohli. I am grateful to all the authors who have made such valuable contribution to JIMSA.

The present issue contains a symposium 'MDRT - Problems & Challenges' under the guest editorship of Prof. DDS Kulpati - a senior consultant in chest medicine; subjects are well selected and contributed by experts in the field. I am confident the symposium will be of immense interest to the readers. I am extremely grateful to Prof. Kulpati and other contributors.

I take this opportunity to thank all the members of editorial/advisory boards for their suggestions, and help in the compilation of this issue. I would also like to thank all the advertisers without whose financial help, this publication would not have been possible.

P.D. Gulati

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Adv. pfizer

# Solitary Thyroid Nodule - A Diagnostic Challenge

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**Abstract:** Most common presentation of thyroid nodule is a lump felt on self examination. They are more common in females; 90% of them are benign in nature, adenoma being the commonest amongst the benign causes. Combined use of fine needle aspiration cytology (FNAC), thyroid scan and ultrasonography (USG) can detect them with 90% accuracy. An effort has been done here to present a diagnostic approach to a solitary thyroid nodule to evaluate the utility of different investigations in achieving the correct diagnosis.

## Introduction

Thyroid nodules are lumps which commonly arise within an otherwise normal thyroid gland. Often these abnormal growths are located at the edge of the thyroid gland, so they can be felt as a lump in the throat. When they are large or are present in thin individuals they can be seen as a lump in the front of the neck. The prevalence of thyroid nodules within a given population depends on a variety of factors that include age, sex, diet, iodine deficiency, and therapeutic and environmental radiation exposure. True solitary nodules occur in 4-7% of the adult population. They are more common in females, and this predisposition exists throughout all age groups. Prevalence increases with age, with spontaneous nodules occurring at a rate of 0.08% per year beginning early in life and extending into the eighth decade. Thyroid nodules are found in 5% of persons at an average age of 60 years.

Most thyroid nodules are benign hyperplastic lesions, but 5-20% of thyroid nodules are true neoplasms. Solitary nodule first seen can be due to asymmetric enlargement of one lobe as in unilateral agenesis, chronic lymphocytic thyroiditis (i.e., Hashimoto thyroiditis), or in simple goiter. In addition, developmental errors, such as ectopic tissue, may cloud the picture. Suspected thyroid nodules merit close attention especially in childhood as the presence of malignancy in such nodules is much more likely than in an adult. This frequency of malignancy is estimated to be 15-25%. In addition, thyroid cancer is much more aggressive in children and is associated with early metastasis to regional lymph nodes and parenchymal organs, most commonly lung and bone.

Major goal in the evaluation of the solitary thyroid nodule is the differentiation of hyperplasia from true neoplasms. Furthermore, the histologic criteria used to distinguish benign from malignant neoplasms can be subtle. Therefore evaluation of solitary thyroid nodules requires the collaboration of the primary care physician, endocrinologist, pathologist, radiologist, and head and neck surgeon to provide comprehensive and appropriate management of this clinical entity. Solitary thyroid nodule may represent a multitude of thyroid disorders, and a thorough knowledge of the epidemiology of thyroid disease is of paramount importance. Comprehensive history and physical examination provides the foundation for decision making in management of thyroid nodules. Currently, a variety of serologic and cytogenetic tests, diagnostic imaging studies, and histopathologic techniques exist for the evaluation of a thyroid nodule. Of these methods, fine-needle aspiration biopsy (FNAB) has become the most important tool in

the assessment of solitary thyroid nodules.

## Causes

The differential diagnosis of solitary thyroid nodule can be broadly classified into benign and malignant. Generally, most thyroid nodules are **benign** and can be classified as Adenomas, colloid nodules, congenital abnormalities, cysts, infectious nodules, lymphocytic or granulomatous nodules, hyperplastic nodules, thyroiditis (Hashimoto and subacute), Radiation to head and neck.

**Malignant** thyroid nodules can be classified as :

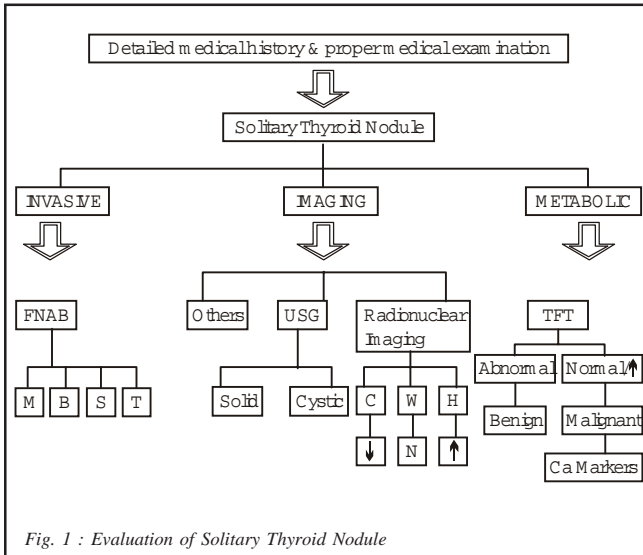
- (a) *Differentiated*:
  - (1) Papillary adenocarcinoma, (a) Pure papillary adenocarcinoma,
  - (b) Mixed papillary and follicular carcinoma (variants including tall cell, follicular, oxyphil, solid)
  - (2) Follicular adenocarcinomas (variants: "malignant adenoma", Hurthle cell carcinoma or oxyphil carcinoma, clear-cell carcinoma, insular carcinoma)
  - (b) *Medullary carcinoma* - (not a tumor of follicular cells)
  - (c) *Undifferentiated* : (1) Small cell (to be differentiated from lymphoma), (2) Giant Cell, (3) Carcinosarcoma.
  - (d) *Miscellaneous* : (1) Lymphoma, sarcoma, (2) Squamous cell epidermoid carcinoma, (3) Fibrosarcoma, (4) Mucoepithelial carcinoma, (5) Metastatic tumor.

## Evaluation of Solitary Thyroid Nodule

The evaluation is done by history, examination, metabolic profile, imaging, invasive procedures. Evaluation should be done keeping three question in mind: (1) **Is the nodule cancerous?** (2) **Is the nodule causing symptoms due to pressure on the adjoining structures of the neck?** (3) **Is the nodule making too much of thyroid hormone?**

How to perform the initial evaluation of a solitary nodule is depicted as flow chart Fig. 1.

**History and examination :** Through initial clinical evaluation of the patient with solitary thyroid nodule includes history of the thyroid mass, past medical history, family and social history, a careful review of systems, and a complete head and neck examination. Symptoms such as neck pain, stridor, dysphonia, and dysphagia increase clinical suspicion of a thyroid malignancy; however, none is diagnostic. Prior history of radiation exposure should be ascertained in all patients presenting with solitary thyroid nodule. Past medical history of family history of pheochromocytoma, hyperparathyroidism, chronic constipation and diarrhea, hypertension, and episodes of nervousness or excitability should alert the clinician of the possibility of familial MEN 2a or



2b syndrome.

A number of features in the history and physical examination significantly influence the statistical probability of malignancy in a thyroid nodule. Factors favoring malignant diagnosis include the following : (a) Age younger than 20 years or older than 70 years; (b) Male sex; (c) Associated symptoms of dysphagia or dysphonia; (d) History of neck irradiation; (e) Prior history of thyroid carcinoma; (f) Firm, hard, or immobile nodule; (g) Presence of cervical lymphadenopathy.

**Factors** favoring benign diagnosis include the following :

- 1 Family history of autoimmune disease (eg, Hashimoto's thyroiditis)
- 1 Family history of benign thyroid nodule or goiter.
- 1 Presence of thyroid hormonal dysfunction (eg, hypothyroidism, hyperthyroidism)
- 1 Pain or tenderness associated with nodule
- 1 Soft, smooth, and mobile nodule
- 1 Multinodular goiter without a dominant nodule

**Physical characteristics** of a thyroid nodule are poor predictors of malignancy. Both malignant and benign solitary thyroid nodules can be soft or firm, smooth or irregular on examination. However, increased size of a thyroid nodule correlates with increased risk of malignancy. Moreover, size is used in tumor staging and is highly predictive of outcome. Fixation to or invasion of surrounding structures and the presence of palpable lymph nodes in the neck are also highly suggestive of malignancy. Vocal cord paralysis is not a reliable indicator of malignancy because it can also occur in benign disorders.

**Metabolic Profile and Other Markers** : Thyroid function tests should be obtained as part of the initial evaluation of solitary thyroid nodule, and findings are usually normal in patients with thyroid cancer. Metabolic evidence of hyperthyroidism is more commonly associated with benign disorders such as an autonomously functioning adenoma or Hashimoto thyroiditis. A strong association exists between Hashimoto thyroiditis and primary thyroid lymphoma. Measurement of serum thyroglobulin levels is not recommended in the evaluation of solitary thyroid nodule because it is also elevated in benign thyroid disorders. Serum

calcitonin and carcinoembryonic antigen (CEA) levels are usually elevated in patients with medullary thyroid carcinoma. However, serum CEA level has low specificity in the initial diagnosis of medullary thyroid carcinoma.

Recently, DNA testing has proven to be an effective method for the diagnosis of MEN 2a and 2b syndromes. *ret* proto-oncogene in the paracentromeric region of the short arm of chromosome 10 is the site of mutation in 90% patients with familial medullary thyroid carcinoma and medullary thyroid carcinoma associated with MEN 2a and 2b. Patients with medullary thyroid carcinoma should undergo direct DNA analysis to identify possible germline mutations in the *ret* proto-oncogene. All family members should undergo similar testing if a *ret* mutation is identified. Family members with the *ret* mutation should undergo genetic counseling and be informed about prophylactic thyroidectomy.

## Imaging

**Ultrasonography** : Ultrasonography is a safe and effective method of determining the size and the presence of solid or cystic components within a thyroid nodule. High-resolution ultrasonography can be used to determine the presence of nonpalpable nodules as small as 1mm within the thyroid tissue. Unfortunately, malignant thyroid nodules cannot be differentiated from benign thyroid nodules by this technique. Its main indications are accurate measurement of size and as a guide for FNAB.

**Radionuclide imaging** : The fact that malignant thyroid tissue concentrates less radioactive iodine than normal thyroid tissue is being utilized in this technique. Thyroid nodules are further classified into cold, warm, and hot according to their ability to accumulate the radioactive isotope. Cold nodules are considered hypofunctional, whereas warm nodules are normal and hot nodules are hyperfunctional. Iodine I 123 and technetium Tc 99m are the most commonly used radionuclides for thyroid imaging. The major limitation of thyroid radionuclide scanning has been its inability to distinguish between benign and malignant thyroid nodules with high accuracy. Other limitations of radionuclide scanning include an inability to delineate thyroid gland and misinterpretation of the functional status of the thyroid nodule if normal functioning thyroid tissue overlies the cold solitary thyroid nodule or if the thyroid gland is asymmetric. Therefore, radionuclide scanning is not the most accurate technique to distinguish benign from malignant thyroid disorders.

**Other imaging techniques** : Computed tomography scanning and magnetic resonance imaging have a limited role in the initial evaluation of solitary thyroid nodule. Indications for these imaging techniques include suspected tracheal involvement, either by invasion or compression, extension into the mediastinum, or recurrent disease. Use of intravenous iodinated contrast agent in computed tomography scanning makes thyroid scanning impossible because of the iodine load.

**Invasive Procedures** : FNAB has become the diagnostic tool of choice for the initial evaluation of solitary thyroid nodule because of its accuracy, safety, and cost effectiveness. Although needle biopsy can be performed easily, but consistently obtaining adequate tissue and processing the specimens to achieve accurate cytopathological interpretation requires expertise and experience. A satisfactory specimen should contain at least 5 or 6 groups of 10-15 well-preserved cells. FNAB specimens are classified as

malignant, benign, indeterminate (suspicious for follicular or Hurthle cell neoplasm), or insufficient for diagnosis. Overall sensitivity, specificity, and accuracy of the FNAB technique has been reported to be 83%, 92%, and 95%, respectively.

Accuracy of FNAB is closely related to the histologic type of thyroid carcinoma that is being evaluated. Diagnosis is correct for papillary thyroid carcinoma in approximately 90-100% of FNAB specimens when correlated with the histology of the final surgical specimen. Undifferentiated (anaplastic) carcinoma, medullary thyroid carcinoma, and primary thyroid lymphoma also have characteristic cytologic features, which aid correct diagnosis in approximately 90% of FNAB specimens.

The main limitation of FNAB is the differentiation of benign from malignant follicular neoplasms. FNAB specimens of follicular neoplasms and Hurthle cells are commonly interpreted as indeterminate or suspicious. This has resulted in low FNAB accuracy rates of approximately 40% for follicular carcinomas. diagnosis of follicular carcinoma also requires the identification of capsular and/or vascular invasion, which is not a possibility with FNAB techniques. Therefore, several techniques in addition to FNAB has been developed to increase the accuracy of FNAB for follicular carcinomas, including immunocytochemistry techniques, large needle biopsy, and intraoperative frozen section analysis.

Thyroid peroxidase (TPO) immunocytochemistry with a monoclonal antibody termed MoAb 47 has been reported to significantly increase the accuracy of FNAB in patients with follicular lesions. Large needle biopsy can also increase the diagnostic accuracy of FNAB, but it also increases the risk of hematoma, tracheal injury, laryngeal nerve injury or injury to other neck structures, and cutaneous implantation of malignant cells.

## Management

Management consists of observation, levothyroxine suppression therapy, or surgery. Patients with **benign solitary thyroid nodule** may undergo observation or levothyroxine suppression therapy as the initial treatment modality. *Levothyroxine* is typically administered for 6-12 months to determine if the solitary thyroid nodule decreases in size. If the nodule decreases in size after treatment with levothyroxine, this medication is discontinued, with follow-up examination of the thyroid nodule in 3-6 months. However, if a benign solitary thyroid nodule increases in size, a repeat trial of levothyroxine and repeat FNAB may be indicated. Additionally, growth of a thyroid nodule during levothyroxine therapy is a strong indication for *surgery*.

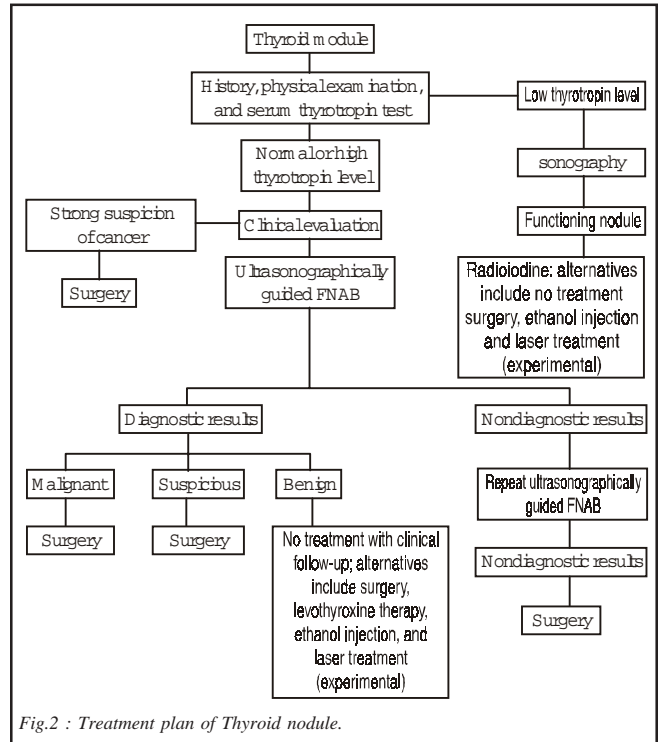


Fig.2 : Treatment plan of Thyroid nodule.

Solitary thyroid nodules that are **malignant**, suspicious, or indeterminate on FNAB require excisional biopsy in the form of thyroidectomy. Considerable controversy exists regarding the extent of surgery for malignant, suspicious, or indeterminate solitary thyroid nodules. However, principle philosophies involved in the arguments for either thyroid lobectomy or total thyroidectomy are beyond the scope of this article. A treatment plan is depicted as a flow chart Fig.2.

## Recommended Reading

1. Hegedus L. The thyroid nodule. *New Eng. Jr. of Medicine* Oct21,2004;351:1764-1771.
2. Daniel JK, Kim M. Evaluation of thyroid nodule. *eMedicine World Medical Library* May 6, 2003.
3. Hebra A, Miller M. Solitary thyroid nodule *eMedicine World Medical Library* Nov 30, 2004.
4. Feld S, Garcia M: *AACE Clinical Practice Guidelines for the Diagnosis and Management of Thyroid Nodules*. 1996.
5. Singer PA: Evaluation and management of the solitary thyroid nodule. *Otolaryngol Clin North Am* 1996 Aug;29(4):577-91.

## Manuscript Submission : For JIMSA

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- (i) Copyright statement/declaration (not submitted or published elsewhere) signed by all the authors.
- (ii) Three hard copies of manuscript with illustrations attached to each; **floppy** in addition will be desirable.
- (iii) **Title page** : Title of manuscript, Name(s) and affiliation of author(s); institution(s) and city(ies) address of corresponding author (Tel; Fax; e-mail).
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- methods, results, discussions ; **Indian literature must be referred**, references numbered **in text** as they appear.
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  - (vii) Each table on separate sheet; maximum number=4 in original article.
  - (viii) Photographs/Figures in envelope, each marked figure number on reverse with legends on separate sheet. Number not to exceed 3, preferably.
  - (ix) Statement regarding adherence to **standard ethical guidelines** prescribed by ICMR 2000. (see page 84)

Adv. Frazenus

# Study of Thyroid Nodule

VIKAS SINHA, AZIZ DHILAWALA, AJAY GEORGE, RIZWAN MEMON, ANKUSH ARYA

Department of Otorhinolaryngology, B.J. Medical College, Civil Hospital, Ahmedabad, India

**Abstract:** A total of 50 cases of thyroid nodule were studied; 86% were females; 64% were between age 30 to 50 years. Besides neck swelling, 2 cases with weight loss had thyrotoxicity; 92% were euthyroid; 2 hypothyroid and 2 thyrotoxic. Ultra-sonography showed solitary nodule in 56%; mixed solid and cystic swelling in 26%. FNAC confirmed benign lesion on histology in 64% seventy percent, with unilateral disease had hemi-thyroidectomy; subtotal thyroidectomy was performed in 18% with bilateral disease; 2 cases with malignant disease had total thyroidectomy.

## Introduction

Thyroid nodules present a challenge in their diagnosis, evaluation and management. The present armamentarium of investigations is packed with the latest technologies of Fine Needle Aspiration Cytology (FNAC), thyroid scan and ultrasonography (USG). But still only 90% accuracy in pre operative diagnosis can be reached. Moreover there are still many controversies in management part, mainly over the point of conservative management against thyroidectomy in benign and malignant lesions.

Hence this study was done with an aim to evaluate the reliability and utility of different investigations in achieving a correct pre operative diagnosis of thyroid nodule and to derive an optimal management protocol for patients with solitary thyroid nodule.

## Material and Methods

Fifty (50) patients with thyroid nodule who presented to our institute from 1999 to 2001 were included in this study. After taking a detailed history, all patients were subjected to a thorough clinical examination. Besides all routine hematological and radiological investigations, special investigations done included thyroid function test, F.N.A.C., USG and thyroid scan. Based on the findings of these investigations, patients were treated accordingly. Treatment modalities ranged from nodule excision of solitary thyroid nodule to total thyroidectomy for malignant lesions. The patients were subsequently followed up for recurrence and complications. The results were collected, tabulated and analysed.

## Results and Discussion

Out of the total of 50 patients, 43 (86%) were female and the rest (14%) were male. This *female preponderance* has been mentioned in all standard text books and the female: male ratio of 6:1 was observed in this study.

The *age distribution* shows a maximum of 19 cases (38%) in the fourth decade of life, 14 cases (28%) in the 40 to 49 year age group and 11 cases (22%) in the 20 to 29 year age group. There were 4 cases (8%) in the sixth decade of life one case each in the second decade and in the above sixty year age groups.

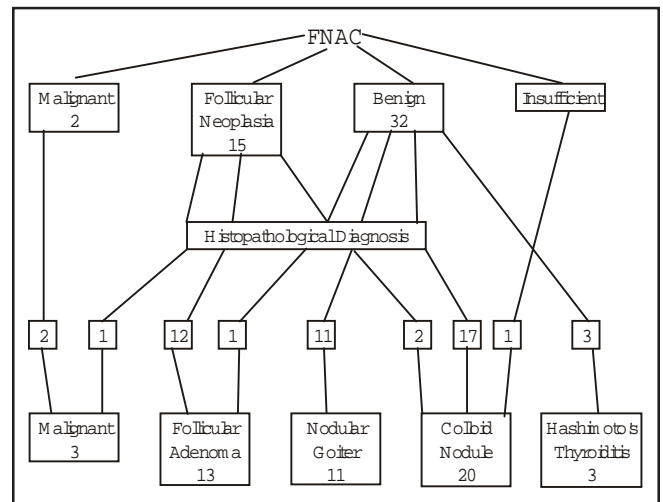
*Symptomatology* shows, besides the obvious complaints of neck swelling in all cases, there was pain in the swelling in 3 cases and in 2 cases each. The patients with pain in the swelling had thyroiditis, whereas the patients with weight loss were thyrotoxic. The other neck swellings were enlarged lymph nodes in cases of malignancy.

*Thyroid function test* revealed hypothyroidism in 2 (4%) cases and hyperthyroidism in 2 (4%) case. 46(92%) cases were euthyroid. That a great majority of thyroid nodules are euthyroid is well documented in text books and numerous contemporary studies.

*Thyroid scan* revealed solitary cold nodule in 28 cases (56%), multiple cold nodules in 10 cases (20%), solitary warm nodule in 10 cases (20%) and 2 cases (4%) of solitary hot nodule. Though thyroid scan is not of much diagnostic importance all the patients underwent this investigation for the purpose of this study. A study by Lowhagen et al<sup>5</sup> showed that though all cold nodules are not malignant, all malignant nodules are always cold. Thus a finding of cold nodule can be considered corroborative for malignancy.

USG of thyroid gland revealed solitary cold nodule in 28 cases (56%), single cystic lesion in 2 cases (4%) and mixed (solid and cystic) lesion in 13 cases (26%). 7 cases (14%) showed multiple solid lesions. 3 cases (6%) were of multiple mixed lesions. USG of thyroid is a very useful investigation as it gives an idea about the type of nodule, extent of lesion location of nodule, state of the remaining gland and surrounding vital structures. Also it can be used for guided FNAC.

FNAC showed benign lesion in 32 (64%) case and malignant lesion in 2 (4%) cases. In 15 (30%) cases no conclusive opinion could be given and in 1(2%) case the aspirated material turned out to be insufficient. The later 2 findings in this study can be attributed to human error. Thus even though FNAC has certain drawbacks like inability to differentiate between follicular adenoma and carcinoma it still is a very reliable and useful investigation.



| Treatment Modalities       | No. of Cases | percentage |
|----------------------------|--------------|------------|
| <b>First Stage</b>         |              |            |
| 1 Nodule excision          | 4            | 8          |
| 1 Hemithyroidectomy        | 35           | 70         |
| 1 Subtotal thyroidectomy   | 9            | 18         |
| 1 Near total thyroidectomy | 2            | 4          |
| 1 Modified neck dissection | 1            | 2          |
| 1 Central Neck dissection  | 1            | 2          |
| <b>Second Stage</b>        |              |            |
| 1 Completion thyroidectomy | 1            | 2          |
| 1 Neck Node Dissection     | 1            | 2          |

The findings of FNAC compared with the final histopathological diagnosis are shown in the flow chart.

Based on the examination and investigation findings, surgical treatment was done as shown in the table. In 4 cases (8%) only nodule excision was done. 35 cases (70%) with unilateral disease were treated with hemithyroidectomy. Subtotal thyroidectomy was done in 9 cases (18%) with bilateral disease. Near total thyroidectomy with berry picking was done in 2 cases (4%) with malignant lesions. In one of these patients, modified neck dissection was done as nodes for positive for metastasis on frozen section examination. In 1 case completion thyroidectomy and neck dissection had to be done as histopathological examination of surgical specimen revealed malignant lesion.

A shortest follow up of 3 months and the longest of 1 year could be achieved. 10 cases were lost to follow up immediately after discharge. there was incidence of recurrence in 1 case where only nodule excision was done. The other cases remained disease free

for variable periods.

### Conclusion

Though the series is too small to comment on comparative benefits of different surgical modalities, certain insights on diagnosis and management can be derived from the study.

A great majority of thyroid nodules are euthyroid and have benign origin. FNAC in proper hands is a very reliable tool in pre operative diagnosis of thyroid nodule with high sensitivity and specificity. Thyroid scan is not of much diagnostic, therapeutic or prognostic significance in thyroid nodule except in cases of toxic nodular goiter. Minimum surgery for thyroid lesions should be hemithyroidectomy as more conservative surgeries are prone to an unacceptably high incidence of recurrence.

### Recommended Reading

1. Ernest L. mazzaferri, Management of solitary thyroid nodule: Current concepts, the New England Journal of Medicine, Vol. 328, No.8, pgs 553-9
2. Gary L. Hoffman et al. The solitary thyroid nodule, Archives of Surgery, Vol. 102 (Aug. 1972), pgs 379-85.
3. Hilal M. et al. Fine needle aspiration cytology in isolated thyroid swelling: A prospective 2 year evaluation, British Journal of Surgery, Vol. 290
4. Ivan D.A. Jhonston, Surgery of thyroid cancer, British Journal of Surgery, Vol. 62(1975), pgs 765-8
5. Lowhagen et al, Aspiration biopsy cytology in nodules of thyroid gland suspected to be malignant, Surgical Clinics of North America, Vol. 59, No.1, Feb. 1979.
6. Shudaya Takashima et al. Thyroid nodule: Clinical effects of ultra sound guided FNAC, Journal of Clinical Ultrasonography, Vol., 22, pgs 535-42.

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# Intestinal Parasites and Anaemic Status in Oral Submucous Fibrosis

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**Abstract:** The study was undertaken to assess the intestinal helminth load of patients with advanced OSF by stool examination for representative pathogens. The findings were correlated with the haematologic profile (anaemic status) of these patients. A statistically significant reduction in haemoglobin levels of test subjects compared to healthy controls was reported. ( $9.47 \pm 0.95 \text{ gm/dL}$  against  $11.70 \pm 0.72 \text{ gm/dL}$ ). This was in agreement with earlier haematological studies on OSF but the concurrent low intestinal parasite load recorded amongst them is difficult to be explained. (Chi-square 2,  $df=1$ ,  $p=0.15$  - not significant). We are lead to believe that intestinal parasites are not contributory, at least amongst the reported cases, in inducing and sustaining iron-deficiency state in the diseased individuals. The association does not seem to be simple and straight forward in the light of the confounders involved in the disease process.

## Introduction

Significant haematological abnormalities have been reported in oral submucous fibrosis (OSF). This includes an increased blood sedimentation rate (ESR), anaemia and eosinophilia, increased gammaglobulin, a decrease in serum iron ( $p < 0.05$ ) and an increase in total iron-binding capacity ( $p < 0.05$ ). The percentage saturation of transferrin also decreased ( $p < 0.001$ ) and a significant reduction in total serum iron ( $p < 0.01$ ) and in albumin ( $p < 0.01$ ) was found<sup>1</sup>. Thus iron-deficiency anaemia appears to be commonly associated with this disorder.

The immune-mediated expulsion of intestinal helminths from their natural host is widely known. This involves the mediation of cytokines like IL-4, IL-9, and IL-13 along with TNF- $\alpha$  and IFN- $\gamma$ . The levels of TNF- $\alpha$  ( $p=0.016$ ) and IFN- $\gamma$  ( $p=0.012$ ) significantly increased with age, suggesting a switch to a more chronic infection phenotype. The predominant parasite specific antibodies produced were IgG1, IgG4, IgA and IgE. The parasite specific IgE correlated positively with host age depicting its chronicity ( $p=0.010$ )<sup>2</sup>. These findings suggest a mixed cytokine response and an IgE associated level of protection in helminthic carriers. Immunologic studies on OSF showed a decrease in cell mediated immune response (CMI) and an increase in serum levels of IgA, IgD and IgE<sup>3</sup>. These studies indicate that the role of altered and foreign tissue antigenic determinants in OSF deserve further study. The circulating immune complexes (CIC) and the immunoglobulin content of which were found to be elevated significantly in both OSF and oral cancer<sup>4</sup>.

The background data available on the haematological and immunological fronts of OSF lead us to hypothesize a putative link between them and the pathogenesis of the disease. A confounder in this regard was the worm infestation status of these patients which was hitherto unexplored, and the clinical spectrum of its is envisaged to have similarities with the disease (haematologic and immunologic). A study was therefore undertaken to assess the intestinal helminthic load of patients with advanced OSF by stool examination for representative pathogens and correlate the findings with the haematologic profile (anaemic status) of these patients. The role, if any, of intestinal parasites in inducing anaemia in this group of patients was expected to be studied.

## Materials and Methods

**Patient selection :** Twenty five (25) cases (age 24 to 70 year 6 males & 19 females) of histologically confirmed OSF comprised the study

group. An equal number of age and sex matched disease free adults formed the control. The intestinal parasitic load was assessed by microscopic examination of the stool samples using the same technique for both test and control groups. For this, stool samples should be properly collected and preserved<sup>5</sup>. The examination was done to detect (a) adult worms, (b) ova and cysts, (c) larvae, (d) trophozoites and (e) cellular exudates such as WBCs, RBCs, macrophages and Charcot-Leyden crystals.

**Macroscopy and Microscopy :** Grossly the points noted were (a) consistency of stool samples, (b) presence of blood and mucous, (c) presence of round worms, thread worms or tape worm proglottids and (d) colour and odour of the stool.

The following techniques were used to detect microscopically the presence of worms, eggs or larvae, protozoan trophozoites and cysts. (a) saline wet mount, (b) iodine wet mount and (c) floatation procedure (saturated salt floatation)<sup>5</sup>. The egg count was done by direct smear count technique. ( $\text{no. of eggs/gram of faeces} = n/2 \times 1000$  where 'n' is the number of eggs). The following intestinal parasites were examined in the stool samples: (a) *Entamoeba histolytica*, (b) trichuriasis, (c) ascariasis *lumbricoides*, (d) *ancylostoma duodenale*, (e) *taenia solium* and (f) *strongyloides stercoralis*.

## Results

Twenty five (25) clinically diagnosed, histologically confirmed OSF (advanced) cases (mean age  $49.72 \pm 11.41$  years, M:F=6:19) comprised the study group. An equal number (25) of age and sex matched, disease free adults (mean age  $50.12 \pm 11.16$  years, M:F=6:19) constituted the controls. The faecal parasite status and percentage distribution of were not significantly different ( $p=0.15$ ) amongst the patient and control groups; fecal helminths were not seen in 1 and 4 of the patient and control group respectively (out of 25 in each group). The distribution of mean haemoglobin levels among cases and controls is given in Table 1.

The types of parasites observed in patients & controls, are given in table 2 & Fig. 1. The results were analysed by the paired Students's 't' test. A 'p' value  $< 0.05$  was considered to be statistically significant.

## Discussion

Iron deficiency anaemia appears to be one of the major and almost consistent haematological variables in OSF<sup>4</sup>. Whether this variability is causative, which is quite unlikely, may have a contributory effect in its progression. Effective management of these haematological deficiencies may help to alleviate the symptoms of this disorder by modulating the disease progression to an atrophic mucosa, which is more vulnerable to the effect of carcinogens.

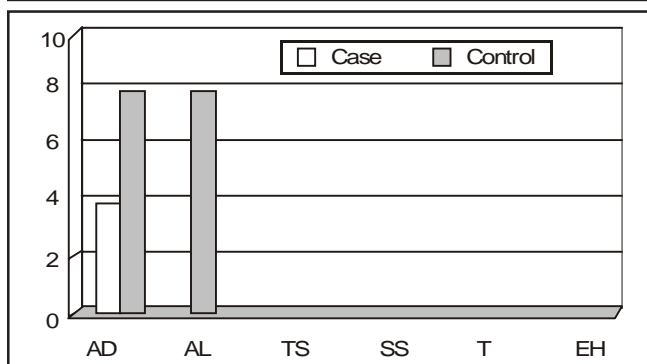
**Table 1 : Distribution of Mean haemoglobin levels among case and control.**

|                      | Group   | N  | Mean  | S.D.  |
|----------------------|---------|----|-------|-------|
| Haemoglobin<br>(gm%) | Case    | 25 | 9.47  | 0.953 |
|                      | Control | 25 | 11.70 | 0.722 |

The mean haemoglobin level in the test cases is 9.47 with a standard deviation of 0.953 and the mean haemoglobin level amongst control is 11.70 with a standard deviation 0.722. This difference is found to be significant ( $t=9.33, p=.001$ ).

**Table 2 : The faecal parasite in test and control samples.**

| Type of Parasite          | Case | Control |
|---------------------------|------|---------|
| Entamoeba Histolytica     | -    | -       |
| Ascaris Lumbricoides      | -    | +       |
| Ancylostoma Duodenale     | +    | +       |
| Taenia Solium             | -    | -       |
| Trichuriasis              | -    | -       |
| Strongyloides stercoralis | -    | -       |

**Fig. 1 : percentage distribution of parasitic load among test and control samples.**

The high incidence of various intestinal parasitic infestation in tropical populations could be responsible for malnourishment and lack of haematopoietic nutrients thus contributing to anaemia. In OSF the type of anaemia reported was principally hypochromic, microcytic variant resultant to iron deficiency. This could be due to poor nutritional status of the cohort compared to control population and/or caused by chronic blood loss, due to parasitic infestations and other causes (blood loss anaemia).

Immunological responses are of great importance in parasitic diseases as a source of tissue damage. Significant immunological alterations were reported in OSF<sup>9</sup>. This includes elevated serum levels of IgA, IgD and IgE along with significant reduction in CMI response (by enumerating the high affinity rosette forming cells - HARFC). Eosinophilia is a characteristic phenomenon related to helminthic infestation. But eosinophilia in peripheral blood is not as frequently observed in helminthic infections that reside in the human gut (eg. hook worm, tape worm). Eosinophils have been demonstrated to play a significant role in host resistance to worm infections, as well as in protection against the tissue stages of these parasites. Although other cells of the immune system may contribute to acquired resistance,

the close association of eosinophilia and helminths points to a specific set of interactions and adaptations to helminthic infection. Tissue eosinophilia is frequently reported in OSF biopsies<sup>6</sup>.

Increase in absolute mast cell count with changes in the mast cell - histamine chain causing fibrosis of the submucosa was outlined earlier in OSF<sup>7</sup>. The mast cell degranulation product of histamine may have direct effects on fibroblasts which range from stimulation of proliferation to inhibition depending on the stage of the cell cycle of the fibroblasts<sup>8</sup>. We reported earlier<sup>9</sup> the infrequency of systemic fibrosis (visceral organ) in OSF even though a strong likelihood exist in its occurrence. The failure of visceral fibroblasts respond in the same manner to that of oral could be explained further in this context. Let us turn first to the fact that the mast cells may be heterogeneous in respect to tissue site of origin within a species and also with respect to the same site of origin between species<sup>10</sup>. The intestinal mucosal mast cells differ from the peripheral mucosal cells and other connective tissue mast cells by virtue of histochemical properties which reflect in their granular contents. It is therefore presumed that oral mucosal mast cells respond differently to the effect of allergenic stimulants by selective degranulation of its contents which could act upon the oral fibroblasts to synthesize excess amount of collagen. This explains rather vividly the localized nature of fibrosis in OSF and the failure to demonstrate similar fibrosis in visceral organs like liver.

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### References

1. Rajendran R, Vasudevan DM, Vijayakumar T. Serum levels of iron and proteins in oral submucous fibrosis. *Ann Dent* 1990;49:23-25.
2. Faulkner H, Turner J, Kamgno J, Pion SD, Boussinesq M, Bradley JE. Age and infection intensity - dependent cytokine and antibody production in human Trichuriasis: The importance of IgE. *J Inf Dis* 2002;185:665-672.
3. Rajendran R, Sugathan CK, Remani P, Ankathil R, Vijayakumar T. Cell mediated and humoral immune responses in oral submucous Fibrosis. 1986;58:2628-31.
4. Remani P, Rajendran et al. Circulating immune complexes as an immunological marker in pre-malignant and malignant lesions of the oral cavity. *Cancer Lett* 1988;40:185-91.
5. Ichhpujani RL, Bhatia R (Eds) *Medical Parasitology*. 2nd Ed. Jaypee Brothers, New Delhi 1998pp. 328-31.
6. Rajendran R. Oral submucous fibrosis: etiology, pathogenesis, and future research. *Bull WHO* 1994;72(6):985-96.
7. Bhat AP, Dholakia HM. Mast cell density in oral submucous fibrosis. *J Ind Dent Asso* 1977;49:187-91.
8. Jordana M. Mast Cells and fibrosis - who's on first? *Am J Respir Cell Mol Biol* 1993;8:7-8.
9. Rajendran R, George B, Sivakaran S, Narendranathan N. Visceral organ involvement is infrequent in oral submucous fibrosis. *Ind J Dent Res* 2001;12:7-20.
10. Bienenstock JB, Befus AD, Pearce F, Denburg J, Goodacre R. Mast cell derivation and function, with heterogeneity; emphasis on the intestine. *J Allergy Clin Immunol* 1982;70:407-12.

### APPEAL

Fellows and Members intending to participate, alongwith their accompanying persons, in **IMSACON 2005** to be held on 22-23-24 Oct. 2005 at Jaipur are requested to register themselves well in time. This will enable organizers to book accommodation properly and avoid rush at the eleventh hour and also encourage and boost the morale of organisers.

**R.R. Thakral**  
Vice-President, IMSA

# Rectus Sternalis Muscle : A Debate For Anatomists, A Puzzle For Radiologists and Surgeons

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**Abstract:** Rectus Sternalis muscle is a rare anomaly of anterior chest wall that has debated origin, innervation and unknown function. In the present case it was bilaterally seen in an adult male cadaver. On right side it was unusually enlarged, distinct and strap-like measuring 15.5 cm in length and 2.4 cm at broadest part. Upper tendinous attachment was continuous with Sternocleidomastoid laterally and Sternohyoid medially. The lower attachment formed an aponeurosis that merged with that of External oblique. The nerve supply came from the medial and lateral pectoral nerves that supplied the muscle from deep aspect after piercing Pectoralis major. Left Sternalis was insignificant with a few fibers only. Lack of awareness of this variation has puzzled radiologists and surgeons in confirming diagnosis, missing it or mistaking it for a breast mass on mammography, CT or MR imaging.

## Introduction

An unusual gross variation nurtures interest of anatomists and causes concern for clinicians when it mimics pathology. Sternalis muscle is a one such variation that challenges our understanding of anatomy of the parasternal region of anterior chest wall. The muscle may be seen unilaterally or bilaterally placed subcutaneously over Pectoralis major, extending parasternally from jugular notch to the costal region. It has been reported in either sex, in Asians and in whites as well as blacks<sup>1,2,3,4</sup>. Carbolis initially observed it but Du Ruy first described it in 1726<sup>5</sup>. The incidence varies in different ethnic groups, ranging from 0.5% in Taiwanese<sup>6</sup> to 17.3% in Chinese<sup>1</sup>. Though noted over centuries, its origin, nerve supply and function are debatable. It is essential for the radiologists and surgeons to acknowledge this entity as it may pose a diagnostic dilemma mimicking a malignant breast mass on mammography, CT or MR imaging so that an exploratory surgery can be avoided<sup>7,2</sup>.

## Case Report

Rectus Sternalis muscle was seen bilaterally in a 40 year old male formalin-preserved cadaver, well defined on the right side, left being inconspicuous and represented by a few short fibers only (Fig.1).

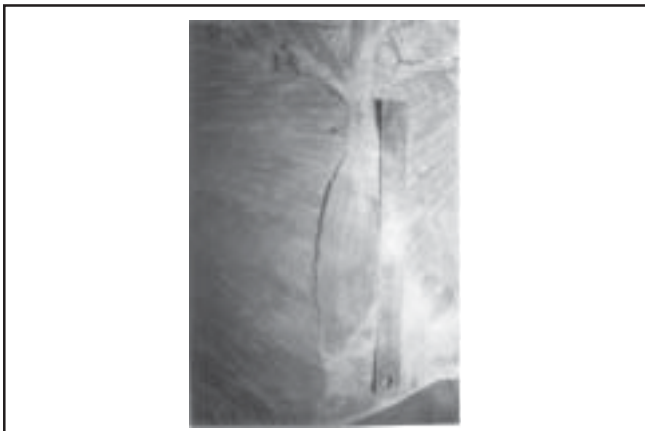


Fig. : Rectus sternalis (RSr) muscle is well developed on right side, only a few fibers seen on left side (RSI). On right side upper tendinous attachment is continuous with sternocleidomastoid (SCM) and sternohyoid (SH). Lower attachment is aponeurotic. Right Pectoralis major (PM).

**Right Rectus Sternalis:** Right Rectus Sternalis observed to be strap like, flattened anteroposteriorly, placed vertically parallel to the sternum, 15.5cm in length and 2.4cm wide at its broadest part. Though it was subcutaneous over the sternal attachment of Pectoralis

major, a few muscle fibers also arose from sixth and seventh costal cartilages. The lateral border showed a lateral convexity, the medial was straight, placed besides the sternal margin. The upper fibers, attached to the anterior surface of manubrium converged into a tendon, that was in continuity with lower tendinous attachments of Sternocleidomastoid (sternal head) laterally and Sternohyoid medially. The lower fibers formed an aponeurosis, which was continuous with the aponeurosis of External oblique. At this end the length of muscle fibers increased from medial to lateral border giving the lower part of the muscle fancied resemblance to a sharp pointed kitchen knife, the tip being directed laterally and downwards. Nerve supply came from medial and lateral pectoral nerves, which supplied this muscle from deep surface after piercing Pectoralis major.

**Left Rectus Sternalis :** Left Rectus Sternalis was seen to be a thin band of fibers measuring only 3 cm in length and 0.6 cm at maximum breadth placed vertically over the sternal head of left Pectoralis major. The fibers were seen to be directed downwards and laterally, and intermingling with the fibers of underlying External intercostal muscle.

## Discussion

Rectus sternalis muscle, a rare variant poses challenge to our understanding of anatomy of the paramedian region of anterior chest wall. It lies parallel to the sternal margin superficial to pectoral fascia, extending from infraclavicular region to costal margin and varies from a few short fibers to a well-developed strap like band of muscle. Kitamura et al<sup>8</sup> reported an isolated case of partial deficiency of Pectoralis major accompanied by an enormous Sternalis muscle.

Although noted in literature, dilemma persists about its origin and nerve supply. Barnister et al<sup>9</sup> view it as a misplaced fibers of Pectoralis major. However, embryologists<sup>10,11</sup> describe it as a part of ventral tip of hypomeres being represented by Rectus abdominis muscle in the abdominal region and by the infrahyoid musculature in the cervical region. In the thoracic region this layer usually disappears but occasionally persists as Sternalis muscle. O'Neill and Folan-Curran<sup>12</sup> highlighted differing views about origin of this muscle viz. Pectoralis major, Rectus abdominis, Sternastoid or Panniculus carnosus. Most workers opined its derivation from Pectoralis major. Barlow claimed it to be a remnant of Panniculus carnosus, a fact not accepted today. Kida et al<sup>13</sup> observed its nerve supply in 40 cases over 15 years and found pectoral nerves supplying it. Anterior branches of cutaneous intercostal nerves often penetrate the muscle to become cutaneous but do not supply Sternalis. In our finding the both medial and lateral pectoral nerves supplied Sternalis from deep surface after piercing and supplying Pectoralis major muscle.

In the light of various high-tech methods used in diagnosis and

therapeutics it becomes imperative to note, record and discuss uncommon anatomical variants. Rectus sternalis muscle can easily be overlooked during breast surgeries and often be puzzling on mammography or CT Scan. This anomaly is highly unpopular among people in medical and surgical fields. A survey conducted among physicians, medical students, surgery and plastic residents and faculty from other disciplines revealed near-total unfamiliarity about this anomaly<sup>14</sup>. It is not due to its low incidence but may be due to paucity of encounter during surgery and imaging. With improved radiological imaging techniques Sternalis muscle will be noted more often than in yesteryears<sup>2</sup>.

Diagnosing sternalis muscle on mammography can often be puzzling since it can mimic a malignant breast mass<sup>7</sup>. Bradley et al<sup>2</sup> gave the first description of this muscle in the breast imaging literature but could establish the fact only after open biopsy for a suspected breast tumor. Later they found 4 Sternalis muscles in 32,000 mammograms done over three years. Bailey<sup>14</sup> noted this muscle in 3 patients undergoing mastectomy over a period of 15 years. The medial side of breast is considered as a potential blind spot on mammography in mediolateral projection. Radiologists must visualize this area in craniocaudal projection with adequate positioning and traction of breast to maximize volume of tissue and include mobile margins<sup>2</sup>. The diagnosis depends on its location, orientation and absence of corresponding abnormality on lateral views<sup>2</sup>. For better visualization CT scan should be done as it clearly defines longitudinal and parasternal course of the muscle.

Thus, we conclude that rectus sternalis muscle can be a puzzle for anatomists, a diagnostic dilemma for radiologists or surgeons who must have the knowledge of this uncommon variant in the anterior thoracic wall otherwise it could be easily misinterpreted during mammography, imaging by computed tomography or magnetic resonance.

## References

1. Barlow RN. The Sternaios, isci on A,erocam wjotes amd Megrpes/ Anat Rec 1935;6:413-426.
2. Bradley FM, Hoover H CJ, Hulka CA, et al. The Sternalis muscle: An unusual normal finding seen on mammography. Am J Roentgenol 1996;166:33-36.
3. Kida MY and Kudoh H. Innervation of the Sternalis muscle accompanied by congenital partial absence of Pectoralis major muscle. Okajimas Folia Anatomica Japonica 1991;67:449-455.
4. Shen CL, Chien CH, Lee SH. A Taiwanese with a pair of Sternalis muscles. Acta Anatomica Nipponica 1992;67:625-654.
5. Turner W. On the musculus Sternalis. J Anat Physiol 1867;1:246-253.
6. Jeng H and Su SJ. The Sternalis muscle: an uncommon anatomical variant among Taiwanese. J Anat 1998;193:287-288.
7. Britton CA. Subpectoral mass mimicking a malignant breast mass on mammography (letter). Am J Radiology 1992;159:221.
8. Kitamura S, Yoshioka T, Kaneda M, et al. A case of the congenital partial defect of the Pectoralis major accompanied by the semalis with enormous size. Kaibogaku Zasshi. J Anat 1985;60:728-732.
9. Bannister LH, Berry M, Collins P, et al. Grays Anatomy, 38th ed., Churchill Livingstone, New York. 1996: 838.
10. Larsen WJ. Human embryology. Churchill Livingstone, New York. 1997:57.
11. Sadler TW. Muscular system. Langman's Medical Embryology. 7th ed. Williams and Wilkins, Baltimore. 1995:168.
12. O'Neill MN, Folan-Curran J. Case report: bilateral Sternalis muscles with a bilateral Pectoralis major anomaly. J Anat 1998;193:289-292.
13. Kida MY, Izumi A, Tanaka S. Sternalis muscle: topic for debate. Clin Anat 2000;13:138-140.
14. Bailey FM, Tzarnas CD. The Sternalis muscle: a normal finding encountered during breast surgery. Plast Recon Surg 1999;103:1189-1190.

## Literature Review

Compiled by Dr. P. Chattzree

**Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated falciparum malaria in adults.** Noedl H, K nirseh C et al. *Infection* 2005;33:170.

Azithromycin may have an important role as an antimalarial due to its safety in children and experience with use in pregnancy. The study was designed as a phase II open label, randomized 28 day inpatient study of acute, uncomplicated falciparum malaria, comparing the safety and efficacy of azithromycin (AZ) - artesunate (AS) combination with AZ-quinine (QN) regimens in 1000 adults patients : (1) 3 days of AZ 750 BID & AS 100mg BID. (2) 3d of AZ 1000 OD & AS 2000D (3) 3d of AZ 750mg BID & QN 10mg / 1kg BID, (4) 3d of AZ 500mg TID daily & QN 10mg 1kg TID.

After completion of the first 50 subject failure rates, PCT & FCT were compared in a preliminary efficacy analysis. The 28 day cure rates for the 4 groups were 100 (95% CI; 71-100), 100 (73.5-100), 72.7 (39.0, 94.0), and 91.7 (61.5 - 99.8) respectively. Two RIIIIs and one RI failure were seen in the BID quinine arm. With a mean PCT & FCT of 34+12 and 26 + 18 hours the artesunate combinations led to a significantly (P<0.001) faster clinical and parasitological improvement than the quinine arms (80+34 and 60+39 hours) Clinical treatment response was closely correlated with in vitro drug sensitivity data. Drug combination were generally well tolerated. These data suggest that both azithromycin-artesunate even when given only once daily for 3 days as well as azithromycin-

quinine TDS are safe and highly efficacious combinations for uncomplicated falciparum malaria.

**Angiotensin receptor blockers and ACE inhibitors are equivalent in type 2 diabetic nephropathy.** Bamett AH, Bain SC, Bouter P et al. *N.Engl. J. Med* 2004;351(19)1952-1961.

In this prospective multicenter, double blind 5 years study. 250 subjects with type II diabetes and early nephropathy were randomly assigned to receive either the angiotensin II receptor blocker telmisartan (80mg daily in 120 subjects) or the ACE inhibitor enalapril (20mg daily in 130 subjects). The primary endpoint was the change in glomerular filtration rate (determined by measuring the plasma clearance of ionexal) between the baseline value and the last available value during the 5 year treatment period. Secondary end points included the annual changes in the GFR, serum creatinine level, urinary albumin excretion, and blood pressure, the rate of end stage renal disease and cardiovascular events and the rate of death from all causes.

After 5 years, the change in glomerular filtration rate was - 17.9 ml/min/1.73m<sup>2</sup> of body surface area; with telmisartan (in 103 subjects) as compared with 14.9ml/min 1.73m<sup>2</sup> with enalapril (in 113 subjects), for a treatment difference of -3.0ml/min/1.73m<sup>2</sup>. The lower boundary of the confidence interval in favour of enalapril was greater than the predefined margin of -10ml/min/1.73m<sup>2</sup>, indicating that telmisartan was not inferior to enalapril. The effects of the two agents on the secondary end points were not significantly different after 5 years.

## Refractory Evans' Syndrome : Therapeutic Options

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### Introduction

Some chronic immune-mediated hematological disorders in adults, such as autoimmune hemolytic anemia (AHA), idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia with thrombocytopenia (Evans' syndrome) will achieve a prompt and last remission after corticosteroid treatment. Nevertheless, many patients will be resistant<sup>1</sup>. They might be requiring high dose corticosteroid therapy or other modalities of treatment such as intravenous high-dose immunoglobulins (frequent but transient improvement),<sup>2</sup> suppression by chemotherapeutic drugs (about 50% response rate) and or splenectomy (50-70% complete or partial remissions). There are reports that have dealt with the beneficial effect of cyclosporin A in refractory cases<sup>3</sup>.

Physicians face therapeutic dilemmas when patients are resistant to known treatment in life-threatening conditions. We report a case of Evans' syndrome that was treated with combination of various medical therapies including high dose steroids, immunoglobulins, anabolic steroids, vitamin C and vincristine. Later cyclosporin was added when patient relapsed on tapering of steroids.

### Case Report

BC 70 year old male had come with chief complaints of jaundice and pallor of 6 month duration. He had developed melena 8 days ago for which he had received 4 blood transfusion outside. Following melena, he developed orthopnea and edema feet for last 6 days. On examination, he had pallor, jaundice, bilateral pedal edema. There was no purpura. His pulse rate was 110 min, blood pressure 160/70mm Hg, and respiratory rate 16/minute. Cardiovascular examination revealed ejection systolic murmur at base. He had bilateral fine basal crepitations and 4cm firm splenomegaly. CNS examination was normal except that bilateral ankle reflexes were absent. Fundus examination showed background retinopathy. With this, working diagnosis of upper GI bleed, portal hypertension with congestive heart failure was made. Ryle's tube showed altered blood. 4 packed red blood cells were transfused slowly. Upper GI endoscopy showed large esophageal ulcer and multiple punctate hemorrhages in the fundus.

On investigations, complete hemogram showed hemoglobin 7.3gm%, total leukocyte count 8000/mm<sup>3</sup>, platelets 50000/mm<sup>3</sup>, reticulocyte count 40% and peripheral smear showed polychromasia, nucleated RBC's, spherocytes and reduced platelets. His biochemical parameters showed blood sugar 456mg%, S. Bilirubin T/D/I 5.6/1.2/4.4 mg%, SGOT/PT 40/44 IU, S. Protein 5.0/1.5/3.5 gm%, Urea 40mg%, Creatinine 1.2mg%, Na 140meq/L and K 4.4 meq/L. Blood gas analysis showed pH 7.26, pO<sub>2</sub> 86mm of hg pCO<sub>2</sub> 26mm of Hg and HCO<sub>3</sub> of 13.4 mmol/L. His coagulogram was within normal limits. Coombs test, both direct and indirect were strongly positive. Antibody subtyping showed it to be IgG (negative for IgM, IgA, C3, and C4). Antiplatelet antibodies were also strongly

positive. Plasma hemoglobin was 20mg%. Bone marrow examination showed erythroid hyperplasia with increase in megakaryocytes. Antinuclear factor was negative, while thyroid profile and prostate specific antigen were normal. Chest X-ray, electrocardiogram, ultrasound abdomen and echocardiogram were within normal limits.

With above findings diagnosis of idiopathic Evans' syndrome i.e. autoimmune hemolytic anemia (Warm-Antibody type) and thrombocytopenia, along with noninsulin dependent diabetes mellitus (NIDDM), essential Hypertension and esophageal ulcer was made. Patient was started on I/V hydrocortisone (100mg I/V 6 hourly) along with antacids, sucralfate and proton pump inhibitor. His diabetic hyperosmolar state was controlled with hydration, central venous pressure monitoring (10-12 cm of water) and insulin therapy. The sepsis was controlled adequately with I/V vancomycin, ceftazidime and amikacin. Congestive heart failure responded to blood transfusions, albumin, furosemide and oxygen.

At one week, GI bleed continued. Repeat upper GI endoscopy showed no active blood, while on colonoscopy, caecum and ascending colon showed multiple hemorrhagic spots with mild ooze of blood. Purpura had also appeared since platelet count remained low i.e. 30000-40000/mm<sup>3</sup> along with low hemoglobin. Multiple platelets transfusions were given followed by single donor platelets. At 10th day, patient was started on intravenous immunoglobulins (.4gm/kg/day for 5 days). Even with this platelet showed no rise, however hemoglobin had shown significant rise of up to 10.0 gm%. From 3rd week, patient was started on Danazol 600mg/day along with vincristine (VCR) 2mg I/V every week for 3 doses. After third dose of VCR, platelet increased to 1.5 Lac/mm<sup>3</sup>. On tapering steroids 5mg every week, platelets count again fell to 50000/mm<sup>3</sup> on 40mg prednisolone at 3½ months. This fall responded to single dose of VCR. After that VCR could not be repeated as, patient was showing signs of peripheral neuropathy. As platelets were showing fall, while lowering steroids, he was started on cyclosporine 5mg/kg/day in two divided doses for 6 days followed by 3 mg/kg/day. Cyclosporin levels at 2 weeks were 170ng/L. Steroids were tapered at 5 mg/week. The patient stabilized on prednisolone 10mg/day and cyclosporin in 3mg/kg/day with platelet count of 1.5 Lac/mm<sup>3</sup> and hemoglobin of 12gm%.

### Discussion

Steroids are the mainstay of therapy for Evans' syndrome. Therapeutic response to oral prednisolone (1-2 mg/kg/day) is seen in 1-2 weeks. If no response is seen in 3-4 weeks, or in case of life threatening emergencies other options are looked for. High dose methyl prednisolone (HDMP) in doses of 20mg/kg for 3 days produces faster response in 3-5 days. HDMP needs to be followed up with oral steroids. Intravenous immunoglobulin (IVIg) are the fastest means of increasing platelets. Platelet counts rises in 24-48 hours. Response rate is 60-80%; however response only lasts a week or more<sup>2</sup>. At present the recommended indications of IVIg are acute life threatening emergencies or preoperative period. Other drugs used include Danazol 600-800/day, however it produces slow therapeutic response (weeks to months). the

major benefit of Danazol is that it sustains partial remission and allows lower doses of steroids. *Cytotoxic immunosuppressants* (azathioprine, cyclophosphamide) have been used in refractory cytopenias<sup>4</sup>. The major indications being disease of months duration and contraindication for splenectomy in patients unresponsive to steroids. The disadvantage is that therapeutic response is slow to achieve (2-4 months), response rate is about 50% and associated side effects are well known. Vincristine has important role in refractory conditions as it achieves therapeutic response within several days. However, response lasts only a few days to weeks, as happened in our patients.

Various treatment modalities have been suggested for Evans' syndrome. In view of high relapse rate after splenectomy, medical treatment with multiagents i.e., IVIG, steroids, vincristine, Danazol and possibly cyclosporin has been advocated<sup>5</sup>. There have been reports in literature regarding the efficacy of cyclosporin in refractory Evans' syndrome. Cyclosporin appears as a salvage treatment in life threatening resistant autoimmune hematological diseases<sup>2,5</sup>. Splenectomy was not considered in our patient because of lack of families consent and well known disadvantages like high relapse rate, procedure related morbidity and mortality and overwhelming

postsplenectomy infection (OPSI).

Hence Evans' syndrome unresponsive to steroids can be a challenging proposition. Situation becomes more complex, when IVIG fails to produce platelet rise. At this stage multiagent treatment modalities need to be used in such life threatening situations.

## References

- 1 George J, El-Harake M, Raskob. Chronic idiopathic thrombocytopenic purpura. *N Engl Med* 1994;331:1207-1211.
- 2 Barrios NJ, Humbert JR, McNeil J. Treatment of acute idiopathic thrombocytopenic purpura with high dose methyl prednisolone and immunoglobulin. *Acta Hematol* 1993;89:6.
- 3 Emilla G, Messora C, Longo G, Bertesi M. Long-term salvage treatment by cyclosporin in refractory autoimmune hematological disorders. *Br J Hematol* 1996;93:341-344.
- 4 Manoharan A Treatment of refractory idiopathic thrombocytopenic purpura in adults. *Br J Hematol* 1991;79:143-147.
- 5 Scaradavou A, Bussel J. Evans' syndrome. Results of pilot study using a multiagent treatment protocol. *J Pediatr Hematol Oncol* 1995;17(4):290-5.

## Drug Profile

### Alfuzosin

Alfuzosin is a selective alpha 1 adrenoreceptor antagonist. It distributes preferentially in the prostate compared to plasma and decreases the prostatic smooth muscle tone.

**Mechanism of Action :** The symptoms associated with benign prostatic hyperplasia (BPH) such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The smooth muscle tone is regulated by Alpha(x) - adrenergic receptors. Alfuzosin exhibits selectivity for alpha adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscle in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in symptoms of BPH. It is a selective antagonist of post-synaptic alpha adrenoreceptors, which are located in prostate, bladder neck, prostate capsule and prostate urethra.

**Pharmacokinetics :** Absolute bioavailability of Alfuzosin 10mg under basal conditions is 49%. Following multiple dosing of 10mg Alfuzosin lead to maximum concentration is 9 hours. It is moderately bound to human plasma proteins (82 to 90%). It undergoes extensive metabolism by the liver; it is metabolized by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism. It is excreted 69% in feces and only 11% of the administered dose is excreted unchanged in urine. Half life is 10 hours. The extent of absorption is 50% under fasting conditions' therefore, alfuzosin should be taken immediately following a meal.

**Indications :** It is indicated for the treatment of the signs and

symptoms of benign prostatic hyperplasia.

**Dosage and administration :** Recommended dose is 10mg daily to be taken immediately after the same meal each day.

**Precautions :** (i) Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore patients thought to have BPH should be examined prior to starting therapy with alfuzosin to rule out the presence of carcinoma of prostate. (ii) **Drug Interactions :** Pharmacokinetic and pharmacodynamic interactions between alfuzosin and other alpha blockers have not been determined. However' interactions may be expected and alfuzosin should not be used in combination with other alpha blockers. (iii) **Coronary insufficiency :** If symptoms of angina pectoris appear or worsen' alfuzosin should be discontinued. (iv) **Hepatic insufficiency :** It should not be given to patients with moderate or severe hepatic insufficiency. (v) **Renal insufficiency :** Systemic exposure increases by approximately 50% in patients with renal insufficiency. (vi) Patients with congenital or acquired Qt prolongation. Worsen with 40mg dose. (vii) Postural hypotension with or without symptoms (e.g. dizziness) may develop within a few hours following administration of extended-release alfuzosin.

**Adverse Reactions :** Dizziness-5.7% URT infection-3%, headache-3.0%, fatigue-2.7%, rarely abdominal pain, dyspepsia constipation nausea. impotence, bronchitis, sinusitis, pharyngitis rashes and tachycardia.

Compiled by Dr. P. Chattree

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# Erectile Dysfunction: Recent Trends in Management

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**Abstract:** Erectile dysfunction (ED) is a widely occurring disorder that affects men of all ages. The prevalence and severity of ED increases with age and results in considerable distress and impact on quality of life. ED often has multiple causes, and diagnostic evaluation should include psychosexual, endocrinological, neurological and vascular factors. Treatment includes oral therapy with sildenafil, tadalafil, apomorphine, phentolamine; intracavernosal and intraurethral alprostadil or papaverine; vacuum erection devices, penile vascular surgery and penile implants. This article presents a brief overview of the diagnosis, treatment options and the upcoming therapies for the management of ED.

**Key Words :** *Erectile dysfunction; Sildenafil; Tadalafil; Alprostadil.*

## Introduction

Erectile dysfunction (ED) can be defined as an inability to sustain or maintain penile erection of sufficient rigidity for satisfactory sexual performance. Penile erection is a complex series of integrated neural and vascular events culminating in the accumulation of blood under pressure in the penis that causes end-organ rigidity. Any insufficiency at any level will result in failure to achieve erection. Thus ED is a multifactorial disease. Its incidence is strongly related to age with a prevalence of 2% at the age of 40 years, rising to 25-30% at the age of 65 years<sup>1</sup>. ED can have a strong negative effect on the well being and quality of life and can cause psychological imbalance. Therefore, it is imperative to examine a patient thoroughly (both medically as well as psychologically) to diagnose the problem of ED and treat it accordingly.

## Etiology

**Psychological :** This is the commonest cause of intermittent erectile failure in young and middle aged men. It usually occurs secondary to some organic dysfunction<sup>2</sup>. Clinically higher levels of serum nor-epinephrine have been reported in patients with psychogenic ED as compared to normal controls or patients with vasculogenic ED.

**Neurogenic :** Any lesion at the level of brain, spinal cord, cavernous and pudendal nerves can cause ED. Parkinson's disease, stroke, tumor and Alzheimer's disease are also often associated with ED. Injuries and disorders at the spinal level (e.g. spina bifida, dislocation, syringomyelia, tumors and multiple sclerosis) may affect the erectile function. Iatrogenic impotence can occur following various surgical procedures like radical prostatectomy, perineal prostatectomy<sup>3</sup>, abdominal perineal resection and external sphincterotomy<sup>4</sup>.

**Endocrinal:** Diabetes mellitus (DM) is the commonest endocrinal disorder causing ED. It has been reported that men with diabetes have fewer sleep related erections, less tumescence time, diminished penile rigidity, lower penile blood pressure than age matched non-diabetic men<sup>5</sup>. DM causes ED through its vascular, neurogenic, endothelial and psychogenic complications rather than insulin deficiency per se<sup>6</sup>. Both hyperthyroidism and hypothyroidism<sup>7</sup>,

decreased testosterone concentration<sup>7</sup> and hyperprolactinemia are associated with diminished libido and ED.

**Vasculogenic :** Adequate venous occlusion is one of the important prerequisite for erectile process. Incidence and age at the onset of coronary artery disease and ED is said to run parallel<sup>6</sup>. Arterial insufficiency, hypertension, hyperlipidemia, cigarette smoking and DM are the common risk factors for vasculogenic ED. Venocclusive dysfunction can also be due to degenerative changes e.g. Peyronie's disease<sup>8</sup>, old age and traumatic injury to albuginea resulting in inadequate compression of subtunical and emissary veins.

**Iatrogenic :** They are often the culprits and around 25% of all ED can be attributed to medications<sup>9</sup>. Antiandrogens (cimetidine, spironolactone, ketoconazole, finasteride), antihypertensives (clonidine, methyl dopa, beta-blockers, thiazides), antidepressants (MAO inhibitors, tricyclic antidepressants, barbiturates and benzodiazepines), digoxin, metoclopramide and anabolic steroids are likely to produce ED.

## Diagnosis

Careful history and physical examination form the initial step in the diagnosis of ED. Blood levels of glucose, creatinine, lipids, thyroid hormones, testosterone, luteinizing hormone and prolactin need to be ascertained and are the organic causes of ED. Nocturnal penile tumescence (NPT) occurs for a total time averaging around 10 min/night<sup>10</sup> during rapid eye movement (REM) sleep and its measurement is used as a marker of erectile functions of an individual. If history of nocturnal erection is questionable, NPT can be measured in a sleep laboratory or with the use of a strain gauge or snap gauge band. In the strain gauge test, the patient wraps a strip of strain gauge around penis before sleeping. If the ring breaks along the line of perfection, the test is considered positive indicating occurrence of a rigid erection<sup>11</sup>. However, the validity of the test is questionable in many cases like psychogenic ED where NPT may be absent<sup>12</sup>. Therefore, NPT is not indicated for routine use. Another test used is the measurement of penile buckling pressure in which a pressure device is pressed against the glans penis and the pressure required to make the penis buckle is measured in mmHg. Normal rigid penis buckles if pressure is more than 100mmHg. If the penis buckles at pressure less than 60 mmHg, it is considered too soft for vaginal penetration<sup>13</sup>.

Apart from measuring the rigidity, penile blood flow can also be

measured by Doppler technique. This technique is called as Penile/brachial systolic pressure index and in this penile systolic pressure (as determined by Doppler technique) is divided by supine brachial systolic pressure (measured simultaneously). An index of <0.6 suggests vasculogenic impotence. However, this test is also not confirmatory as it evaluates the blood flow through dorsal penile artery which is not involved in the erectile process and not through cavernosal arteries which are actually involved in erection. Thus, when cavernosal arteries are diseased and dorsal artery of penis is normal, the test will fail to detect impotence. Pulsed doppler analysis and high-resolution ultrasonography can also be used in conjunction with intracorporeal injection of alprostadil to assess blood flow in the cavernosal arteries<sup>14</sup>. A simple papaverine stimulation test (usually 40mg with or without 2mg of phentolamine to potentiate its effect) distinguishes responders from non-responders and help select candidates for self-injection treatment<sup>15</sup>. Color Doppler imaging after inducing maximal intracavernous smooth muscle relaxation with papaverine provides detailed information about penile hemodynamics and is particularly useful in distinguishing arterial insufficiency from venoocclusive dysfunction<sup>16</sup>. No single test is confirmatory, therefore clinician needs to correlate clinical findings with laboratory investigations to diagnose ED and its etiology and offer the patient, most suitable treatment option.

## Management

**Psychosexual counseling :** Psychosexual counseling is essential in treating ED as other treatment will fail in patients of primary psychogenic ED. It is aimed at decreasing performance anxiety by increasing the range of sexual activities and this requires close cooperation of the sexual partner. Therefore both the partners should be counseled.

**Hormonal therapy :** In young hypogonadal men, depot preparations of testosterone should be given every 2-3 weeks. This treatment improves both the libido and the potency. However, there is a risk of benign prostatic hyperplasia and prostate cancer<sup>15</sup>. Thus close monitoring of prostate specific antigen (PSA) and urinary flow rate is recommended before and during this treatment.

### First Line Drug Therapy :

**Sildenafil :** It is a potent inhibitor of phosphodiesterase type V (PDE5)- the predominant isoenzyme responsible for degradation of cGMP<sup>17</sup>. Since the drug only potentiates the action of cGMP rather than stimulating its production, it acts only in response to sexual stimulation. It is predominantly eliminated by hepatic metabolism (mainly by cytochrome P450 3A4) and converted to an active metabolite S-desmethyl-sildenafil. Half-life of both sildenafil and its metabolite is about 4 hours<sup>18</sup>.

Sildenafil (25,50 and 100mg) has been evaluated clinically in various trials. A review of these studies indicates that it is effective in a broad range of ED patients regardless of etiology, severity and age. In a randomized, double blind, placebo controlled study, in patients with ED due to diabetes mellitus (n=268), 57% of patients receiving sildenafil reported improved erections versus 10% on placebo (P<0.0001)<sup>19</sup>. Report of another randomized, double blind, placebo controlled, crossover, flexible-dose (up to 100mg) study<sup>20</sup> in patients with ED resulting from spinal cord injury have shown highly statistically significant score in sildenafil

group versus placebo. Improvement in erectile function was seen in 16 of 25 (64%) patients with no residual erectile function and 111 of 143 (78%) patients with erectile function (P<0.0001) after sildenafil (doses ranging from 25-100mg). Commonly reported adverse effects in trial 21 were headaches (16%), flushing (10%), dyspepsia (7%), nasal congestion (4%), urinary tract infection, diarrhea (all 3%), dizziness (2%) and abnormal vision, Till November 1998<sup>22</sup>, more than 6 million sildenafil prescriptions were dispensed and the FDA had reported 130 deaths in patients who were prescribed the drug in US. In 48 patients, causes of death were unknown, 41 patients had a known or suspected myocardial infarction, 27 had cardiac arrest, 3 had coronary artery disease. The interval between ingestion of sildenafil to death was between 4-5 hours (34%) patients, and time interval were unknown for 48% patients. Cardiovascular risk factors existed in 70% of patients<sup>22</sup>. It is contraindicated in patients taking nitrates or nitric oxide donors because of potential danger of hypotensive episodes and ischemia during coitus<sup>18</sup>. The drug should also be avoided in those for whom sexual activity carries a major cardiovascular risk. It should be used with caution or better avoided in patients with unstable angina, heart disease, with recent history (<6 months) of heart attack activity carries a major cardiovascular risk. It should be used with caution or better avoided in patients with unstable angina, heart disease, with recent history (<6 months) of heart attack, stroke or life threatening arrhythmia, hypotension or uncontrolled hypertension and retinitis pigmentosa<sup>23</sup>.

**Tadalafil :** Another PDE5 inhibitor tadalafil, had been shown to be about 20,000 to 44,000 and 800 times more selective inhibitor of PDE3 and PDE5 versus PDE5 respectively. Thus, the PDE5:PDE6 selectivity ratio of tadalafil more than 2 orders of magnitude higher than that of sildenafil. Further, the maximum serum tadalafil concentration is reached in 2 hours, but the geometric mean half-life of tadalafil is 17.5 hours<sup>24</sup>. This pharmacological profile is consistent with a broader clinical period of responsiveness. This long half-life (>17h), with a comfortably long window of opportunity, releases couples from the need to plan sexual activities and therefore provides the highest amount of spontaneity for sexual activities. Neither drug-related serious cardiovascular adverse events nor color vision disturbances were encountered in the European daily-dosing trial and placebo-controlled, fixed-dose (10-and 20-mg) trial in diabetic patients<sup>25</sup> with this drug.

**Vardenafil :** It is another selective, orally active PDE5 inhibitor with a mean tmax of 34 minutes and has already undergone phase 2 clinical trials. It has been shown to be effective in ED regardless of age, etiology, or severity of ED in a phase 3 trial. In these patients on the 20-mg dose, adverse events > 2% included flushing (10-11%), headache (15%) and dyspepsia (7%), vision disturbances (4%)<sup>26</sup>.

### Second line drug therapy

**Alprostadil :** Intra-cavernosal injection of PGE-1 causes smooth muscle relaxation and vasodilatation leading to erection. It is metabolized by enzyme prostaglandin 15-OH dehydrogenase, which is active in corpus cavernosum<sup>27</sup>. After IC injection, 96% of PGE-1 is locally metabolized within 1 hour and no change in peripheral blood levels has been observed<sup>28</sup>. Usually a good response is seen with a dose of 20µgm alprostadil. In one large

trial<sup>29</sup> (n=187) of ED patients, use of PGE-1 was associated with good erectile response and sexual satisfaction in 91% of recipients. In another open flexible dose study<sup>30</sup> (n=683) ED patients were given PGE-1. Out of those receiving PGE-1, 87% of patients reported a satisfactory sexual performance. In another trial,<sup>31</sup> comparing papaverine and phentolamine mixture (7.5-60mg papaverine + 0.25-2 ng phentolamine) with alprostadil 10-20mcg), adequate erection was seen in 67.1% of 51 patients given papaverine + phentolamine mixture and in 79.1% of 76 patients given alprostadil side effects reported were pain at injection site (16.1%), ecchymosis and hematoma (1.5%), priapism (1.3%). The incidence to priapism was less in comparison to papaverine.

Alprostadil can also be given trans-urethraly and the technique is called as medicated Urethral System for Erection (MUSE). It involves the placement of PGE-1 pellet into the urethra by an applicator after the man has passed urine. Within 10 min, up to 80% of PGE-1 is absorbed by the urethral mucosa, leading to a significant increase in cavernosal artery blood flow. The effectiveness of MUSE was studied in a double blind placebo controlled prospective study<sup>32</sup> where in 1511 men aged between 27 and 88 years with ED of varying etiology were enrolled. In clinical testing with MUSE, an erection adequate for intercourse was attained in 65.9% of administration. The MUSE was found to be effective regardless of age of the patient and etiology of ED. The most common side effect reported was penile pain.

In a direct comparative trial of IU and IC alprostadil, Porst showed that IC alprostadil had clinical advantages over the IU administration route. The percentage of subjects showing completely rigid erections with maximal cavernous smooth-muscle relaxation was 48 and 10% respectively. Moreover the rate of penile pain or burning was nearly 3 times higher with IU than IC alprostadil and circulatory adverse events (e.g., dizziness, sweating, hypotension) were reported only in the IU alprostadil group<sup>33</sup>.

### **Third Line drug therapy :**

**Apomorphine :** It has been found to work effectively in patients of ED with a wide range of etiology, severity and co-morbidity. It is well tolerated if given by sublingual (SL) route. In a cross-over study comparing apomorphine (3mg SL) with placebo, it produced a rapid response with 71% of erections occurring within 20min<sup>34</sup>. Three mg apomorphine SL was significantly more effective than placebo ( $p < 0.001$ ) for the percentage of attempts resulting in erections firm enough for intercourse and resulting in intercourse, as assessed by both patient and partner. Median time to erection was 18.8 min. About 5% of patients treated with this medication at a dose of 2mg or 3mg report nausea, and the recommended dose regimen of apomorphine SL can cause a transient vasovagal syndrome (incidence  $< 0.2\%$ ) with fainting/syncope<sup>34</sup>.

**Phentolamine :** It is non-specific alpha-receptor antagonist that has been shown to have erectogenic activity. In one study erectile response rates of 30-40% were reported with buccal administration of phentolamine compared with 15-20% with placebo<sup>35</sup>. Lawless and Cree<sup>36</sup> reviewed the clinical efficacy of phentolamine in ED. They concluded that patients with non-organic dysfunction received the greatest effect of phentolamine, with that effect possibly being dose dependent as well. Oral route provided a much better response in comparison to buccal phentolamine of lower dosages.

**Yohimbine :** It is an orally administered iminoalkaloid alkaloid agent with peripheral alpha-2 adrenergic receptor blocker activity and central noradrenergic agonist activity. In a double-blind partial cross-over study<sup>37</sup>, 82 patients with ED were given yohimbine. After 1 month of treatment, 14% experienced full and sustained erection, 20% reported partial response and 65% reported no improvement. The 34% response was encouraging because there was a high incidence of diabetes and vascular pathological condition in the population enrolled in the study. It appears that yohimbine may be useful in younger patients, with ED of shorter duration ( $< 2$  years), independent of the degree of severity. The recommended dose is 27 mg given 30 min prior to sexual activity<sup>38</sup>. The most common adverse effects with yohimbine include anxiety, increased urinary frequency, tachycardia, and increased arterial pressure<sup>38,39</sup>. In a trial by Rowland et al,<sup>40</sup> the more common adverse effects in the yohimbine group included disturbed sleep, mild diarrhea, lack of energy, and, surprisingly, lower sexual desire. Susset et al<sup>38</sup> assessed 82 patients with ED of mixed causes to study which patients might benefit most from yohimbine treatment. Patients received either placebo or 5.4mg of yohimbine four times daily. The dose of yohimbine was gradually increased to 10.8 mg four times daily throughout the 4-week study. Positive results were found in 34 percent of patients taking yohimbine. The authors found that patients who had mild dysfunction, short duration of erectile dysfunction (less than 2 years), lower levels of arterial insufficiency, and high-normal testosterone levels responded significantly better. Thus, yohimbine is not a very effective agent for organic ED patients and should be preferably used for psychogenic or non-organic ED. However, Hatzichristou and Pescatori<sup>41</sup> who reviewed treatment of erectile dysfunction concluded that studies demonstrating significant efficacy of Yohimbine suffer from methodological flaws and therefore do not have a significant advantage even in psychogenic ED.

**Moxisylyte hydrochloride :** It is alpha-1 selective adrenergic blocker. In a placebo controlled study<sup>42</sup> in patients of neurogenic ED, an IC injection of 10-30 mg of moxisylyte resulted in a complete erection in 58% patients compared with 0% in placebo group. A study showed that in comparison to PGE-1, the efficacy of moxisylyte is quite low. While moxisylyte resulted in successful sexual intercourse in 46% of patients, 81% patients using PGE-1 reported sexual intercourse. Thus moxisylyte is only of value in patients who cannot tolerate PGE-1 induced pain, fibrosis of priapism.

**Pentoxifylline :** Patients taking this drug for treatment of claudication of lower limbs reported improved sexual function while on this medication<sup>43</sup>. Therefore, pentoxifylline 1.2 g in three divided doses orally for 8 weeks was assessed in patients with ED due to borderline arterial insufficiency (n=36) in ED patients. Therapy was found to increase peak systolic velocities (PSVs) at the end of the treatment. The mean change in PSV achieved by pentoxifylline treatment (6.25 cm/s) was significantly higher than that achieved by placebo (0.38 cm/s). Seven patients had a positive response (successful coitus achieved after treatment with pentoxifylline). No serious side effects were reported<sup>44</sup>.

**Serotonergic drugs :** In experimental studies, serotonergic system had exhibited an inhibitory effect on sexual behavior and therefore agents with anti-serotonergic properties have been tried in ED<sup>45</sup>. In a double blind, randomized, placebo controlled trial<sup>46</sup>, trazodone,

ketanserin, and mianserin given orally were investigated in terms of effectiveness in ED. Patients aged 23-68 years believed to have ED of non-organic etiology were selected on the basis of their response to intra-cavernosal papaverine. The patients were randomized into 4 groups, 25 in each group received 50mg trazodone tid or 20 mg ketanserin bid or 10mg mianserin tid or placebo for 30 days. The positive response in trazodone group was higher (65.2%) as compared to ketanserin (19%), mianserin (31.6%) and placebo (13%). In trazodone group, one patient reported priapism, one experienced severe sedation, while two had xerostomia and one blurred vision. Currently these drugs have no role in the management of ED because of their limited efficacy, greater side effects and availability of safer agents.

**Papaverine :** Papaverine inhibits phosphodiesterase enzyme leading to an increased cAMP and cGMP in penile erectile tissue. It also blocks voltage dependent calcium channels, decrease in calcium influx and impairment to calcium activated potassium and chloride currents<sup>47</sup>. All these mechanisms lead to relaxation of cavernous smooth muscle cells and penile vessels. Papaverine, metabolized in liver has a half-life of 1-2 hours. It has been shown to be effective in both psychogenic and neurogenic ED. The advantages are its low cost and stability at room temperature. Important side effects are priapism (up to 35%), corporal fibrosis (up to 33%) and elevation of liver enzymes.

#### Therapies under development

**Vasoactive intestinal polypeptide (VIP):** VIP, originally isolated from small intestine, is a potent smooth muscle relaxant. It is proposed that VIP may be a neurotransmitter for penile erection. Studies showed that IC injection of VIP only leads to tumescence and does not produce rigid erection<sup>48</sup>. Therefore, it was combined with other drugs like phentolamine and was found to be very effective<sup>49</sup>. In a study of 52 men with ED of mixed etiology who exhibited full response to papaverine, IC injection of 30µg + 0.5-2 mg phentolamine led to a functionally rigid erection in 100% cases. Even after 6 months of follow up, there were no complaints of pain, corporeal fibrosis or priapism. The combination of VIP and phentolamine is efficacious and a safe alternative for patients who suffer from PGE-1 induced pain.

**Calcitonin gene related peptide (cGRP):** It is a potent vasodilator and has been shown to relax strips of cavernosal smooth muscles *in vitro*. Immunohistochemical techniques have localized cGRP in cavernosal nerves, within the walls of cavernous arteries and in cavernous smooth muscles<sup>50</sup>. Moreover, cGRP injection induced an increase in the penile arterial inflow, cavernous smooth muscle relaxation and cavernous outflow occlusion. Dose-related increase in penile blood flow. Clinically the combination of cGRP and alprostadil has been reported to be effective in 56% of patients in whom other drugs had failed<sup>51</sup>. Systemic side effects included facial flushing and hypotension. cGRP is contraindicated in sickle cell anemia, severe psychiatric disorders like schizophrenia and severe venous incompetence.

**Transcutaneous nitroglycerin :** Using ultrasound, Heaton et al<sup>52</sup> have showed a 46% increase in penile arterial diameter 10min after applying glyceryl trinitrate locally to the shaft of penis. In a randomized placebo controlled study<sup>53</sup> of transcutaneous nitroglycerin therapy in 26 patients with ED, satisfactory sexual function was reported in 46% of patients and some erectile

improvement in a further 35% while placebo showed an improvement in only 1 patient. Headache was the most common side effect noted and 15% of patients were excluded from the trial because of persistent headache.

#### Topical Creams

**Triple Vasodilator Combination :** A topical cream containing 3 vasodilators (3% aminophylline 0.25% isosorbide dinitrate and 0.05% codergocrine mesylate) was evaluated in a double blind placebo controlled cross over study<sup>54</sup> in 36 men with ED of mixed etiology. Results showed that 58% of men using cream attained an erection adequate for sexual intercourse compared to 8% using the placebo. The cream was particularly effective in men with psychogenic ED. With duplex scanning, a significant increase in penile arterial flow was observed on application of the cream as compared to the placebo.

#### Mechanical Intervention

**Vacuum erection devices (VEDs):** These devices use a vacuum pump to increase blood flow to the corpora cavernosa to induce an erection. They also have a constrictor ring to retain blood within the corpora and thus maintain the erection. VEDs are a safe, reasonably affordable and effective and can be offered as a noninvasive first-line therapy, particularly in patients for whom oral drug therapy is contraindicated. However VEDs are cumbersome to use and lack spontaneity. As this technique is based on the retention of static blood within the corpora, it can cause penile coldness. Further skin bruising may also occur in some patients.

**Penile vascular surgery :** It should only be used in young impotent patients, with pure arteriogenic impotence secondary to blunt pelvic or perineal trauma and with no evidence of generalized atherosclerosis of other vascular risk factors.

**Penile Implants :** The most invasive and usually the last resort in the treatment of ED is insertion of a penile implant. This procedure is usually performed when all other methods or drugs fail. Penile implants are more reliable but have the disadvantage of potential life changing surgery. It is important to inform the patient that penile implants surgery is irreversible.

#### Conclusion :

With the increase in geriatric population and diabetes, the number of patients with ED is bound to increase in near future. Therefore physicians have to be updated about the therapeutic options available. It is mandatory to obtain a detailed medical history with a thorough medical examination before diagnosing ED. Apart from PDE5 inhibitors and others under development (e.g., vardenafil), treatment with the dopamine agonist apomorphine, local therapies with vasoactive agents (e.g., alprostadil) either alone or in combination with PDE5 inhibitors, and penile implants represent sound second-and third-line clinical options. Intra-cavernosal therapy suffers from a high rate of discontinuation because of pain at the site of injection, ecchymosis and priapism. Sildenafil has come out as a boon in patients with ED. But it should be cautiously prescribed in patients with cardiovascular risk. Along with drugs psychotherapy plays a major role in treating ED. Lawless and Cree, 1998 reviewed the data of various treatment modalities in ED on the basis of subjective benefit to the patient and safety, tolerability, efficacy, and cost-effectiveness of

therapy. They concluded that yohimbine is effective in 60 to 80% of patients of psychogenic ED and not effective in organic ED. Sildenafil is effective in 56 to 85% of ED of mixed etiology and >80% effective in patients with non-organic ED. Phentolamine was 30 to 40% effective in combined populations and 70% effective in purely non-organic ED (Lawless and Cree, 1998). In comparison to these oral therapies, vacuum constriction devices have a success rate of >80% for achieving an erection sufficient for intercourse, and penile injection therapy has a success rate >89% for all causes of dysfunction. Thus in comparison with these therapies, the efficacy of oral medications was quite less. However, drugs are still preferred over the non-drug modalities as they are non-invasive and allow more spontaneity.

## References

- Furlow WL. Prevalence of impotence in the United States. *Medical Aspects of Human Sexuality*. 1985;19:13-16.
- Walsh AB, Retik ED, Vaughan AJ, Wein WB, Tom F Lue. Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. *Campbell's Urology 7th Edn. Vol-II*. 1998;1157-1179.
- Finkle AL, Taylor SP. Sexual potency after radical prostatectomy. *J Urol*. 1981;125:350.
- McDermott DW, Bates RJ, Heney NM, Althausen A. Erectile impotence as complication of direct vision cold knife urethrotomy. *Urology*. 1981;18:467-469.
- Jevitch MJ, Edson N, Jaman WD. Vascular factors in erectile failure among diabetics. *Urology*. 1982;19:163-168.
- Michal V, Ruzbarsky V, Zorniootti AW, Rossi G. Histological changes in the penile arterial bed with aging and diabetes. *Proceedings of the First International Conference on corpus cavernosum revascularization*. 1980;113-119.
- Cunningham GR, Hirshkowitz M, Korenman SG, Karacan I. Testosterone replacement therapy and sleep-related erections in hypogonadal men. *J Clin Endocrinol Metab*. 1990;70:792-797.
- Metz P, Ebbehøj J, Uhrenholdt A, Wagner G. Peyronie's disease and erectile failure. *J Urol*. 1983;130:1103-1104.
- Wein AJ, Van AK. Drug induced male sexual dysfunction. *Urol Clin North Am*. 1988;15:23-31.
- Karacan I, Williams RL, Thornby JT. Sleep-related penile tumescence as a function of age. *Ann J Psych*. 1975;132:932.
- Barry JM, Bkank B, Boileau M. NPT monitoring with stamps. *Urology*. 1980;15:171.
- National Institutes of Health. Impotence. Consensus development Conference statement. *Int J Impot Res*. 1993;5:181.
- Karacan I, Scott PJ, William RL. The role of the sleep lab in treatment of impotence. *Williams Textbook of Sleep Disorders, Diseases and Treatment*. 1982.
- Lue TF, McClure RD. Functional devaluation of penile arteritis with papaverine. *Contemporary management of impotence and infertility*. 1988;57-64.
- Kirby Rs. Impotence: diagnosis and management of male erectile dysfunction. *EMJ*. 1994;308:957-961.
- Lue TF, Hricak H, Marich KW, Tarago EA. Vasculogenic impotence evaluated by high resolution ultrasonography and pulsed Doppler spectrum analysis. *Radiology*. 1985;155:777-781.
- Boolel M, Gopi AS, Gingell JC, Allen MJ. Sildenafil a novel effective oral therapy for male erectile dysfunction. *Br J Urol*. 1996;78:257-261.
- Morales A, Gingell C, Collins M, Wickes PA, Osterloh JH. Clinical safety or oral sildenafil citrate (Viagra™) in the treatment of ED. *Int. J. Impot. Res*. 1998;10:69-74.
- Rendell TS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of ED in men with diabetes: a randomized controlled trial. *JAMA*. 1999;281:421-6.
- Holmgren E, Givliano F, Hultling C. Sildenafil (Viagra™) in the treatment of ED caused by spinal cord injury: a double blind placebo controlled, flexible dose, two way cross over study. *Neurology*. 1997;50:A127.
- Osterloh I, Eardley I, Carson C, Padma-Nathan H. Sildenafil: a selective phosphodiesterase PDE 5 inhibitor in the treatment of ED. In: Carson C, Kirby R, Goldstein I (eds). *Textbook of Erectile Dysfunction*. Isis Medical Media: Oxford. 1999;285-308.
- US food and drug administration. Postmarketing safety of sildenafil citrate (viagra). 24 Nov 1998, Rockville, USA.
- Goldstein I et al. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *New Eng J Med*. 1998;338:1397-1404.
- Padma-Nathan H, Rosen RC, Shabsingh R, Saikali K, Watkins V, Pullman B. IC351 (Cialis) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction (ED). Program and abstracts of the 96th Annual Meeting of the American Urological Association; June 2-7,2001; Anaheim, California.
- Porst H. IC351 (tadalafil, Cialis): update on clinical experience. *Int J (Impot Res 2002 Feb;14 Suppl 1):S57-64*.
- Porst H, Rosen R, Padma-Nathan H, et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. *Int J Impot Res*. 2001;13:192-199.
- Roy AG, Adaiakan PG, Sen DK, Ratnam SS. Prostaglandin 15-OH dehydrogenase activity in human penile corpora cavernosa and its significance in PG-mediated penile erection. *Br J Urol*. 1989;64:180.
- Van Ahlen H, Perkar BA, Sticht G, Hertfelder HJ. Pharmacokinetics of vasoactive substances administered into the human corpus cavernosum. *J Urol*. 1999;151:1227.
- Porst H, Von Ahlen, Block T, Block T, Halbig W, Hautaman R, Lochner-Ernst. Intracavernosal self injection of prostaglandin E1 in the therapy of erectile dysfunction. *VASA* 1989;28 (suppl): 50-56.
- Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. *N Eng J Med*. 1996;334:873-877.
- Lui SMC, Lin JSN. Treatment of impot: Comparison between the efficacy and safety of IC injection of papaverine plus phentolamine [rigitine] and PGE<sub>1</sub>. *Int J Impotence Res*. 1990;1:147.
- Padma-Nathan H, Hellstrom MJC, Kaiser FE. Treatment of men with erectile dysfunction with transurethral alprostadil. *N Engl J Med*. 1997;336:1-7.
- Porst H. Transurethral alprostadil with MUSE (medicated urethral system for erection) vs intracavernous alprostadil-comparative study in 103 patients with erectile dysfunction. *Int J Impot Res*.1997;9:187-192.
- Dula E, Bukofzer S, Perdok R, George M, and the Apomorphine SL Study Group. Double-blind crossover comparison of 3mg apomorphine SL with placebo and with 4mg apomorphine SL in male erectile dysfunction. *Eur Urol*. 2001;39:558-564.
- Wagner G, Lucy S, Levir R, Zogniothi A. Buccal phentolamine: a pilot trial for male erectile dysfunction at 3 separate clinics. *Int J Impotence Res*. 1994;Suppl-1:D-78.
- Lawless C, Cree J. Oral medications in the management of erectile dysfunction. *J Am Board Fam Pract*. 1998 11(4):307-14.
- Morales A, Condra M, Owen JA, Surridge DH, Fenemore J and Haris C. Is yohimbine effective in the treatment of organic impotence? Results of a controlled trial. *J Urol*. 1987;137:1168.
- Susset JG, Tessier CD, Wincze J, Bansal S, Malhotra C, Schwacha MG. Effect of yohimbine hydrochloride on erectile impotence: a double blind study. *J Urol*. 1989;141:1360-1363.
- Mann K, Klingler T, Noe S, Roschke J, Muller S, Benkert O. Effects of yohimbine on sexual experiences and nocturnal

- penile tumescence and rigidity in erectile dysfunction. Arch Sex Behav 1996;25:1-16.
40. Rowland DL, Kallan K, Slob AK. Yohimbine, erectile capacity, and sexual response in men. Arch Sex Behav 1997;26:49-62.
  41. Hatzichristou DG, Pescatori ES. Current treatment and emerging therapeutic approaches in male erectile dysfunction. BJU International 2001;88(suppl).31:11-17.
  42. Costa P, Sarrazin B, Bressolle F, Mottet N, Louis JF, Saudoiray F. Is the volume injected, a parameter likely to influence the erectile response observed after intracavernosal administration of an alpha blocking agent. Eur Urol. 1993;24:43-47.
  43. Allenby KS, Burris JF, Mroczek WJ. Pentoxifylline in the treatment of vascular impotence—case reports. Angiology. 1991;42:418.
  44. Peskircioglu L, Karabulut A, Deniz E, Germiyanoglu C, Erol D. The role of pentoxifylline in the treatment of erectile dysfunction due to borderline arterial insufficiency. Br J Urol 1996;77:563-565.
  45. Andersson KE, Wagner G. Physiology of penile erection. Physio Rev. 1995;75:191-236.
  46. Kurt U, Ozkardes H, Ugor A, Germiyanoglu C, Gordal M, Erol D. The efficacy of antiserotonergic agents in the treatment of erectile dysfunction. J Urol. 1994;152:407.
  47. Brading AF, Burdyga TV, Scripnyuk ZD. The effect of papaverine on the electrical and mechanical activity of the guinea pig ruets. J Physiol. 1983;334:79.
  48. Wagner G, Gerrtenberg TC. Intracavernosal injection of VIP does not induce erection in man. World J Urol. 1987;5:7.
  49. Gerrtenberg TC, Metz P, Ottenren Fabrenkrig J. Intracavernosal self injection with VIP and phentolamine in management of erectile failure. J Urol 1992;147:1277-1279.
  50. Steif C, Bernard F, Bosch RULH, Aboscif SR, Lue TF, Tanagho EA. A possible role for calcitonin gene-related peptide in the regulation of the smooth muscle tone of the bladder and penis. J Urol. 1990;143:392.
  51. Djamilian M, Stief CG, Kvezyk M, Jonas U. Follow up results of a combination of CGRP and PGE-1 in treatment of erectile dysfunction. J Urol. 1993;149:1296-1298.
  52. Heaton JP, Moralert OJ. Topical glyceryltrinitrate causes measurable penile arterial dilatation in impotent men. J Urol. 1990;143:729.
  53. Claes H, and Baert L. Transcutaneous nitroglycerine therapy in the treatment of impotence. Urol Int. 1989;44:309-312.
  54. Gomma A, Shalaby M, Osman M, Eissa M, Ezzat A, Mahmoud M. Topical treatment of erectile dysfunction: a randomized double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate and co-dergocrine mesylate. BMJ.1996;312:1512-1515.

#### ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails on new drugs, a number of diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest and distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

#### Literature Review

Compiled by Dr. PD Gulati

**Decline of renal function is associated with proteinuria and systolic blood pressure in the morning in diabetic nephropathy.** Suzuki H, Kanno Y, Nakamoto H, Okada H, Sugahara S. *Clin Exp Hypertens.* 2005 27(2-3):129-38.

The aim of this study was to investigate a significance of increased proteinuria in the morning and the effects of antihypertensive treatment on proteinuria and arterial blood pressure in the progression of chronic renal insufficiency in type 2 diabetic patients with hypertension and nephropathy. In three 24-hr urine samples and blood pressure monitoring, separated into a night- and daytime and spot urine in the morning, variation in protein-creatinine ratio (g/g) and blood pressure were assessed in 24 (58 ± 3years old; M/F: 17/7) diabetic patients with hypertension and nephropathy. Furthermore, the effects of antihypertensive therapy of combinations of angiotensin converting enzyme (ACE) inhibitor, calcium antagonists, diuretics, and alpha blocker were evaluated in 3 years. Home blood pressure measurement was carried out every month and 24-hr urine was collected every 2 months. The baseline urine excretion of protein-creatinine ratio and blood pressure were (1.22 ± 0.13 g/g creatinine: 154/96 ± 6/5 mmHg) in daytime and (1.39 ± 0.13: 168/88 ± 15/7) in the morning. At the end of the study, significant associations among a decline of 24-hr creatinine clearance and both of the urine excretion of protein-creatinine ratio (r=0.47, p<.01) and the levels of systolic blood pressure (r=0.46, P<.01) and between the levels of systolic blood pressure and the urine excretion of protein-creatinine ratio in the morning (r=0.57, p<.001) were demonstrated. However, there were no significant associations among other variables. Analysis of patients who had systolic blood pressure in the morning less than 140 mmHg revealed that 65% of these patients received doxazosin-averaged

doses of 4.8 ± 1.5mg daily. The levels of both blood pressure and proteinuria-creatinine ratio in the morning mainly associate with progression of renal function in diabetic patients with hypertension and nephropathy.

**Why Are Indian More Prone to Diabetes.** V. Mohan. *JAPI.* 2003; 780-781.

Diabetes, a global public health problem, is now emerging as a pandemic and by the year 2025, three-quarters of the world's 300 million adults with diabetes will be in non-industrialized countries and almost a third in India and China alone. There is evidence from several studies that the prevalence of Type 2 diabetes is increasing in migrant Indians. Today, the prevalence of diabetes in the urban metros of India is approaching the figures reported in the affluent migrant Indians. Environmental and lifestyle changes resulting from industrialization and migration to urban environment from rural settings may be responsible to a large extent, for this epidemic of Type 2 diabetes in Indians. Obesity, especially central obesity and increased visceral fat due to physical inactivity, and consumption of a high-calorie/high-fat and high sugar diets are major contributing factors. There is also strong evidence that Indians have a greater degree of insulin resistance and a stronger genetic predisposition to diabetes. As several of the factors associated with diabetes are potentially modifiable, the epidemic of diabetes can be curbed if proper measures are taken to increase physical activity and reduce obesity rates in adults, and most importantly, in children. In addition, strategies to achieve healthy fetal and infant growth and encouraging the use of traditional diets rich in fibre are also important steps. Such interventions should be attempted in those who are genetically predisposed to diabetes in order to tackle explosion of, and thereby reduce the burden due to, diabetes within the Indian subcontinent.

# The Threat of Bioterrorism, Clinical Recognition and Management

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**Abstract:** Bioterrorism is an emerging public health and infection control threat. Potential biological agents include smallpox, plague, botulinum toxin, brucellosis, Q fever, viral encephalitis, haemorrhagic fever and staphylococcal enterotoxin B. An understanding of the epidemiology, clinical manifestation, and the management of the more likely candidate agent is critical to limiting morbidity and mortality from biological events. Effective response requires an increase index of suspicion for usual diseases or syndromes, with prompt reporting to health authorities to facilitate recognition of outbreak and subsequent intervention. The clinical manifestation and management is discussed in this review.

**Key Words :** *Biological warfare, Bioterrorism.*

## Introduction

Biological weapons include any organism or toxin found in nature that can be used to incapacitate, kill or otherwise impede an adversary. Biological weapons are characterized by low visibility, high potency, substantial accessibility, and relatively easy delivery. Prior to the 20th century, biological warfare took on 3 main forms: (1) deliberate poisoning of food and water with infectious material, (2) use of microorganisms or toxins in some form of weapon system, and (3) use of biologically inoculated fabrics.

In the 12th century AD, during the battle of Tortona, Barbarossa used the bodies of dead soldiers to poison wells. In the 14th century AD during the siege of Kaffa, the attacking Tartar force hurled the corpses of those who died of plague into the city to attempt to inflict a plague epidemic upon the enemy<sup>1</sup>. Biological warfare became more sophisticated against both animals and humans during the 1900s. During World War I, the Germans developed anthrax, glanders, cholera, and a wheat fungus for use as biological weapons. In 1925, the Geneva Protocol was signed by 108 nations, including the 5 permanent members of the UN Security Council. This was the first multilateral agreement that extended prohibition of chemical agents to biological agents<sup>2</sup>. No method for verification of compliance was addressed. Currently, 17 countries are suspected of having an offensive BW program. Dissemination of BW agents may occur by aerosol sprays, explosives (artillery, missiles, detonated bombs), or food or water contamination. *Preliminary criteria for suspicious outbreak of disease that could provide indications of a possible biological weapons include the following :* (i) Disease (or strain) not endemic; (ii) Unusual antibiotic resistance patterns; (iii) Atypical clinical presentation; (iv) Case distribution geographically and/or temporally inconsistent (eg, compressed time course); (v) Other inconstant elements (eg. number of cases, mortality and morbidity rates, deviations from disease occurrence baseline)

## Anthrax

*Bacillus anthracis* is a large, aerobic, gram-positive, spore forming, nonmotile bacillus. Infection occurs predominantly through the cutaneous route and only rarely via the respiratory or gastrointestinal (GI) route<sup>3</sup>.

(i) *Cutaneous* : more than 95% of cases of anthrax are cutaneous. After inoculation, the incubation period is 1-5 days. The disease first appears as a small papule that progresses over 1-2 days to a vesicle containing serosanguinous fluid with many organisms and a paucity of leukocytes. The vesicle ruptures,

leaving a necrotic ulcer. The ulcerbase develops a characteristic 1- to 5-cm black eschar<sup>4</sup>. (The black appearance of the eschar gives anthrax its name [Greek *anthrakos* = coal].

(ii) *Inhalation* : Also known as **wool sorter's disease**. Initial manifestations are nonspecific and this is followed by the sudden onset of increasing respiratory distress with dyspnea, stridor, cyanosis, increased chest pain, and diaphoresis. pneumonia is an uncommon finding. Mortality is nearly 100% despite appropriate treatment. Inhalation anthrax is the most likely form of disease to follow military or terrorist attack<sup>5</sup>.

*Treatment* : Most naturally occurring strains of anthrax are sensitive to penicillin, and penicillin historically has been the preferred therapy for the treatment of anthrax. Experts currently recommend initiation of ciprofloxacin or other fluoroquinolones in adults with presumed inhalation anthrax infection. Following a terrorist attack, resistance to penicillin and tetracycline class antibiotics is assumed until laboratory testing demonstrates otherwise. In adults, ciprofloxacin 400mg IV q12h is recommended. Traditionally, ciprofloxacin and other fluoroquinolones are not recommended for use in children younger than 16-18 years because of a link to permanent arthropathy in adolescent animals and transient arthropathy in small number of children. Balancing these small risks against the real risk of death and resistant strains of *B anthracis*, experts recommend that ciprofloxacin be given to a pediatric population for initial therapy or postexposure prophylaxis following anthrax attack. In children, ciprofloxacin at 20-30 mg/kg/d IV in 2 daily doses (not to exceed 10g/d) is recommended. If antibiotic susceptibility testing allows, substitute intravenous penicillin for the fluoroquinolones. For adults and children older than 12 years, penicillin G at 4 million U IV q4h is recommended for 60 days. Doxycycline at 100mg IV q12h for 60 days is an acceptable alternative for adults. For children younger than 12 years, penicillin G is dosed 50,000 U/kg q6h for 60 days.

*Prevention* : No FDA-approved chemoprophylactic regimens are available following exposure to an anthrax aerosol. For postexposure prophylaxis, experts recommend the same oral regimen as that recommended for treatment of mass casualties<sup>7</sup>. A licensed vaccine, an aluminum hydroxide-adsorbed preparation, is derived from culture fluid supernatant taken from an attenuated strain. The vaccination series consists of 6 subcutaneous doses at 0, 2, and 4 weeks, then at 6, 12, and 18 months, followed by annual boosters. If information indicates that a BW attack is imminent or may have occurred, prophylaxis of unimmunized

individuals with ciprofloxacin (500 mg PO bid) or doxycycline (100mg PO bid) is recommended. Should an anthrax attack be confirmed, continue chemoprophylaxis for at least 4 weeks and until all those exposed receive 3 doses of vaccine (at 0, 2, and 4 wk).

## Plague

Plague is a zoonotic infection caused by *Yersinia pestis*, a gram-negative coccobacillus. Throughout history, the oriental rat flea (*Xenopsylla cheopis*) has been largely responsible for spreading bubonic plague.

**Clinical features :** Plague is characterized by the abrupt onset of high fevers, painful lymphadenopathy, and bacteremia. Septicemic plague sometimes can ensue from untreated bubonic plague or, de novo, after a fleabite. Patients with the bubonic form of the disease may develop secondary pneumonic plague. Pneumonic plague is the most severe form of disease and, untreated, has a mortality rate approaching 100%. If *Y. pestis* were used as BW agent, it most likely would be inhaled as an infectious aerosol and result in primary pneumonic plague (epidemic pneumonia)<sup>8</sup>. If fleas were used as carriers of disease, bubonic or septicemic plague would result. Patients typically have a productive cough with blood-tinged sputum within 24 hours of symptom onset.

**Treatment :** Isolate patients with plague for the first 48 hours after treatment initiation. If pneumonic plague is present, continue isolation for 4 days. Since 1948, streptomycin has been the treatment of choice for bubonic, septicemic, and pneumonic plague. It is administered in a dose of 30 mg/kg/d IM divided bid. In patients with meningitis or hemodynamic instability, intravenous chloramphenicol (50-75 mg/kg/d) divided qid dose is added. Gentamicin has had much less clinical usage but can be used as an alternative to streptomycin. Treatment is continued for a minimum of 10 days or 3-4 days after clinical recovery. In patients with very mild bubonic plague who are not septic, tetracycline can be used orally at a dose of 2 g/d divided qid for 10 days. Doxycycline, ofloxacin, and ceftriaxone have been demonstrated to be effective in animal models<sup>9</sup>.

**Prevention :** Contacts of patients with pneumonic plague and individuals who have been exposed to aerosols are treated with tetracycline 15-30 mg/kg/d divided qid for 6 days. If tetracycline is not available, doxycycline 100mg bid is an effective alternative. Only individuals at high risk for plague should be immunized with a licensed, killed, whole cell vaccine<sup>10</sup>.

## Cholera

Cholera is an acute and potentially severe GI disease caused by *Vibrio cholerae*. *V. cholerae* is a short, curved, motile, gram-negative, nonsporulating rod. Two serogroups (O1, O139) have been associated with cholera in humans. The O1 serotype exists as 2 biotypes, classical and El Tor<sup>11</sup>. They do not invade the intestinal mucosa but rather adhere to it. Cholera is the prototype toxigenic diarrhea, which is secretory in nature.

**Clinical Features :** Infection generally occurs within a week of exposure and is classically of abrupt onset following a brief nonspecific prodrome. The syndrome is characterized by sudden onset of nausea and vomiting and profuse diarrhea with a classic rice water appearance. The rapid loss of body fluids often leads to toxemia and frequent cardiovascular collapse.

**Treatment :** Treatment depends on replacement of fluids and electrolyte losses. This is best accomplished using oral rehydration therapy, but intravenous fluid replacement is occasionally necessary for persistent vomiting or high rates of stool loss (10mL/kg/h). Antibiotics shorten the duration of diarrhea and reduce fluid losses.

Tetracycline (500 mg q6h for 3d) or doxycycline (300mg once or 100mg bid for 3d) is an acceptable alternative. However, due to resistance, ciprofloxacin (500mg q6h for 3d) or erythromycin (40mg/kg/d divided qid for 3d) also has been accepted<sup>12</sup>.

**Prevention :** A licensed, killed vaccine is available for use in those considered to be at risk for exposure. The vaccination schedule is an initial dose followed by another dose 4 weeks later, with booster doses every 6 months. An inactivated oral vaccine (WC/rBs) is safe and provides rapid short-term protection. WC/rBs requires 2 doses and has approximately 85% efficacy lasting 2-3 years for both El Tor and classic biotypes.

## Brucellosis

Brucellosis is a zoonotic infection of domesticated and wild animals caused by an organism of the genus *Brucella*. The ease of transmission by aerosol suggests that *Brucella* species may be useful as a BW agent<sup>13</sup>. The disease often becomes chronic and may relapse, even with appropriate treatment.

*Brucella* species are small, nonmotile, nonsporulating, aerobic, gram-negative coccobacilli that may represent a single species. Only *Brucella melitensis*, *Brucella suis*, *Brucella abortus*, and *Brucella canis* cause disease in man. *Brucella* species can enter mammalian hosts through skin abrasions or cuts, the conjunctiva, the respiratory tract, and the GI tract.

**Clinical Features :** Patients usually have nonspecific symptoms such as fever, sweats, fatigue, anorexia, and muscle or joint aches. Neuropsychiatric symptoms, focal infection of bones, joints, or the genitourinary tract may occur. Cough and pleuritic chest pain also may be noted. Pyelonephritis, cystitis, and in males, epididymo-orchitis may occur. Hepatitis and rarely, liver abscess also occur. *Brucella* endocarditis, a rare but feared complication, accounts for 80% of deaths from brucellosis.

**Treatment :** Therapy with a single drug has resulted in a high relapse rate, so use combined antibiotic regimens is used whenever possible. A 6-week regimen of doxycycline 200mg/d PO with the addition of streptomycin 1g/d IM for the first 2 weeks is effective in most adults with most forms of brucellosis. Patients with spondylitis may require longer treatment. A 6-week oral regimen with both rifampin 900 mg/d and doxycycline 200mg/d is effective. Endocarditis likely is best treated with a combination of rifampin, streptomycin, and doxycycline for 6 weeks.

## Q Fever

Q fever is a zoonotic disease caused by *Coxiella burnetii*, a rickettsialike organism of low virulence but remarkable infectivity. The potential of *C. burnetii* as a BW agent is related directly to its infectivity. It has been estimated that 50 kg of dried *C. burnetii* would produce casualties at a rate equal to that of similar amounts of anthrax or tularemia organisms<sup>14</sup>.

**Clinical Features :** Q fever in humans may be manifested by asymptomatic seroconversion, acute illness, or chronic disease. Dever, chills, and headache are the most common signs and symptoms. Diaphoresis, malaise, myalgias, fatigue, and anorexia are also common. Encephalopathic symptoms and acute hepatitis have been reported. Chronic infection with *C. burnetii* usually is manifested by infective endocarditis, which also is the most severe complication of Q fever.

**Treatment :** Tetracycline has been the mainstay of therapy since the 1950s. Macrolide antibiotics, such as erythromycin and azithromycin, are also effective. In cases of infective endocarditis at least 2 years of therapy are required, usually with a tetracycline combined with rifampin or a quinolone, although trimethoprim-

sulfaethoxazole also has been used<sup>15</sup>.

**Prevention** : Although an effective vaccine (Q-Vax) is licensed in Australia, all Q fever vaccines used in the US are investigational. Q fever can be prevented by immunization.

## Smallpox

Variola, the causative agent of smallpox, is the most notorious of the poxviruses (family Poxviridae). In 1980, the World Health Organization (WHO) declared endemic smallpox eradicated, with the last occurrence in Somalia in 1977. Variola represents a significant threat as a BW agent. Currently, 2 WHO-approved and inspected repositories remain: the CDC in the US and Vector Laboratories in Russia; however, clandestine stockpiles may exist. Variola virus is highly infectious by aerosol, environmentally stable, and can retain infectivity for long periods<sup>16</sup>.

**Clinical Manifestations** : After a 7- to 17-day incubation period, symptoms begin acutely with high fever, headache, rigors, malaise, myalgias, vomiting, and abdominal and back pain. After 2-3 days, an exanthem develops. The lesions progress synchronously from macules to papules to vesicles to pustules. Centrifugal distribution of the rash is an important diagnostic feature.

**Treatment** : Strict quarantine with respiratory isolation for 17 days is applied to all people in direct contact with the index case or cases. All personnel exposed to either weaponized variola or clinical cases must be vaccinated immediately. Vaccinia immune globulin (VIG) is given to patients who cannot receive the vaccine. Treatment of smallpox is mainly supportive. The antiviral agent, cidofovir, is effective in vitro and may be involved in treatment of symptomatic illness.

**Prevention** : Smallpox vaccine (attenuated vaccinia virus) is administered by intradermal inoculation with a bifurcated needle. The permanent scar results from a process known as scarification.

## Viral Hemorrhagic Fevers

Viral hemorrhagic fevers are caused by 4 families of viruses, which include the Arenaviridae (Lassa, Argentine, Bolivian, Brazilian, Venezuelan hemorrhagic fevers), Bunyaviridae (Rift Valley, Crimean-Congo, Hantaan), Filoviridae (Marburg, Ebola 4 Fs), and Flaviviridae (Yellow, Dengue, Kyasanur Forest, Omsk HFs). The best known of the viral hemorrhagic fever agents is Ebola virus. All agents are highly infectious via the aerosol route, and most are stable as respiratory aerosols. Thus, they possess characteristics ideal for use by terrorists.

**Clinical Manifestations** : All viral hemorrhagic fevers primarily target vascular beds. They produce microvascular damage and enhance vascular permeability. Clinical manifestations include fever, myalgia, prostration, conjunctival injection, mild hypotension to severe shock, and mucosal and petechial hemorrhages, Neurologic, hematopoietic, hepatic, and pulmonary involvement can be found with more severe disease.

**Treatment** : Treatment for a viral hemorrhagic fever is largely supportive. Patients benefit from rapid nontraumatic hospitalization to prevent damage to the capillary bed. Sedative and pain-relieving medications are helpful, but aspirin and other antiplatelet agents should be avoided. Avoid intravenous lines and catheters unless absolutely necessary. Secondary infections should be sought and aggressively treated. Immunosuppressive agents such as steroids are contraindicated. The treatment for bleeding is controversial. Generally, mild bleeding should not be treated, whereas severe hemorrhage requires appropriate replacement therapy.

Specific treatment with ribavirin has been used and currently is

being investigated as therapy for Lassa fever, Hantavirus, Crimean-Congo, and Rift Valley Fever. The dosage is 130mg/kg IV followed by 15mg/kg q6h for 4 days, then 7.5mg/kg q8h for 6 days. Treatment is most effective if begun within 7 days<sup>8</sup>. Ribavirin has poor activity against the filoviruses and flaviviruses.

## Ricin

Ricin, a plant protein toxin derived from the beans of the castor plant, is one of the most toxic and easily produced of the plant toxins. The worldwide ready availability of castor beans and the ease with which toxin can be produced give it significant potential as a biological weapon.

**Clinical Manifestations** : Ricin is extremely toxic to cells and acts by inhibiting protein synthesis. Inhalation exposure causes primarily pulmonary symptoms, ingestion causes GI symptoms, and intramuscular exposure results in a localized reaction<sup>17</sup>. In a BW or terrorist situation, exposure is likely to occur by inhalation of a toxin aerosol. Treatment is supportive. Inhalation injury may require treatment of pulmonary edema, with respiratory support as indicated. Intravenous crystalloid infusion and pressor support may be necessary for patients with hypotension.

## Botulinum Toxin

The anaerobic, spore-forming, gram-positive bacillus, *Clostridium botulinum*, produces botulinum toxins. Botulinum toxins are the most lethal toxins known, with an estimated lethal dose to 50% of the exposed population (LD50) of 0.001 mcg/kg in humans. Since botulinum toxin is so lethal and easy to manufacture and weaponize, it represents a credible threat as a BW agent. When used as a BW or terrorist agent, exposure is likely to occur following inhalation of aerosolized toxin or ingestion of food contaminated with the preformed toxin or microbial spores. Botulinum toxins bind to the presynaptic nerve terminal at the neuromuscular junction and cholinergic autonomic sites. This prevents the presynaptic release of acetylcholine and blocks neurotransmission.

**Clinical Manifestations** : Initial signs and symptoms include blurred vision, mydriasis, ptosis, dysphagia, dysarthria, dysphonia, and muscle weakness. After 24-48 hours, neuromuscular manifestations progress to symmetric descending paralysis and respiratory failure. Postural hypotension may occur from autonomic insufficiency. Oral exposure can be detected by analyzing serum or gastric contents with a mouse neutralization assay.

**Treatment** : The most serious complication of toxicity is respiratory failure. With supportive care and ventilatory assistance, fatalities should be less than 5%. For confirmed exposures, a trivalent equine antitoxin is available. After a negative skin test, the antitoxin is administered at a dose of 10mL IV over 20 minutes, which is repeated until improvement ceases<sup>18</sup>.

**Prevention** : A toxoid for *C botulinum* was used to immunize US military troops in the Persian Gulf War. The current schedule for immunization is at 0, 2, and 12 weeks with an annual booster. Currently, no indication exists for prophylactic use of the antitoxin except under specialized circumstances.

## Mycotoxins

The trichothecene mycotoxins are highly toxic compounds produced by certain species of filamentous fungi (*Fusarium*, *Myrothecium*, *Cephalosporium*, *Trichoderma*, *Verticillium*, *Stachybotrys* species). Strong evidence suggests that trichothecenes ("yellow rain") have been used as a BW agent in Southwest Asia and Afghanistan.

**Clinical Manifestations** : The trichothecene mycotoxins are cytotoxic to most eukaryotic cells by way of inhibiting protein synthesis and electron transport. After exposure to the mycotoxins, early symptoms begin within minutes. Cutaneous manifestations include burning, tender erythema, edema, and blistering with progression to dermal necrosis and sloughing of large skin areas in lethal cases. Respiratory exposure results in nasal itching, pain, sneezing, epistaxis, rhinorrhea, dyspnea, wheezing, cough, and blood-tinged saliva and sputum. GI toxicity consists of anorexia, nausea and vomiting, abdominal cramping, and watery and/or bloody diarrhea. Death may occur within minutes to days depending on the dose and route of exposure.

**Treatment** : Treatment is supportive. If unprotected during an attack, the outer clothing should be removed within 4-6 hours and decontaminated with 5% sodium hydroxide for 6-10 hours. The skin should be washed with copious amounts of soap and uncontaminated water. The eyes, if exposed, should be irrigated with copious amounts of normal saline or sterile water. Early use of systemic steroids increases survival time by decreasing the primary injury and shocklike state that follows significant poisoning<sup>8</sup>.

### References

1. Christopher GW, Cieslak TJ, Pavlin JA, Eitzen EM: Biological warfare. A historical perspective. JAMA 1997 Aug 6; 278(5):412-7.
2. Ferguson JR: Biological weapons and US law. JAMA 1997 Aug 6; 278(5):357-60.
3. CDC: Bioterrorism alleging use of anthrax and interim guidelines for management-United States, 1998. MMWR Morb Mortal Wkly Rep 1999 Feb 5;48(4):69-74.
4. Dixon TC, Meselson M, Guillemin J, Hanna PC: Anthrax. N Engl J Med 1999 Sep 9; 341(11):815-26.
5. Inglesby TV, Henderson DA, Bartlett JG, et al: Anthrax as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA 1999 May 12;281(18):1735-45.
6. Pile JC, Malone JD, Eitzen EM, Friendlander AM: Anthrax as a potential biological warfare agent. Arch Intern Med 1998 Mar9;158(5):429-34.
7. Leaderberg J: Infectious disease and biological weapons. Prophylaxis and mitigation. JAMA 1997 Aug 6;278(5):435-6.
8. Rosenbloom M, Leiken JB, Vogel SN, Chaudry ZA: Biological and chemical agents: a brief synopsis. Am J Ther 2002 Jan-Feb;9(1):5-14.
9. US Army Medical Research Institute of Infectious Disease. Medical Management of Biological Casualties Handbook, 4th ed. Fort Detrick, Frederick, Maryland: February 2001.
10. Holdstock D: The plague wars. Nurs Times. 1998 Jul 22-28;94(29):38-9.
11. Van Baar EL, Hulst AG, Wils ER: Characterisation of cholera toxin by liquid chromatography-electrospray mass spectrometry. Toxicon. 1999 Jan;37(1):85-108.
12. Franz DR, Jahrling PB, Friedlander AM, et al: Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997 Aug 6;278(5):399-411.
13. Henderson DA: The looming threat of bioterrorism. Science 1999 Feb 26; 283(5406):1279-82.
14. Moblely JA: Biological warfare in the twentieth century: lessons from the past, challenges for the future. Mil Med 1995 Nov; 160(11):547-53.
15. Headquarters, Department of the Army, Washington, D.C.: Field Manual 8-284, Treatment of Biological Warfare Agent Casualties. 17 July 2000.
16. Breman JG, Henderson DA: Poxvirus dilemmas-monkeypox, smallpox, and biologic terrorism. N Engl J Med 1998 Aug 20;339(8):556-9.
17. Zajtchuk R, Bellamy RD, eds: Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare, Part 1. Washington, DC: Office of the Surgeon General, US Dept of the Army; 1997.
18. Keim M, Kaufmann AF: Principles for emergency response to bioterrorism. Ann Emerg Med 1999 Aug;34(2):177-82.

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## Drug Induced Liver Injury

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**Abstract:** A large number of chemical agents used for diagnostic and therapeutic purposes can produce varying types of hepatic injury by different mechanisms. Drug induced liver injury accounts for 3-9% of all adverse drug reactions. Various drugs that have been implicated in causing liver injury include non steroidal antiinflammatory drugs (NSAIDs), antituberculous agents, nucleoside reverse transcriptase inhibitors, non nucleoside reverse transcriptase inhibitors, protease inhibitors, penicillins, cephalosporins, tetracyclines, macrolides, sulfonamides and trimethoprim, antifungal agents, antidepressants, antipsychotics, anticonvulsants, anti-anxiety drugs, acetylcholinesterase inhibitors, alcohol, cocaine, ecstasy, antihypertensive agents, oral hypoglycemics, and a few others like statins, estrogens, halothane, amiodarone, methotrexate, nitrofurantoin, disulfiram, omeprazole, D-Penicillamine, and heparin. This review focuses on the different types of drug induced liver injuries, their mechanisms, and the individual drugs causing liver injury.

### Introduction

A large number of chemical agents used for diagnostic and therapeutic purposes can produce varying types of hepatic injury by different mechanisms. More than 600 agents are known to cause hepatic injury<sup>1</sup>. The incidence of drug induced liver injury has been increasing perhaps due to a large number of new compounds introduced into clinical use. Drug induced liver injury manifests most commonly as acute toxicity. It accounts for 3-9% of all adverse drug reactions<sup>2</sup>.

### Drugs Causing Liver Injury (Table 1)

#### *Anti-inflammatory (Analgesic Agents)*

**Non Steroidal Antiinflammatory Drugs (NSAIDs) :** The NSAIDs are widely used as analgesics and antipyretics, both as prescription drugs and over the counter purchases. Although the risk of clinically apparent liver injury is low (1-8 cases per 100,000 patient years of NSAID use), it can be serious and can create confusion in diagnosis. Hepatic injury is considered a class effect of NSAIDs by USFDA. An idiosyncratic reaction (immunologic or metabolic) is generally implicated in NSAID induced liver injury.

**Salicylates :** Salicylates have been documented to cause dose-

dependent liver injuries since the 1970's. Aspirin generally causes an acute, mild, and reversible form of hepatic injury. Aminotransferase values are elevated in the mild to moderate range with AST levels somewhat higher than ALT levels<sup>3</sup>. Severe hepatic injury with aspirin is reported in only 3% of the cases with patients presenting with encephalopathy, coagulopathy, and death. Serum levels of 15mg/ml or greater cause hepatic injury although lower levels have also been reported<sup>4</sup>. Susceptibility to aspirin induced hepatotoxicity is seen in patients with juvenile rheumatoid arthritis, systemic lupus, rheumatic fever, and preexisting liver disease. The mechanism of aspirin induced liver injury is thought to be the accumulation of toxic metabolites. The association between aspirin and Reye's syndrome has been widely reported<sup>5</sup>. This syndrome is characterized by severe hepatic damage and encephalopathy occurring in children and usually preceded by a respiratory viral disease or varicella.

**Acetaminophen :** Acetaminophen is well tolerated at the usual therapeutic doses. However, it is the leading cause of liver failure when used in intentional overdoses. A fatal dose is estimated to be 10-15g. The histological picture is one of hepatocellular necrosis with serum ALT and AST levels markedly elevated at presentation (>3000IU/L)<sup>6</sup>. During the first 1-2 days, nausea, vomiting, and abdominal pain occur. The symptoms subside in the next 24 hrs and the third phase of injury develops after 48 hrs when signs of hepatic damage and associated cardiotoxicity and renal failure develop. An unstable quinone metabolite, N-acetyl-p-benzoquinone imine is the toxic moiety responsible and early treatment with N-acetyl cysteine is generally effective.

**Diclofenac :** Diclofenac has been implicated in over 200 instances of hepatocellular injury with several fatalities<sup>7</sup>. Anorexia, nausea, and malaise are the early symptoms with fever and rash occurring in 25% of the patients. Acute injury generally resembles acute viral hepatitis. The prognosis is usually good although rare cases of fulminant hepatic failure have been reported with diclofenac.

#### Antimicrobial Agents

Antimicrobial agents have been associated with different forms of hepatotoxicity ranging from minor abnormalities in liver function tests to fulminant hepatic failure. The reactions are generally

**Table 1 : Drugs causing acute hepatocellular injury.**

|                          |                                       |
|--------------------------|---------------------------------------|
| <b>NSAIDs/Analgesics</b> |                                       |
| Acetaminophen            |                                       |
| Oxaprozin                |                                       |
| Diclofenac               |                                       |
| Piroxicam                |                                       |
| Etodolac                 |                                       |
| Phenylbutazone           |                                       |
| <b>Antimicrobials</b>    | <b>Anticonvulsants</b>                |
| Sulfonamides             | Phenytoin                             |
| Erythromycin             | Carbamazepine                         |
| Isoniazid                | Valproic acid                         |
| Rifampicin               |                                       |
| Pyrazinamide             |                                       |
| Tetracycline             | <b>Miscellaneous</b>                  |
| Paraaminosalicylic acid  | Anabolic and contraceptive steroids   |
|                          | Disulfiram; Troglitazone; Nefazodone; |
|                          | Flutamide; Propylthiouracil           |

Table 2 : Drugs causing chronic liver injury.

|                          |                            |
|--------------------------|----------------------------|
| <b>Chronic Hepatitis</b> | <b>Chronic Cholestasis</b> |
| Isoniazid                | <b>Antibiotics</b>         |
| Isoniazid                | Ampicillin                 |
| Methyldopa               | Tetracycline               |
| Sulfonamides             | Cotrimoxazole              |
| Nitrofurantoin           | Erythromycin               |
| Dantrolene               | Clindamycin                |
| Propylthiouracil         |                            |
| Ethanol                  | <b>Antipsychotics</b>      |
| Methotrexate             | Chlorpromazine             |
| Amiodarone               | Haloperidol                |
| Tolbutamide              |                            |
| Oral contraceptives      | <b>Miscellaneous</b>       |
| Thioguanine              | Tolbutamide                |
| Organic arsenicals       | Terbinafine                |
|                          | Cimetidine                 |
|                          | Azathiopurine              |
|                          | Ticlopidine                |
|                          | Ibuprofen                  |

unpredictable and idiosyncratic and the injury is usually self-limiting once the offending agent is withdrawn.

### Antituberculous Therapy

Antitubercular drugs frequently cause liver injury with significant liver enzyme elevations in 20% of those treated<sup>8</sup>.

**Isoniazid** : Isoniazid causes serious hepatic injury (acute hepatocellular necrosis) resembling acute viral hepatitis in upto 1% of patients<sup>9</sup>. Susceptibility to isoniazid induced hepatotoxicity is enhanced in pregnancy, older subjects, and in those with hepatitis B infection. Fast acetylators are more prone to developing hepatotoxicity.

**Rifampin** : Rifampin rarely causes hepatotoxicity when used alone. The use of rifampin in combination with isoniazid is more hepatotoxic because rifampin enhances the production of the toxic metabolite, acetylhydrazine.

**Pyrazinamide** : Pyrazinamide based antitubercular regimens have been associated with a higher frequency as well as a more severe pattern of liver injury than those without it.

### Antiviral Agents

Antiretrovirals have been associated with hepatic injury of varying patterns. About 5-15% of all patients receiving highly active antiretroviral therapy (HAART) develop elevations in liver enzymes<sup>10</sup>.

**Nucleoside reverse transcriptase inhibitors (NRTI's)** : NRTI's have occasionally led to episodes of acute hepatitis and steatohepatitis. Zidovudine is the NRTI that is most commonly associated with hepatocellular injury<sup>11</sup>. Didanosine in high doses has been associated with hepatocellular injury and fulminant hepatic failure.

**Non Nucleoside reverse transcriptase inhibitors (NNRTI's)** : Hepatotoxicity with NNRTI's is seen in about 10% of cases<sup>12</sup>. Nevirapin has been associated with a number of clinical hepatic events when used for postexposure prophylaxis in non-HIV infected patients.

**Protease Inhibitors** : Among the protease inhibitors, ritonavir carries the highest risk of hepatotoxicity. Indinavir and atazanavir cause a benign increase in unconjugated bilirubin in HIV infected

patients.

### Beta Lactams

**Penicillins** : Natural penicillins rarely produce liver injury. However, semisynthetic penicillins are responsible for a wide range of hepatotoxic reactions. Cholestatic hepatitis has been associated with oxacillin, cloxacillin, dicloxacillin, and flucloxacillin. Amoxicillin in combination with the beta lactamase inhibitor clavulanic acid, is associated with significantly increased hepatotoxicity, the incidence being one in every 80,000 - 90,000 prescriptions<sup>13</sup>. Clinical manifestations such as nausea, vomiting, fatigue, malaise, abdominal pain, fever, jaundice, and pruritus generally occur within four weeks of starting treatment and recovery usually occurs within 1-8 weeks.

**Cephalosporins** : Cephalosporins are closely related to penicillins and show cross reactivity with them. Hepatotoxicity with cephalosporins has been rarely reported. However, moderate elevations of plasma aminotransferase levels are known to occur with all cephalosporins and are seen in about 6% patients with the 3rd generations agents<sup>14</sup>.

**Tetracyclines** : Oral tetracyclines are rarely associated with hepatic injury. The intravenous form, which was in use previously, produced a syndrome resembling acute fatty liver of pregnancy. Minocycline has been reported to cause an early onset, hypersensitivity reaction associated with hepatitis and eosinophilia as well as a delayed onset chronic hepatitis presenting as a systemic lupus erythematosus like syndrome.

**Macrolides** : Hepatotoxicity with macrolides has been known since the 1960's when cholestasis was first reported with erythromycin estolate. It has been seen that all erythromycin esters can produce cholestasis with jaundice and pruritus occurring within 3 weeks of exposure. Recovery is usually complete and fatal hepatitis doesn't occur<sup>1</sup>. Although the hepatotoxic potential of newer macrolides is low, reports of cholestasis have been there with azithromycin, clarithromycin, and roxithromycin<sup>15</sup>.

**Sulfonamides and trimethoprim** : Sulfonamides have been known to produce a wide spectrum of liver injuries including acute hepatocellular injury, granulomas, as well as cholestasis<sup>16</sup>. Immunoallergy is the mechanism responsible and the patients present with rash, fever, and eosinophilia. Fatal liver injury is reported with sulfasalazine, usually within 8 weeks of starting therapy. Cotrimoxazole (Trimethoprim sulfamethoxazole) characteristically produces a cholestatic or mixed pattern that can progress to fulminant liver failure. Dapsone therapy produces a sulfone syndrome with fever, rash, jaundice, and anemia.

### Antifungal Agents

**Azole antifungals** : The most common antifungal agent associated with hepatic injury is ketoconazole with severe liver injury seen in 1 in 15,000 recipients<sup>17</sup>. Fluconazole and itraconazole are less frequently associated with hepatitis.

Table 3 : Drugs causing hepatic granulomas.

|                |              |
|----------------|--------------|
| Quinidine      | Sulfonamides |
| Hydralazine    | Penicillin   |
| Allopurinol    | Methyldopa   |
| Halothane      | Gold         |
| Phenylbutazone |              |

**Terbinafine** : Terbinafine produces hepatocellular and cholestatic injury in 1 in 50,000 persons<sup>18</sup> usually 4-6 weeks after initiation of therapy.

**Other antifungal agents** : Lipid formulations of amphotericin B have been associated with hepatic necrosis. Flucytosine has been associated with hepatotoxicity when used in combination with other antifungals.

### Antidepressants

Older antidepressants such as monoamine oxidase inhibitors have been associated with liver injury. MAO inhibitors are derivatives of hydrazine and are potential hepatotoxins. Iproniazid led to overt hepatitis in 1% with case fatalities approaching 20%<sup>19</sup> following which it was withdrawn. Tricyclic antidepressants produce predominantly cholestatic liver injury. Usage of noncyclic antidepressants such as nefazodone has led to episodes of acute liver failure with symptoms occurring 7-28 weeks after treatment. Trazodone also has been implicated in cases of acute cholestatic liver injury as well as chronic active hepatitis and the period of onset of symptoms has been as long as 18 months. The selective serotonin reuptake inhibitors (SSRI's) are one of the most commonly used antidepressants and around 0.5% of long term recipients of fluoxetine show asymptomatic mild elevation in liver enzymes. Cases of acute hepatitis and cholestatic jaundice have also been reported with fluoxetine usage<sup>20</sup>.

### Antipsychotics

Many antipsychotics are associated with liver injury. Cholestatic jaundice is an important side effect with chlorpromazine and occurs within the first month of therapy. There is around 8-10 fold elevation of liver alkaline phosphatase and aminotransferases<sup>21</sup>. Manifestations of hypersensitivity like fever and eosinophilia can occur in 70% of patients. Recovery of liver function from jaundice occurs within 2-8 weeks of stoppage of drug but protracted cholestasis has been seen in few affected individuals. Haloperidol usage in some cases is also associated with cholestasis. Newer drugs such as clozapine and risperidone are known to cause hepatocellular injury, while acute hepatitis has been seen with olanzapine.

### Anticonvulsants

Many antiepileptic drugs are known to cause liver injury. Drugs such as phenytoin, carbamazepine, and phenobarbitone are known to cause a type of antiepileptic hypersensitivity syndrome. Frequency of occurrence of this syndrome is approximately 1 in 3000 exposures and the onset of syndrome is within the first 2-8 weeks after starting the treatment. The syndrome is characterized by a triad of fever, skin rash and involvement of internal organs such as liver, kidney, and bone marrow. The syndrome is reversible but in certain cases despite the discontinuation of the offending drug, the syndrome might progress and may be fatal. Valproic acid usage especially in the paediatric age group has been associated with hepatocellular injury. The onset of injury is within 4-16 weeks of treatment with mild to moderate elevations of ALT and AST values. Anorexia, nausea, vomiting, and somnolence are common symptoms of valproic acid hepatotoxicity. Fatal hepatotoxicity is seen in around 1% of patients. Use of lamotrigine is also associated with incidence of acute hepatitis, the onset of

**Table 4 : Drugs causing hepatic neoplasms.**

|                          |   |
|--------------------------|---|
| Adenoma                  | Danazol, contraceptive and anabolic steroids                      |
| Hepatocellular Carcinoma | Thorium dioxide (Thorotrast), contraceptive and anabolic steroids |
| Cholangiocarcinoma       | Thorium dioxide (Thorotrast)                                      |
| Angiosarcoma             | Vinyl chloride, Thorium dioxide, inorganic arsenicals             |

which occurs between 2 and 3 weeks<sup>22</sup>. Histologically, it presents as acute hepatic necrosis or focal hepatitis with mild portal inflammation. Serious hepatotoxicity has been reported with the use of felbamate<sup>23</sup>. The period of onset of injury is between 1-7 months of starting therapy. A reactive metabolite atropaldehyde is seen to be responsible for causing liver injury.

### Anti-anxiety Drugs

Benzodiazepines, such as chlordiazepoxide, diazepam, and flurazepam, have very low hepatotoxic potential, with only a few case reports demonstrating a cholestatic pattern of injury<sup>24</sup>.

### Acetylcholinesterase inhibitors

Tacrine is a reversible cholinesterase inhibitor used for Alzheimer's disease. The ALT levels exceed upper limit of normal in upto 50% of recipients in the first 12 weeks of tacrine therapy. tacrine is metabolized by CYP1A2 to reactive metabolites that may cause hepatotoxicity.

### Drugs of abuse

**Alcohol** : Ethanol produces a variety of dose related deleterious effects in the liver. The primary effects are fatty infiltration of the liver, hepatitis, and cirrhosis. The accumulation of fat results from both inhibition of the tricarboxylic acid cycle and the oxidation of fat. Chronic inflammation and necrosis lead to fibrosis, and subsequently cirrhosis of the liver. the histologic hallmark of cirrhosis is the formation of 'Mallory bodies' related to an altered intermediate cytoskeleton.

**Cocaine** : Cocaine causes dose-related hepatotoxicity. Although cocaine induces oxidative stress in hepatocytes, its mechanism is controversial. Cocaine hepatotoxicity has been well characterized in mice. Its occurrence in humans is very rare.

**Ecstasy** (3, 4-methylenedioxymethamphetamine MDMA) : There have been a number of case reports of severe acute hepatotoxicity in response to MDMA with a latent period of days to weeks. An immune mechanism is postulated with tissue eosinophilia seen in some cases.

### Antihypertensive Agents

**Methyldopa** : Methyldopa is a well known cause of liver injury. this develops within first 3 months of therapy in 90% patients and usually resolves when the drug is discontinued.

**ACE inhibitors and Angiotensin II receptor blockers** : ACE inhibitors (captopril, enalapril, fosinopril) usually cause bland cholestasis or cholestatic hepatitis. Fulminant hepatic failure has been reported with enalapril and lisinopril<sup>25</sup>. Among the Angiotensin II receptor blockers, liver toxicity has been observed with losartan, irbesartan, and candesartan. However, long term follow-up data

with these are still unavailable.

**Calcium channel blockers (CCB's)** : Only few reports of CCB related liver injury are available. Diltiazem has been associated with granulomatous hepatitis whereas nifedipine has caused lesions containing Mallory bodies<sup>1</sup>. Mild elevations in aminotransferase levels are reported with amiodarone. Chronic injury, including an alcohol-like illness, is also seen with amiodarone as a consequence of its long half life.

### Oral Hypoglycemics

**Sulphonylureas** : The prototype sulphonylureas including acetohexamide, methohexamide, carbuthamide, and glibuthiazole have been withdrawn because of severe hepatotoxicity<sup>2</sup>. Hepatic injuries with chlorpropamide, tolbutamide, and tolazamide have been reported occasionally. Cholestatic jaundice is seen with sulphonylureas in 1% of recipients<sup>26</sup>.

**Thiazolidinediones** : Troglitazone, a peroxisome proliferator activated receptor gamma agonist, was withdrawn after it caused over 100 cases of hepatotoxicity<sup>27</sup>. Patients with troglitazone hepatotoxicity presented with nausea, vomiting, and jaundice after an average of 4 months. There have been two reports of hepatotoxicity with rosiglitazone<sup>28</sup> and one report of reversible acute hepatocellular injury with pioglitazone<sup>29</sup>. FDA recommends liver function tests at baseline and every two months thereafter during first year of treatment with thiazolidinediones. The drug is to be discontinued if ALT levels remain persistently elevated (>3ULN).

**Others** : There have been two reports of acute cholestatic hepatitis with metformin whereas several reports of hepatotoxicity are available with acarbose<sup>22</sup>.

### Lipid lowering agents

Mild transient elevations in ALT and AST levels have been reported with most lipid lowering drugs. Statins produce liver test abnormalities in < 5% of patients. Frequency of acute liver failure is low with statins (0.2 per 100,000 patients)<sup>30</sup>, with cholestatic injury predominating. Autoimmune hepatitis has been seen with fenofibrate. Dose related hepatotoxicity is also seen with nicotinic acid.

### Hormones

Jaundice with oral contraceptives, albeit rare, is usually seen in the first month of therapy. The incidence of hepatic adenomas with long term oral contraceptive use is about 3.4 per 100,000<sup>10</sup>. Tamoxifen has been known to cause cholestasis, hepatocellular carcinoma, acute hepatitis, steatosis, and steatohepatitis. The incidence of hepatic steatosis is approximately 30% with tamoxifen and 10% with toremifene, an analog of tamoxifen<sup>31</sup>. Anabolic steroids having an alkyl group at the C-17 position are hepatotoxic. Jaundice is seen with high doses of androgens often accompanied by malaise, pruritus, and anorexia. Hepatic adenomas and carcinomas are also seen to occur with androgens. Among the antiandrogens, flutamide causes hepatotoxicity in 1-5% subjects. Danazol and cyproterone acetate have led to elevations in plasma aminotransferase levels to the extent of 30-50%.

### Anesthetics

Halothane can produce fulminant hepatic necrosis at approximately

1 in 10,000-35,000 exposures<sup>1</sup>. Patients present with fever, nausea, anorexia, and vomiting accompanied by a rash and peripheral eosinophilia. The mechanism behind halothane hepatitis is thought to be an immune response to trifluoroacetylated proteins on hepatocytes.

### Miscellaneous Agents

**Amiodarone** : Amiodarone causes abnormal liver tests in 15-80% patients whereas clinically significant disease occurs in 0.6-3%. It is the drug most commonly implicated in steatohepatitis<sup>32</sup>. Amiodarone induced steatohepatitis occurs after exposure to the drug for long durations, the mean being 21 months. Patients present with fatigue, nausea, vomiting, malaise, and weight loss.

**Methotrexate** : Prolonged treatment with methotrexate can lead to hepatic fibrosis and cirrhosis. Risk factors include alcohol ingestion, obesity, diabetes, and underlying liver disease.

**Nitrofurantoin** : Nitrofurantoin produces diverse patterns of hepatotoxicity including acute hepatocellular, mixed, cholestatic, and granulomatous reactions. A chronic active hepatitis reaction with nitrofurantoin is common in elderly women exposed for longer than six months. This may progress to cirrhosis and hepatic failure.

**Disulfiram** : Disulfiram causes hepatic abnormalities in 25% of patients who present with nausea, fatigue, malaise, and occasionally jaundice 2-8 weeks after starting the drug.

**D-penicillamine** : Many cases of cholestatic jaundice with d-penicillin have been reported within the first 2-4 weeks of initiating therapy<sup>33</sup>.

**Heparin** : Abnormalities of liver function tests occur frequently in patients receiving heparin either subcutaneously or intravenously. Mild elevations of the activities of hepatic transaminases in plasma occur without an increase in bilirubin levels or alkaline phosphatase activity.

### Reference

- Zimmerman HJ: Hepatotoxicity. The adverse effects of drugs and other chemicals in the liver, ed 2. Philadelphia, Lippincott Williams and Wilkins, 1999.
- Friis H, Andreasen PB. Drug-induced hepatic injury: an analysis of 1100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. *J Intern Med* 1992;232(2):133-8.
- Zimmerman HJ. Effects of aspirin and acetaminophen on the liver. *Arch Intern Med* 1981;23:141(3Spec No):333-42.
- Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic venoocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. *Gastroenterology* 1985;88(4):1050-4.
- Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. Reye's syndrome in the United States from 1981 through 1997. *N Engl J Med* 1999;340(18):1377-82.
- Wootton FT, Lee WM. Acetaminophen hepatotoxicity in the alcoholic. *South Med J* 1990;83(9):1047-9.
- Banks AT, Zimmerman HJ, Ishak KG, Harter JG. Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995;22(3):820-7.
- Van den Brande P, van Steenberghe W, Vervoort G, Demedts M. Aging and hepatotoxicity of isoniazid and rifampin in pulmonary tuberculosis. *Am J Respir Crit Care Med*

- 1995;152(5 Pt 1):1705-8.
9. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid associated hepatitis in 114 patients. *Gastroenterology* 1975;69(2):289-302.
  10. Gisolf EH, Dreezen C, Danner SA, Weel JL, Weverling GJ; Prometheus Study Group. Risk factors for hepatotoxicity in HIV-1-infected patients receiving ritonavir and saquinavir with or without stavudine. Prometheus Study Group. *Clin Infect Dis* 2000;31(5):1234-9.
  11. Gradon JD, Chapnick EK, Sepkowitz DV. Zidovudine-induced hepatitis. *J Intern Med* 1992;231(3):317-8.
  12. Reisler K. High hepatotoxicity rate seen among HAART patients. *Aids Alert* 2001;16(9):118-9.
  13. Hewitt J, Hammond L. Adverse hepatic events associated with drug therapy. *Med J Aust* 1996;165(6):347-350.
  14. Meyers BR. Comparative toxicities of third-generation cephalosporins. *Am J Med* 1985;9:79(2A):96-103.
  15. Pedersen FM, Bathum L, Fenger C. Acute hepatitis and roxithromycin. *Lancet* 1993;23:341(8839):251-2.
  16. Tonder M, Nordoy A, Flgjo. Sulfonamide-induced chronic liver disease. *Scand J Gastroenterol* 1974;9(1):93-6.
  17. Lewis JH, Zimmerman HJ, Benson GD, Ishak KG. Hepatic injury associated with ketoconazole therapy. Analysis of 33 cases. *Gastroenterology* 1984;86(3):503-13.
  18. Gupta AK, del Rosso JQ, Lynde CW, Brown GH, Shear NH. Hepatitis associated with terbinafine therapy: three case reports and a review of the literature. *Clin Exp Dermatol* 1998;23(2):64-7.
  19. Rosenblum LE, Korn RJ, Zimmerman H. Hepatocellular jaundice as a complication of iproniazid therapy. *Arch Intern Med* 1960;105:115-125.
  20. Aranda-Michel J, Koehler A, Bejarano PA, Poulos JE, Luxon BA, Khan CM, Ee LC, Balistreri WF, Weber FL Jr. Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999;16:130(4 Pt 1): 285-8.
  21. Lewis JH. Drug-induced liver disease. *Med Clin North Am* 2000;84(5):1275-311.
  22. Andrade RJ, Lucena M, Vega JL, Torres M, Salmeron FJ, Bellot V, Garcia-Escano MD, Moreno P. Acarbose-associated hepatotoxicity. *Diabetes Care* 1998;21(11):2029-30.
  23. O'Neil MG, Perdun CS, Wilson MB, McGown ST, Pat Felbamate-associated fatal acute hepatic necrosis. *Neurology* 1996;46(5):1457-9.
  24. Fang M, Ginsberg A, Dobbins W III. Hepatic jaundice associated with flurazepam hydrochloride. *Ann Intern Med* 1978;89:363-364.
  25. Jeserich M, Ihling C, Allgaier HP, Berg PA, Heilmann C. Acute liver failure due to enalapril. *Herz* 2000;25(7):689-93.
  26. Goodman RC, Dean PJ, Radparvar A, Kitabchi AE. Glyburide-induced hepatitis. *Ann Intern Med* 1987;106(6):837-9.
  27. Vella A, de Groen PC, Dinneen SF. Fatal hepatotoxicity associated with troglitazone. *Ann Intern Med* 1998;15:129(12):1080.
  28. Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med* 2000;18:132(2):118-21.
  29. Maeda K. Hepatocellular injury in a patient receiving pioglitazone. *Ann Intern Med* 2001;21:135(4):306.
  30. Tolman KG. Defining patient risks from expanded preventive therapies. *Am J Cardiol* 2000;22:85(12A):15E-9E.
  31. Clark JA, Zimmerman HJ, Tanner IA. Labetalol hepatotoxicity. *Ann Intern Med* 1990;1:113(3):210-3.
  32. Farrell GC. Drug induced liver disease. Edinburgh: Churchill Livingstone; 1994.
  33. Barzilai D, Dickstein G, Enat R, Bassan H, Lichtig C, Gellei B. Cholestatic jaundice caused by D-penicillamine. *Ann Rheum Dis* 1978;37(1):98-100.

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**EDITORIAL Multidrug Resistant Tuberculosis (MDR-TB)**

Tuberculosis - the most common cause of death due to single infectious agent worldwide in adults, has assumed alarming dimensions in view of emergence of multidrug resistance tuberculosis (MDR-TB). The abysmal failure of national tuberculosis programme indicate that MDR-TB is due to failure of organizational authorities, physicians and the patients; it is a "Man-made problem".

It is a worldwide problem both in immunocompetent and HIV+ individuals. The 5 year survival rate is only 50%. MDR-TB is particularly problematic because it threatens both the individual and the community. For the individual, MDR-TB often results in treatment failure, increased relapse, progressive disability and death, particularly in resource poor countries unable to provide expensive complicated 'second line' treatment. The duration of therapy has increased (18-24 months) and the resulting toxicity from the drugs. It has also created a potential need for resection or surgery and even hospitalization. It has also resulted in massively increased expenses to 1.5 to 2 lacs for an individual. For the community, the patient with chronic MDR-TB disease represents an infectious reservoir of resistant tubercle bacilli.

Today, MDR-TB is a dreadful reality and is continuously on the rise. The rising trend of AIDS in our country may add fuel to fire. Countries, like India, which today contribute to maximal number of tuberculosis patients of the world, remain exposed to this monumental threat i.e. "double-trouble". The due has increased the morbidity, mortality, relapse, decreased survival rate.

MDR-TB is caused by *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin, with/without resistance to other drugs. About 1.7 billion, one third of the world's population, carry the tubercle bacillus, and every year there are 8 million new cases of tuberculosis causing death to 3 million people. In India, it is estimated that there are 14

million patients, out of which at least 25% have multidrug resistant tuberculosis (MDR-TB) while host genetic factors may probably contribute; irregular, incomplete and inadequate treatment is the single most important factor, resulting in the development of MDR-TB. In India, prevalence of drug resistance in 'new cases' in adults is about 6 to 13% for isoniazid, 0 to 1.9% for rifampicin and 1 to 5.8% for streptomycin. In 'previously treated' patients, the rates of drug resistance are much higher i.e. 4 to 53% (median 10.6) for isoniazid, 0 to 14.5% (median 2.4%) for rifampicin and 0 to 19.4% (median 4.9%) for streptomycin. In India, overall prevalence of MDR-TB is 13.3%. Understanding the epidemiological aspects of MDR-TB and the mechanisms of development of drug resistance is an 'initial step' in the management of MDR-TB. Early bacteriological diagnosis along with drug sensitivity pattern is the cornerstone for detecting and managing MDR-TB. Laboratory delays in both identification of *M. tuberculosis* and the recognition of drug resistance (eg 2 to 9 months after specimen collection) contributed to MDR-TB outbreaks. Today, sputum smear results are expeted within 24 hours of specimen collection, culture identification of *M. tuberculosis* within 10 to 14 days and drug susceptibility results within 15-30 days. State of art knowledge of various laboratory diagnostic methods and their "proper application" are of utmost importance. The judicious use of second line drugs, supervised individualised treatment, focussed clinical, radiological and bacteriological follow-up, use of surgery at the appropriate juncture, are key factors in the successful management of patients with MDR-TB.

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# Multidrug - Resistant Tuberculosis (MDR-TB): Epidemiology, Mechanisms of Drug Resistance

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**Abstract:** Multidrug-resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin with or without resistance to other drugs. World-wide, about 3% of all newly diagnosed patients and a considerably higher proportion of patients who have previously received antituberculosis treatment have MDR-TB. While host genetic factors may probably contribute, irregular, incomplete and inadequate treatment is the single most important factor resulting in the development of MDR-TB. Management of MDR-TB is a challenge as it requires prolonged use of expensive second-line drugs that are not widely available with a significant potential for toxicity. Furthermore, centres equipped with reliable laboratory service for mycobacterial culture and *in vitro* sensitivity testing are seldom available. Given these constraints, the best method to contain this menace appears to be.

**Key Words :** Multidrug-resistant tuberculosis, MDR-TB, epidemiology, diagnosis, drug resistance mechanisms.

## Introduction

Globally, tuberculosis (TB) is considered to be a major public health hazard. According to the recent estimates, in 2000 there were an estimated 8.3 million new cases of TB worldwide; 95% of TB cases and 98% of TB deaths are in developing countries<sup>1,2</sup>. With the availability of definitive antituberculosis treatment and the introduction of "short-course treatment", cure for TB became a reality. However, there has been a global recurrence of TB with the advent of HIV infection-the acquired immunodeficiency syndrome (AIDS) pandemic<sup>3,4</sup>.

## Definition

Isoniazid, and rifampicin are the keystone drugs in the management of TB. While resistance to either of them may be managed with other first line drugs, resistance to both isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs with limited sterilising capacity that are not suitable for short-course treatment<sup>5</sup>. It is possible to strictly define a given isolate of *Mycobacterium tuberculosis* as "multidrug-resistant" only after performing mycobacterial culture and *in vitro* sensitivity testing. The term MDR-TB has been used in this review in the strict sense of the definition referring to isolates resistant to both isoniazid and rifampicin with or without resistance to other drugs since the therapeutic implications are different. Presently, the terms resistance among new cases, and resistance among previously treated patients are preferred over the older terms such as primary and acquired resistance as these are more precise.

## Epidemiology

**World :** Though earlier studies suggested that drug resistance was a potential problem, it was the emergence of MDR-TB in the USA in the 1990s which attracted the attention<sup>6</sup>. The report by the World Health Organization (WHO)-International Union Against Tuberculosis and Lung Disease (IUATLD) Global Project on Anti-tuberculosis Drug Resistance Surveillance between 1994 and 1997 which describes the prevalence of resistance to four first-line antituberculosis drugs in 35 countries<sup>6</sup>. In this study<sup>6</sup> resistance to antituberculosis drugs was found in all 35 countries surveyed suggesting that it is a global problem. The median prevalence of acquired MDR-TB was 13%, with a range of 0% (Kenya) to

54.4% (Latvia). Subsequently, WHO-IUATLD survey (6) was extended to define this problem further<sup>7</sup>. Between 1996 and 1999, patients in 58 geographic sites were surveyed<sup>8</sup>. The median prevalence of MDR-TB among new cases of tuberculosis was only 1%, but the prevalence was much higher in Estonia (14.1%), Henan Province in China (10.8%), Latvia (9%), the Russian oblasts of Ivanovo (9%) and Tomsk (6.5%), Iran (5%), and Zhejiang Province in China (4.5%). Results of resistance surveys from 64 countries, together with data predictive of resistance rates from 72 others suggest that an estimated 273,000 new cases of MDR TB occurred worldwide in 2000 and constituted 3.2% of all new TB cases (8). Further details are expected to be known in the third report on the Antituberculosis drug resistance in the world that is likely to be available on-line soon.

**India :** Reliable data on the epidemiology of MDR-TB are lacking from India<sup>9</sup>. In India, prevalence of primary MDR-TB in newly diagnosed cases has been observed to be 3.4% or less<sup>5,9</sup>. Data meticulously collected at the Tuberculosis Research Centre (TRC), Chennai over the last three decades suggest that MDR-TB levels in newly diagnosed patients has been 1% or less<sup>5,9,10</sup>.

Prevalence of MDR-TB among previously treated patients has been observed to be higher ranging from 9% to 80%<sup>5,9,10</sup>. However, caution has to be exercised in interpreting the prevalence figures published in studies with a small sample size because of inherent methodological concerns.

## Biologic and Molecular Basis of Drug Resistance

Spontaneous chromosomally borne mutations occurring in *Mycobacterium tuberculosis* at a predictable rate is thought to confer resistance to antituberculosis drugs<sup>5,12,13</sup>. A characteristic feature of these mutations is that they are unlinked. Thus, resistance to a drug is usually not associated with resistance to an unrelated drug. This means that, if mutations causing resistance to isoniazid occur in about 1 in 10<sup>6</sup> replications of bacteria, the probability of spontaneous mutations causing resistance to both isoniazid and rifampicin would be 10<sup>6</sup> × 10<sup>6</sup> = 1 in 10<sup>14</sup>. Given that this number of bacilli cannot be found even in patients with extensive cavitary pulmonary tuberculosis (a tuberculosis cavity usually contains 10<sup>7</sup> to 10<sup>8</sup> bacilli), the chance of spontaneous dual resistance developing is practically remote<sup>5,12,13</sup>. Thus, the fact that mutations are "unlinked", forms the scientific basis of antituberculosis chemotherapy. Currently, the primary mechanism of multiple drug

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resistance in tuberculosis is due to perturbations in the individual drug target genes. Table 1 lists the molecular mechanisms of antituberculosis drug resistance that are considered to be important<sup>5,12,13</sup>. Multidrug transporters comprise four families of transmembrane efflux proteins that actively pump out a broad range of structurally unrelated compounds from the interior of the cell, using either proton motive force or ATP supplied energy<sup>5</sup>. The potential contribution of these multidrug transporter proteins in the causation of MDR-TB merits further evaluation. These transmembrane efflux proteins also appear to be novel target for drug therapy in future<sup>5</sup>.

**Table 1 : Molecular mechanisms implicated in antituberculosis drug resistance.**

| Drug             | Gene(s) involved in drug resistance                    |
|------------------|--|
| Isoniazid        | Enoyl acp reductase ( <i>inhA</i> )                    |
|                  | Catalase-peroxidase ( <i>katG</i> )                    |
|                  | Alkyl hydroperoxide reductase ( <i>ahpC</i> )          |
|                  | Oxidative stress regulator ( <i>oxyR</i> )             |
| Rifampicin       | RNA polymerase subunit B ( <i>rpoB</i> )               |
| Pyrazinamide     | Pyrazinamidase ( <i>pncA</i> )                         |
| Streptomycin     | Ribosomal protein subunit 12 ( <i>rpsL</i> )           |
|                  | 16s ribosomal RNA ( <i>rrs</i> )                       |
|                  | Aminoglycoside phosphotransferase gene ( <i>strA</i> ) |
| Ethambutol       | Arabinosyl transferase ( <i>emb A,B and C</i> )        |
| Fluoroquinolones | DNA gyrase ( <i>gyr A and B</i> )                      |

Adapted from reference 5

## Potential Causes of Drug Resistance

Various factors have been implicated in the causation of MDR-TB<sup>5</sup>. These are discussed below.

**Genetic factors :** Though there is some evidence to postulate host genetic predisposition as the basis for the development of MDR-TB, it has not been conclusive<sup>5</sup>. It is likely that these loci for the alleles linked with them play a permissive role in conferring increasing susceptibility to the development of MDR-TB.

### Factors related to previous antituberculosis treatment:

**Incomplete and inadequate treatment :** Review of published literature strongly suggests that the most powerful predictor of the presence of MDR-TB is a history of treatment of tuberculosis. Irregular, incomplete, inadequate treatment appears to be the most common means of acquiring drug resistant organisms. Use of single drug to treat TB is another common predisposing cause in the India setting. This could have occurred because of ignorance; use of penicillin/streptomycin combinations; use of rifampicin for other diseases; and economic constraints. There is also the risk of use of unreliable drugs with poor bioavailability. Use of antituberculosis drugs by unqualified persons or alternative medicine practitioners resulting in bizarre regimens for inadequate periods.

**Poor treatment compliance :** The change over from fully supervised sanatorium treatment to unsupervised domiciliary treatment has affected compliance significantly. Poor compliance with treatment is also an important factor in the development of acquired drug resistance. Non-compliance with prescribed treatment is often underestimated by the physician and is difficult to predict. The drug defaulter, just like placebo reactor is not a consistent or readily identified person. In the west, demographic factors such as age, sex marital status, education level and socio-economic status have not been found to correlate with the degree of compliance. On the other hand, certain factors such as psychiatric illness, alcoholism, drug addiction and homelessness do predict

non-compliance. This may not be entirely true in the Indian context and the relevance of these factors in the Indian scenario merits further study<sup>5</sup>.

**Lack of laboratory diagnostic Facilities :** Good, reliable laboratory support is seldom available in developing nations, the areas where MDR-TB is a major health hazard. When facilities for culture and sensitivity testing are not available, therapeutic decisions are most often made by algorithms or inferences from previous treatment<sup>14</sup>. Programmatic approach has been observed to fail in some settings and published data suggest that standard short-course chemotherapy, based on first-line drugs, is an inadequate treatment for some patients with drug-resistant TB<sup>15,16</sup>. Although the DOTS strategy is the basis of good TB control, the strategy should be modified in some settings to identify drug-resistant cases sooner, and to make use of second-line drugs in appropriate treatment regimens<sup>17,18</sup>.

**Predictors for the development of MDR-TB :** In most of the published studies, previous history of tuberculosis and past history of antituberculosis treatment have been implicated in the causation of MDR-TB<sup>5</sup>.

## Implications for treatment

Second-line drugs are very difficult to obtain in small towns and rural areas in India. Therefore, reliable supply of drugs is a difficult problem. Moreover, there is a wide variation in the price range between different pharmaceutical brands. Reliable pharmacokinetic data regarding bioavailability of most of these formulations is not available either. Moreover, there is no assurance that the most expensive brand names have the best bioavailability profile. Even considering the cheapest brand names available, the cost of drug treatment alone is much beyond the means of the average Indian patient. Therefore, long term compliance is not very good. All these factors constitute significant therapeutic challenges for the clinicians treating MR-TB in the field setting. Population migration due to poverty to seek better job opportunities, because of natural disasters, wars political instability and regional conflicts also create mobile populations. These factors make treatment of MDR-TB difficult, as it is not easy for persons who are forced to move for any of a variety of reasons to complete 24 months of treatment<sup>5</sup>.

## References

1. The global tuberculosis epidemic. Available at URL: <http://www.theglobalfund.org/en/about/fighting/tuberculosis/default.asp>. Accessed on 12 December 2004.
2. Harries A, Maher D, Graham S. TB/HIV: a clinical manual. 2nd edition. Geneva: World Health Organization;2004. WHO/HTM/TB/2004.329.
3. Mohan A, Sharma SK. Epidemiology. In: Sharma SK, Mohan A, editors. Tuberculosis. New Delhi: Jaypee Brothers Medical Publishers;2001.p.14-29.
4. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 2003;163:1009-21.
5. Shama SK, Mohan A. Multidrug-resistant tuberculosis. Indian J Med Res 2004;120:354-76.
6. Anti-tuberculosis drug resistance in the world. The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994-1997. WHO/TB/97.229. Geneva: World Health Organization;1997.
7. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, et al. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against

- Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 2001;344:1294-303.
8. Dye C, Espinal MA, Watt CJ, Mbiaga C, Williams BG. Worldwide incidence of multidrug-resistant tuberculosis. *J Infect Dis* 2002;185:1197-202.
  9. Paramasivan CN, Venkataraman P. Drug resistance in tuberculosis in India. *Indian J Med Res* 2004;120:377-86.
  10. Paramasivan CN. Status of drug resistance in tuberculosis after the introduction of rifampicin in India. *J Indian Med Assoc* 2003;101:154-6.
  11. Vareldzis BP, Grosset J, de Kantor I, Crofton J, Laszlo A, Felten M, Raviglione MC, Kochi A. Drug-resistant tuberculosis: Laboratory issues. World Health Organization recommendations. *Tuber Lung Dis* 1994;75:1-7.
  12. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis*: 1998 update. *Tuber Lung Dis* 1998;79:3-29.
  13. Eltringham IJ, Drobniewski F. Multiple drug resistance tuberculosis: aetiology diagnosis and outcome. *British Med Bulletin* 1998;54:569-78.
  14. Crofton J, Chaulet P, Maher D, Grosset J, Harris W, Horne N, et al. Guidelines for the management of drug-resistant tuberculosis. Geneva: World Health Organization; 1997.
  15. Coninx R, Mathieu C, Debacker M, Mirzoeff F, Ismaelov A, de Haller R, Meedings DR. First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculosis* in prisons. *Lancet* 1999;353:969-73.
  16. Espinal MA, Kim SJ, Suarez PG, Kam MK, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis. Treatment outcomes in 6 countries. *JAMA* 2000;283:2537-45.
  17. Espinal MA, Dye C, Raviglione M, Kochi A. Rational 'DOTS plus' for the control of MDR-TB. *Int J Tuberc Lung Dis* 1999;3:561-3.
  18. O'Brien RJ, Vernon AA. New tuberculosis drug development: how can we do better? *Am J Respir Crit Care Med* 1998;157:1705-7.

### IMSA News

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# Diagnosis of MDR Tuberculosis

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**Abstract:** Tuberculosis is responsible for 7% of all adult deaths and 25% of preventable adult deaths. Multi-drug resistant tuberculosis strains are viewed as mainly a problem of the developing world and are resistant to at least two drugs, INH and Rifampicin. Acquired resistance or secondary resistance is more common than primary resistance. Primary drug resistance is that when a patient who has not been previously on anti tubercular therapy (ATT) and develops resistance whereas acquired resistance develops while on an inappropriate ATT regimen. The frequency of multi drug resistance varies geographically. High resistance was found in erstwhile countries of the USSR, the Baltic Republics, Argentina, Nepal and China. In our centre resistance observed has been 5%-7%. Survey of initial MDR TB cases in community is important for redesigning the effective regimen for new cases and also for planning appropriate regimen for cases requiring re-treatment.

## Introduction

According to WHO, approximately 7 to 8 million people have tuberculosis and around 3 million die annually due to this infection. In India about 2 million cases are infected every year. Multi-drug resistant tuberculosis (MDR-TB) strains are resistant to at least two drugs i.e. INH and rifampicin; frequency of such resistance varies geographically (Table 1). MDR-TB is being highlighted as a problem of the developing world; prevalence varies from 14.5% in Korea to 33.8% Gujarat (India); In our centre drug resistance varies from 5 to 7 percent (Fig.1).

Table 1 : Percent Drug resistance from different parts of World and India<sup>2</sup>.

| Place/Year of Reporting   | One or more drug | INH   | Rifam-picin | Strepto-mycin | EMB   | PZA | MDR  | Remarks  |
|---------------------------|------------------|-------|-------------|---------------|-------|-----|------|----------|
| Japan 2003                | 1.9              | 0.81  | 5.1         |               | 0.81  |     | 0.32 | Primary  |
|                           | 9.7              | 11.5  | 7.3         |               | 2.4   |     | 6.1  | Acquired |
| Madagascar (2000)         |                  |       |             |               |       |     | 5    | Acquired |
| Gambia 2003               | 4                |       |             |               |       |     |      |          |
| China 2002                | 17.5             |       |             |               |       |     | 21   | Primary  |
| Ajajbei-jan Prison (2001) |                  |       |             |               |       |     | 52.3 | -        |
| Central India 2001 (4)    |                  | 54.2  |             | 41.5          |       | 50  | 81   | -        |
| Saudi Arabia 2002         | 50               | 91    | 28          | 36            | 16    | 5   | 28   | -        |
| Jodhpur 2000 (5)          |                  | 16.67 | 6.67        | 16.67         | 6.67  |     | 33   | Primary  |
|                           |                  | 61.76 | 70.59       | 51.52         | 39.39 |     | 38.2 | Acquired |

EMB: Ethambutol, PZA: Pyrazinamide; MDR: Multidrug resistance

It is essential to understand that for **laboratory diagnosis** of MDR-TB, the most important step is the firm diagnosis of tuberculosis; the question of its resistance needs be settled later. This is also a fact that in certain percent cases culture is not positive for *M. tuberculosis*. Since it is not easy to achieve the gold standard there is a consensus evolving round the world whether culture - so far gold standard, needs to be altered in favour of compelling clinical evidence fortified with newer molecular tools.

To diagnose MDR-TB nothing different needs to be done than the methods used for diagnosing a sensitive strain of *M. tuberculosis*. But identification of acid-fast bacilli (AFB) with regard to its species is equally important. The role of NIM has become more pronounced with the advent of the scourge of HIV, more so in

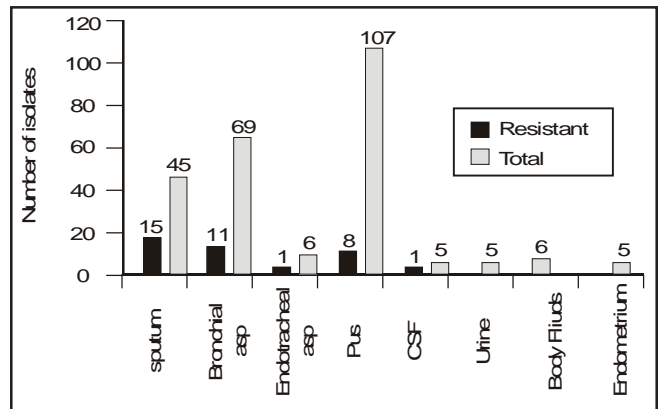


Fig. 1 : Resistant isolates at SGRH

advanced countries where tuberculosis had been brought under control. However, in developing countries where tuberculosis is still rampant, atypical mycobacteria are still a minority. There is no evidence in their being transmitted directly from man to man. They are generally resistant to the antitubercular drugs and might be diagnosed as MDR-TB. As the generation time of mycobacteria is much longer than the other usual pathogenic organisms, advent of rapid culture methods along with molecular techniques can produce faster results with speculation as well. Table 1 gives the prevalence of drug resistance (MDR) in India and abroad.

## Sample Collection

Sputum is the most frequently examined specimen for the detection of AFB, it is important to evaluate sufficient number of samples from each patient to ensure recovery of even low numbers of mycobacteria. Besides this, the quality of the specimen is of paramount importance. Clinician should spend time explaining to the patient the method of producing good quality sputum. Three deeply expectorated morning sputum samples on three consecutive days are usually adequate.

When sputum is unavailable or the findings are constantly negative in patients with convincing clinical evidence of pulmonary tuberculosis, gastric lavage may be necessary and such samples must reach the laboratory promptly since mycobacteria do not survive for long period in acidic gastric washing. The recommended guidelines for the collection of various types of samples are given in Table 2. The significance of representative sample collection in adequate quantity and with minimum

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transportation time helps in proper evaluation for mycobacterial disease. This is more true for samples like C.S.F., pleural fluid and other body fluids. (Table 2)

**Table 2 : Recommended guidelines for sample collection.**

|                          |   |
|--------------------------|---|
| Aspirates-Fluids         | Sterile syringe, container, or direct inoculation on culture media.                               |
| Blood, Bonemarrow        | Isolator or direct inoculation on culture media   |
| BAL                      | Sterile cotainer  |
| Gastric lavage           | Sterile container with 100mg of sodium carbonate; may be useful if sputum is difficult to obtain. |
| Sputum                   | Expectorate from lungs by a productive cough (not saliva), sterile container.                     |
| Stool                    | Clean container   |
| Tissues biopsy specimens | Sterile container, do not add formalin  |
| Urine                    | Firt whole morning void at least 100ml; do not pool over 24 hours.                                |

(Reproduced from suppl. Indian J Paediatr 2002;69:S11-S19)

## Microscopy

It is a rapid and the best method to identify the presence of the organism viable or nonviable in a clinical sample. It has been estimated that when using concentration techniques approximately  $10^4$  AFB/ml of sputum are required for a microscopy to be positive. Patients with extensive disease shed large number of mycobacteria with good correlation between positive culture and smear. In patients with minimal or less advanced disease the correlation of positive smears to positive cultures may be only 25%-40%<sup>1</sup>.

Two types of acid fast staining can be used: (i) *Ziehl-Neelson (ZN)* and (ii) *Auramine-Rhodamine (AR) Fluorochrome staining*. Approximately 18% of ZN smear negative but culture positive patients can in addition be diagnosed using A-R staining<sup>2</sup>. Similar results were also seen in SGRH as reflected in fig 2. Dead mycobacterial cells will also stain with fluorochrome stain leading to smear positive and culture negative situation in approx. 10% of cases and need be kept in mind while assessing treatment efficacy. Smear positive does not indicate treatment failure<sup>2</sup>.

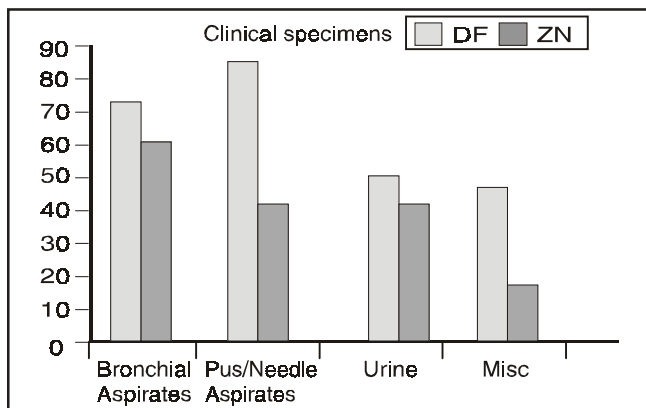


Fig. 2 : Comparative analysis of DF and ZN in SGRH

(Reproduced from suppl. Indian J Paediatr 2002;69:S11-S19)

## Culture

**1 Conventional Mycobacterial Culture :** As low as 10-100 bacilli/ml can result in a culture positivity. It is mandatory that all highly suspect samples be subjected to culture. A variety of

methods and media are in use to culture mycobacteria in-vitro. The most popular media in clinical laboratory is Lowenstein Jensen as a solid media and Middlebrook 7H9 being its liquid counterpart. this age-old method of mycobacterial culture takes a very long time i.e. 6 to 8 weeks (average 21 to 28 days) for *Mycobacterium tuberculosis* to form colonies & the same time is required for sensitivity in this medium. Thus a total of 12-16 weeks is required for culture and sensitivity using this method.

## 2 Rapid Mycobacterial culture methods :

**2a Bactec Systems/MB-BacT :** Substantial improvement in the time to detection and the total number of positive cultures can be achieved if automated or semi-automated liquid culture systems such as BACTEC™ 460TB that use Middlebrook 7H12 is used. This radiometric system can detect growth much earlier than the eye can see on solid conventional media (LJ). Widely used BACTEC™ 460TB system utilises 7H12 broth containing Carbon 14(<sup>14</sup>C) labeled palmitic acid along with the mixture of antibiotics (PANIA, BBL). The growth can be ascertained by the liberation of <sup>14</sup>C<sub>2</sub> by the mycobacteria. But other contaminant bacteria can also break down palmitic acid and result in false positive results.

New systems that rely on non-radiometric growth have been developed such as MB BacT/3D (bioMerieux) (fig.3), Mycobacterial Growth Indicator Tube (MGIT-Becton Dickinson) and BACTEC™ 9000TB automated culture systems, appear to be more promising. The time required for isolation is reduced from 6 weeks to 3 weeks. In addition the turn around time using BACTEC/MB BacT-3D systems is reduced; smear positive specimens can be positive within 8 days as compared to 18 days in conventional medium In smear negative samples the mean time to detection with rapid culture is 14 to 16 days as compared to 26 days for the conventional medium<sup>3</sup>. Antibiotic sensitivity also can be done using these instruments by adding a known MIC of the drug to

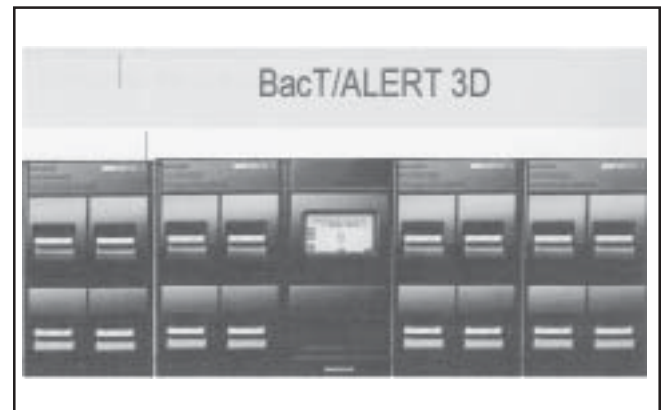


Fig. 3

the liquid media & reduce mean time for detection o almost 11 to 18 day<sup>3</sup>.

**2b Septi-Check System :** Another broth based system introduced is Septi-Chek AFB (BBL) which uses a biphasic media and provides rapid growth and drug susceptibility without need for routine subculturing. Detection time is shorter than with conventional agar but significantly longer than the BACTEC/MB-BacT-3D systems.

**2c Isolator lysis centrifugation system :** The isolator tube (WAMPOLE) provides a unique approach to the recovery of mycobacteria from blood. Approximately 10ml of blood is collected into the Isolator tube containing an anticoagulant and saponin,

which will lyse the red blood cells, releasing any microbe within. After centrifugation at 3000x g for 30 minutes, the sediment is removed and inoculated into a variety of automated mycobacterial system and 80% isolats were recovered with the mean time to detection as 14.4 days.

**2d The Luciferase Reporter mycobacteriophage (LRP) test** - a virus that infects mycobacterium has a cloned gene responsible for production of Luciferase Reporter enzyme which emits light in the presence of mycobacterium. This method is very sensitive, specific and rapid test and is equally effective as MGIT 960 in detecting MTB<sup>5</sup>.

## Identification

**a Conventional methods** for identification rely on morphology and biochemical reactions like tube catalase at 68°C, niacin, and nitrate tests which are cumbersome and could take as long as two months using standard methods, in contrast to accuprobe which identifies it from culture in less than an hour.

### b Rapid Mycobacterial identification techniques

**bl. the Accuprobe (GenProbe, USA) system (fig.4)** : Tests for the identification of MIB complex is a rapid DNA probe test which utilizes the technique of nucleic acid hybridization for the specific identification of MIB complex isolated from the culture. The TB complex includes following species; *M.tuberculosis*, *M.bovis*, *M.bovis BCG*, *M.africanum*, *M.microti*, and *M.canettii*<sup>6</sup>. *M.tuberculosis* is most common pathogen isolated from humans, *M.bovis BCG* may be transmitted from infected animal to humans, and the others primarily infects animals. *M.africanum* causes pulmonary tuberculosis is tropical Africa. For most clinical laboratories identification of an isolate as TB Complex is sufficient because the probability that an isolate is a species other than *M.tuberculosis* is extremely small<sup>7</sup>.



Fig. 4 : Accuprobe Luminometer (GEN-PROBE)

**Principle** - The accuprobe system uses a single stranded DNA probe with a chemiluminescent label that is complementary to the ribosomal RNA of the target organism. After the RNA is released from the organism it forms a stable RNA-DNA hybrid. The selection reagent allows for the differentiation of non hybridised and hybridized probe. The labeled DNA-RNA hybrid are measured in a luminometer. A positive result is aluminometer reading equal to or greater than the cut off. A value below the cut off is a negative result.

**In Our experience at SGH** : Out of 38 smear positive samples processed since June 15 - Dec 9, 2004, 29 were Bactalert 3D (bio-Merieux, France) culture positive and subsequently accuprobe

positive for MIB - complex; whereas 5 culture positive were accuprobe negative for MIB; thereby indicating that 5 smears and culture positive cases were NIM, if not speciated would have been presumed to be *M.tuberculosis* and treated with no or diminished response to ATT. Such cases run a risk of being labelled as MDR-TB. Break up details of NIM positive cases can be obtained from figure 5.

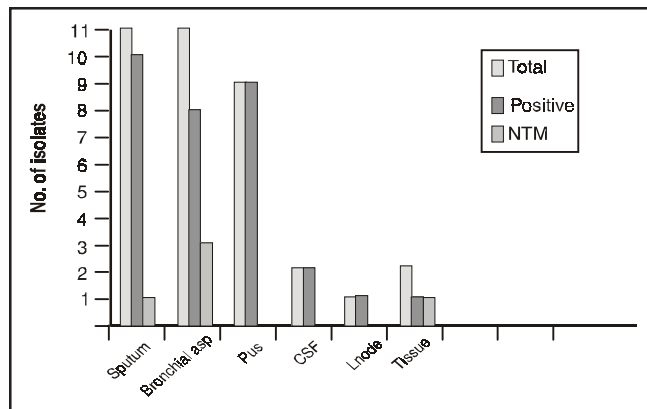


Fig. 5 : Accuprobe results

## Molecular Assays in the Diagnosis of Tuberculosis

### Amplification assays - DNA or RNA based.

#### A. DNA amplification assays

**1 Polymerase chain reaction (PCR)** : First described in 1988, it was used to detect *M.tuberculosis* from the clinical samples like C.S.F., urine and other body fluid and blood using molecular methods. A positive PCR result using *M. tuberculosis* specific primers on a smear positive sample would indicate that AFB seen were *M.tuberculosis* whereas a negative PCR would suggest an NIM, as long as proper controls are included in the assays. With a smear negative specimen, however a negative PCR does not exclude the presence of *M.tuberculosis*. Inhibitors are known to exist in CSF or pus samples that can inhibit amplification in any molecular assay<sup>8</sup>. PCR cannot differentiate between the dead or live mycobacteria.

**2 Other DNA application assays** : are Ligase Chain reaction LCR, Strand displacement assay SDA and  $\phi$  replicase amplification which has not gained as much prominence as PCR. Advantage of these assays are that they are sensitive but cannot differentiate dead from a living bacilli.

#### B. RNA amplification assays -

**1 NASBA** : Nucleic acid sequence based amplification assay (NASBA) used in identifying MIB and NIM (from a positive bottle) using specific probes. (NASBA; bio-Merieux/Organon & Technika).

**2 TMA**: Transcription mediated amplification (TMA; Genprobe, bio-Merieux).

Both are isothermal amplification methods. Instead of using DNA as the target, uses 16S rRNA, which is more abundant than the corresponding DNA making it more sensitive than PCR. The rRNA is transcribed by a reverse transcriptase forming a transcription complex from which isothermal amplification of the target sequence is catalysed by RNA polymerase. The amplified nucleic acid is detected using electro-chemiluminescence technique. The sensitivity and specificity of such tests have been well established in both single and comparative evaluations. The sensitivity and specificity for most of the above tests fall within

the same range of values given for PCR.

**Advantage over DNA assays :** The detection of *Mycobacterium tuberculosis* By NASBA 16S rRNA also gives an added information regarding the viability of the organism as compared to the DNA based PCR technique which could pick up even dead sequences as mentioned earlier.

**C Other Assay** available commercially as a kit is (LiPA MYCOBACTERIA; Innogenetics Zwijndrecht, Belgium) based on reverse hybridisation system principle<sup>9</sup>. PCR is used to amplify the 16S-23S ribosomal spacer region and the product is hybridised to probes bound to a nylon strip; binding is identified colorimetrically. Unlike acuprobe, a single test can identify the range of species using specific probes. This technique can be used for identification of mycobacteria isolated from MB BacT/3D system.

Needless to say, appropriate infrastructure, staff training and quality control procedures are essential to avoid cross contamination events leading to false positive results in all the above mentioned molecular assays. Moreover the laboratory report is as good as the quality of the specimen submitted.

### Seroassay for MIB

ELISA for TB was found positive in 79.4% of sputum AFB positive patients but was also positive in 56.2% of AFB negative sputum samples<sup>10</sup>. All seroassays must be evaluated in light of the clinical evidence and should not be taken as the sole evidence of infection. Seroassay moreover has no role in diagnosing MDR-TB.

### Detection of Drug Resistance

There is a limitation in adequate interpretation of drug resistance due to lack of standardisation of laboratory procedures resulting in misleading reports with poor reproducibility, as a result a poor knowledge of the true incidence of drug resistance exist.

There are three widely used methods for drug sensitivity on the Lowenstein-Jensen medium:

**1 The absolute concentration method** also termed as minimum inhibitory concentration (MIC) method - a standardised inoculum of the organism is inoculated on a drug free media (control) and media containing graded concentration of the drug as a test. Resistance is expressed as the lowest concentration of the drug that inhibits growth on all or almost all tubes indicating MIC.

**2 The resistance ratio method :** Resistance of the test organism is compared with that of a standard laboratory strain and expressed as the ratio of the MIC of the test strain with that of the standard strain against each drug.

**3 The proportion method :** If the number of colonies at the known MIC of a drug is > 1% of the colonies grown in drug free medium then the strain is considered clinically resistant. Culture and sensitivity test can also be done using other medias like 7H9, 7H10 or 7H11 Middlebrook. A direct sensitivity on smear positive cases where the drug can be incorporated in the medium can hasten the results to 6-8 weeks, which otherwise could take 12-16 weeks.

**4 E-Test :** It is a gradient minimum inhibitory concentration technique and is found to be quick, accurate, reliable and easy to perform and the results are available between 7-10 days. Agreement between L-J and E test methods is 87% while between L-J and MH11 methods is 79%<sup>11</sup>. It is especially of great value in drug resistant cases where MIC is important. Hausdorfer et al demonstrated more than 90% correlation between E test and agar proportion method for all the four first line antitubercular drugs<sup>12</sup>.

Automated methods currently used for rapid susceptibility testing

of *M. tuberculosis* include MB-Bactalert-3D, BACTEC<sup>TM</sup> 460 radiometric method etc.

### Molecular Diagnosis of Antimicrobial Resistance

The frequency of resistance mutations has been estimated to be 1 in 10<sup>8</sup> for R & 1 in 10<sup>6</sup> for H, respectively and 1 in 10<sup>5</sup> for S, EMB, para aminosalicylic acid (PAS), ethinamide (N), cycloserine and thiazetazone.

**Rifampicin :** More than 95% of rifampicin-resistant MIB isolates have mutations in rpoB, the gene encoding the RNA polymerase  $\beta$ -subunit<sup>13</sup>. INH-Resistance to INH is more complex. Many resistant organisms have mutations in the katG gene encoding catalase-peroxidase that result in altered enzyme structure<sup>14</sup>. S resistant strains have a mutation on the rrs and rpsL gene encoding a 16S rRNA and a S12 ribosomal subunit protein, respectively<sup>15</sup>. Resistance to pyrazinamide (Z) is caused by mutations in the gene pncA, encoding pyrazinamidase resulting in diminished enzyme activity.

**Ethambutol** resistance in approximately 60% of organisms is due to amino acid replacements at position 306 of an arabinosyl transferase encoded by the embB gene.

Similarly **Fluoroquinolones** resistance is associated by gyrA gene mutation. Kanamycin resistance is due to nucleotide substitutions in the rrs encoding 16S rRNA.

Various molecular probes for detection of such resistance genes are being used for predicting resistance but are still not available for commercial use.

### The Future

The current knowledge does not permit utilisation of molecular resistance detection assays as a matter of routine. Molecular assays have a good correlation in smear positive cases only and is recommended for use only in such cases at present by FDA (USA). The issue of quality control (QC) in molecular assays remains yet to be resolved due to the absence of the availability of universally acceptable standard controls allowing acceptable reproducibility of the assay world over.

However genotypic analysis involving amplifications of the genomic region conferring resistance-using PCR, followed by post amplification analysis of mutation causing drug resistance by single strand conformation polymorphism (PCR-SSCP) can reduce the turn around time. Reverse hybridisation based line probe assay also have been used reliably to detect the mutations causing drug resistance. Molecular beacon assays is used in real time PCR to detect as little as a single nucleotide substitution causing drug resistance can be used<sup>16</sup>. The only silver lining in the name of molecular diagnosis of MDR-TB could be the detection of rifampicin or INH resistant cases earlier. early case detection could help in containment of the spread of MDR-TB strains.

Other methods, which can also be used to detect drug resistance, are heteroduplex analysis, dideoxyfingerprinting, an RNA/RNA duplex base pair mismatch assay, rRNA/DNA bioluminescence labeled probe assay and luciferase mycobacteriophage assay in which only viable mycobacteria can allow replication of the phage whereas the dead ones cannot. Isolate grown in the presence of drug will not emit light on addition of luciferin substrate if it is susceptible whereas resistant isolate will.

A commercial kit for detection of mutated gene for resistance would serve as a valid surrogate marker for MDR-TB.

Based on diverse lines of evidence, the fitness estimates of drug-resistant *M. tuberculosis* are quite heterogeneous and may preclude

the ability to predict future trends of this pathogen<sup>17</sup>.

## References

- Koneman E W, Allen SD. *Mycobacteria. Color Atlas And TextBook of Diagnostic Microbiology* ed 5 Philadelphia, Lippincott 1997:893-908.
- Mahon CR Manuseelis G. *Mycobacterium tuberculosis and Nontuberculous Mycobacteria. Text Book of Diagnostic Microbiology* ed 2 Philadelphia, W.B. Saunders 2000:669-705.
- Benjamin WH, Waites KB, Beverly A, et al. Comparison of the MB/Bac T System with a revised antibiotic supplement kit to the BACTEC 460 system for detection of mycobacteria in clinical specimens. *J Clin Microbiol* 1998;36:3234-8.
- Hanna BA, Ebrahimzadeh A, Elliot LB, et al. Multicenter evaluation of the BACTEC MGIT 960 system for recovery of mycobacteria. *J Clin Microbiol* 1999;37:748-52.
- Bardarov S Jr, Dou H, Eisenach K, Banaiee N, Ya S, Chan J, Jacobs WR Jr, Riska PF. Detection and drug-susceptibility testing of *M. tuberculosis* from sputum samples using luciferase reporter phage: comparison with the Mycobacteria Growth Indicator Tube (MGIT) system. *Diagnostic Microbiology and Infectious Disease*, January 2003;45.1:53-61.
- Rossau R, Traore H, De Beenhouwer H, et al. Evaluations of the INNO-LIPA Rif. TB assay, a reverse hybridisation assay for the simultaneous detection of Mycobacterium tuberculosis complex and its resistance to rifampin. *Antimicrob Agetns Chemother* 1997;41:2093-8.
- Sommers HM, Good RC. 1985. Mycobacterium, 216-248. In E.H. Lennette et al (ed.) manual of Clinical Microbiology, 4th ed. American Society of Microbiology, Washington, D.C.
- Boddinghaus B, Wichelhaus TA, Brade V, Bittner J. Removal of PCR inhibitors by silica membrane: evaluating the Amplicor Mycobacterium tuberculosis kit. *J Clin Microbiol* 2001;39:3750-52.
- Koneman EW, Allen SD. *Mycobacteria. Color Atlas And TextBook of Diagnostic Microbiology* ed 5 Philadelphia, Lippincott. 1997:895-912.
- Bardarov S Jr, Dou H, Eisenach K, Banaiee N, Ya S, Chan J, Jacobs WR Jr, Riska PF. Detection and drug-susceptibility testing of *M. tuberculosis* from sputum samples using luciferase reporter phage: comparison with the Mycobacteria Growth Indicator Tube (MGIT) system. *Diagnostic Microbiology and Infectious Disease*, January 2003;45.1:53-61.
- Muralidhar S, Srivastava L. Evaluation of three methods to determine to determine the antimicrobial susceptibility of *M.tuberculosis*. *Indian J of Med Research* 120, Nov 2004:463-467.
- Hausdorfer J, Sompek E, Allberger F et al. E test for susceptibility testing for *M. tuberculosis*. *Int. J. Tuberc. Lung Disease* 1998;2:751-5.
- Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. *Tuber Lung Dis*. 1998;79(1):3-29.
- Torres MJ, Criado A, Gonzalez N, Palomares JC, Aznar J. Rifampin and isoniazid resistance associated mutations in Mycobacterium tuberculosis clinical isolates in Seville, Spain. *Int J Tuberc Lung Dis*. 2002 Feb;6(2):160-3.
- Taniguchi H. Molecular mechanisms of multidrug resistance in Mycobacterium tuberculosis J UOEH. 2000 Sep 1;22(3):269-82.
- Piatek A, Taleati A, Murray M, et al. Genotypic analysis of mycobacterium tuberculosis in two distinct populations using molecular beacons: Implications of rapid susceptibility testing. *Antimicrobial agents and Chemotherapy*, Jan 2000;44(1):103-110.
- Cohen T, Sommers B, Murray M. The effect of drug resistance on the fitness of Mycobacterium tuberculosis. *Lancet Infect Dis*. 2003 Jan;3(1):13-21.

## FIRST ANNOUNCEMENT

## IMSACON 2006

Annual Conference 'IMSACON 2006' will be held on 3-4-5 November 2006 at Lahore (Pakistan) Dr. Shaheena Asif, Surgimed Hospital Lahore is the Organising Secretary.

**Theme :** 'Update in Medical and Dental Sciences'

**Venue :** Lahore Medical & Dental College  
Canal Bank North, Tulpura, Lahore-53400, Pakistan

**Visa :** Visa is required for Pakistan and must be obtained before travel. Please allow 3 months before Conference Date for application to be processed.

| Conference Fee            | Before 1st May06 | Before 1st Aug.06 | 1st Aug.06 onwards |
|---------------------------|------------------|-------------------|--------------------|
| Delegates                 | Rs. 2200         | Rs. 2800          | Rs. 3600           |
| Accompanying Person       | Rs. 1500         | Rs. 2000          | Rs. 2500           |
| Foreign Delegates         | 250 USD          | 300 USD           | 350 USD            |
| Accompanying Person       | 100 USD          | 150 USD           | 200 USD            |
| Trade Delegates           | Rs. 2200         | Rs. 2800          | Rs. 3600           |
| <b>Pre Conference CME</b> |                  |                   |                    |
| PG Students               | Rs. 500          | Rs. 700           | Rs. 1000           |
| Delegates                 | Rs. 800          | Rs. 1000          | Rs. 1200           |
| Accompanying Person       | Rs. 500          | Rs. 700           | Rs. 1000           |

## Abstract Submission

The Scientific Committee invites Abstracts for Poster and Oral Presentations. The abstract must be in approximately 300 words in English. Only original work having relevance to Clinical practice may be submitted. The paper must clearly state the objective, methods, results and conclusions. The presentation must have a title, names of all authors and the institution where the work was done. Please mention the name of the author who will present the paper and complete address, email and phone numbers.

Last date of submission of abstract 30 June 2006. Kindly send on diskette or CD by mail or email to the Conference Secretariat.

**IPS Kalra**  
Secretary General IMSA

# Management of Multidrug Resistant Tuberculosis (MDR-TB)

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**Abstract:** Tuberculosis has been a scourge of the mankind from times immemorial and is still an important health problem. The developments in pharmacotherapy and health programmes indicated the tuberculosis could be contained and probably eradicated. But the present day reality is a stunning contradiction to optimism of the earlier days tuberculosis seems to have struck back with a vengeance. Today, multi drug resistant tuberculosis (MDR-TB) is a dreadful reality and advancing its march to destroy the national programmes to control tuberculosis.

Current prevalence of primary and acquired multidrug resistance in India is 3.4% and 13.3% respectively. Susceptibility testing is the 'Gold-standard' for the diagnosis of MDR-TB which is not the 'absolute' parameter to dictate therapy but should be used to guide therapy along with complete clinical profile. The treatment of MDR-TB is difficult, complicated, much costlier, less frequently affordable, challenging needs experience and skill and individualized for the needs of the particular patient. The therapy once instituted should be carried out despite all discomfort to prevent morbidity, mortality and transmission of MDR-TB as this is, probably the last chance between life and imminent death.

The WHO-programme of 'DOTS-PLUS' highlights the comprehensive management strategy to control MDR-TB optimal treatment of MDR-TB, alone, will not curb or control the epidemic but 'prevention' of ultimate emergence of MDR-TB should be focussed therapy by effective use of firstline drug is absolutely essential.

## Diagnosis of MDR-TB

Early diagnosis and treatment of MDR-TB is of paramount importance not only from the patients perspective but also for the community at large. Consideration of the following are generally contributory to the diagnosis of MDR-TB<sup>1,2,3</sup>.

### High Risk population<sup>4,5</sup> :

- 1 History of contact with known case of MDR-TB.
- 1 History of previous or many irregular or regular treatment of Tuberculosis.
- 1 Cavitory pulmonary tuberculosis.
- 1 Presence of infection with HIV-positive patients are not more prone to MDR-TB than to drug susceptible TB. Rather, epidemiological association of HIV-positive status and MDR-TB reflects nosocomial transmission of TB (some being MDR-TB) and propensity of HIV-positive patients to progress rapidly to active disease<sup>6</sup>.
- 1 Clinical presentation with, interstitial infiltrate, hilar or mediastinal adenopathy, cavitation on chest radiograph has been suggested to be more typical of drug-resistant rather than drug-susceptible disease in HIV-positive patients. There is no convincing evidence for these assertions. Some have found higher rate of cavitation among HIV-positive patients with MDR-TB while others have actually documented fewer cavitory lesions in such patients<sup>7</sup>.
- 1 History of contact with family members and health care professionals of MDR/TB.

### Clinical diagnosis

#### (a) High suspicion :

- 1 *Fall and rise phenomenon* : on antitubercular therapy, sputum

smear initially becomes negative (or less positive) and later becomes persistently positive. This indicates failure usually due to either the patient having ceased to take the drugs or to the development of resistance to all the drugs, patient is receiving.

- 1 *Persistently positive sputum smear* for AFB even after 5 months of WHO or other retreatment regimens.
- 1 Development of *distant complications* of pulmonary tuberculosis during therapy.
- 1 Presence of *extensive multicavitory disease*.

#### (b) Relative Suspicion -

- 1 History of *contracted infection* from a known source.
- 1 *Radiological deterioration* : Even after regular and adequate chemotherapy for 3 months change in size of cavities, increase in existing lesion and appearance of new lesion is an indication of disease progression. However, radiological worsening in addition to, positive sputum-smear for AFB and/or clinical worsening may indicate MDR-TB.
- 1 *Clinical deterioration*: This is the least reliable evidence of MDR-TB, if not associated with bacteriological or radiological deterioration. Failure to defervesce after 2 weeks of treatment with a standard four drug regimen is an independent marker of MDR-TB. In areas with a high prevalence of MDR-TB, broader empirical treatment may be indicated for patients who fail to defervesce<sup>8</sup>.

However, this approach has several limitations. For example, not all patients with TB present with fever. Persistent fever can also be caused by severe miliary disease or another concomitant infection, and is therefore not a specific sign of MDR-TB.

Of the patients who are initially smear-positive, 75% will become

smear-negative after 2 months of treatment with a regimen containing isoniazid and rifampicin, and over 95% will have converted by 5 to 6 months. Smear positivity at 2 months may be caused by nonadherence with treatment, cavitation and heavy initial bacillary load or presence of drug resistance<sup>9,10,11</sup>.

1. **Inadequate and irregular therapy:** In a drug-o-gram (listing of all drugs taken in the past) evidence of inadequate dosage or monotherapy, adequate therapy but for shorter duration is present. At the same time a list of drug 'never' used in therapy and drugs with cross-resistance may also be prepared.

**c Unreliable suspicion :**

1. Past history of antitubercular therapy and has come with fresh relapse.
1. Not gaining weight.
1. No radiological improvement.
1. Radiological deterioration without clinical deterioration.
1. Development of a cavity in exudative lesion on treatment.
1. New shadows may not, necessarily, be tuberculosis.

### Bacteriological diagnosis

Laboratory evidence of resistance to rifampicin and INH is a gold standard for the diagnosis of MDR-TB. There are limitations of these highly specific test-as the technique is complex and difficult to perform accurately even when skilled personnel are available and laboratory facilities are of high standard. One must also consider that sampling of different population of bacilli, and laboratories varying in reliability, errors occurring in laboratory, may be the factors for the different sensitivity reports obtained of the same patient from different laboratories. There is lack of standardization, coordination and cross checking with national laboratories in our country. The conservative approach is to assume that any drug resistance that has been reported is real irrespective of the reputation of the testing laboratory. However the results of sensitivity should not be accepted uncritically. Correlation with history, smear results and radiology should be used as a guide for future therapy and therapy should not be changed if the patient is improving satisfactorily. Newer techniques have greatly shortened the time of obtaining the reports with increased "sensitivity and specificity. Previous therapy with a drug, which has been associated with a reduced clinical response to that drug, despite apparent "Susceptibility" in in-vitro laboratory tests has also to be considered. The presence of dead bacilli can also produce "false positive" smear early in treatment. Patients who were initially smear and culture positive may have culture conversions, but may continue to have positive smears 4 to 20 weeks after commencing treatment. This "Smear positive/culture negative reaction" was more common among patients with cavitory disease and also in those treated with rifampicin containing regimens. WHO recommends extending the intensive four drug treatment phase, for a further month in patients with positive smear at 2 months. However drug treatment is only changed if smear remains positive at 5 months.

### Assessment of patients with MDR-TB

Planning drug therapy for a patient with MDR-TB requires experience, skill and time. The treatment history of the patient must be thoroughly chronicled listing the previous treatments (including preparations that might have been obtained privately from the pharmacists), the patients adherence with these regimens, and the bacteriological response. Clinical and radiological changes should also be recorded. However, these changes can be affected by intercurrent conditions (pneumonia, emolism) and are, therefore, less reliable parameters of progress. The patient's previous drug susceptibility results should also be recorded including those performed at other hospitals.

### Treatment of MDR-TB

The management of MDR-TB is an area that has been shrouded in lot of myths and misconceptions, and therefore, utterly chaotic. Though, WHO guidelines are useful in managing MDR-TB patients but they may not be applicable to every patient. Therefore, therapy should be individually tailored to the needs of a particular patient.

### Basic Principles of Chemotherapy with MDR-TB

- 1.(a) *When sensitivity tests are not available :* A likely resistance pattern can be inferred from the patients history and previous susceptibility results. A patient, who had drug susceptible TB and adhered to a satisfactory treatment regimen, presenting with a relapse years later, is likely to have drug-susceptible disease and will respond to the WHO-retreatment regimen. In contrast, a patient who has failed therapy, is likely to have drug resistant tuberculosis. In this circumstance, a "Retreatment regimen" is used comprising a minimum of 4 to 5 drugs in the "initial phase" and at least 3 of the most active and best tolerated drugs, in the "continuation phase". this regimen should contain drugs to which the bacilli are certainly sensitive i.e. not received previously as the bacilli are unlikely to be resistant to the drugs. A "first line" drug that the patient has received previously may be added to this regimen, if resistance appears unlikely, based on patients previous treatment history. However, such additional drugs must not be relied upon until results of new susceptibility tests are available<sup>2</sup>.

Thus, treatment regimen should ideally contain multiple drugs with "bactericidal activity (a) injectable agent, a quinolone, pyrazinamide, or ethionamide) with the "bacteriostatic" drugs (cycloserine, para-aminosalicylic acid (PAS) added to prevent the development of furter resistance. The initial phase of at least 6 months and continuation phase of 12-18 months, after the sputum has become negative is usually needed.

- (b) *When sensitivity tests are available :* the treatment regimens are straight forward (Table 1).
  - (c) Depending upon the *history of antituberculosis drugs used previously and non availability of sensitivity tests, various combinations, of resistance may be anticipated.*
2. Drugs must be given in adequate dosage (corrected according to weight and duration).

Table 1 : Standard treatment regimen considered suitable if sensitivity lists are available

| Resistance to                                      | Initial phase   |                            | Continuation Phase           |             |
|--|---|----------------------------|------------------------------|-------------|
|  | Drugs   | Minimum duration in months | Drugs months                 | Duration in |
| Isoniazid (streptomycin, thioacetazone)            | Rifampicin  | 2-3                        | rifampicin                   | 6           |
|  | Aminoglycoside <sup>c</sup>                                     | 2-3                        | ethambutol                   | 6           |
|  | Pyrazinamide  | 2-3                        |                              |             |
|  | Ethambutol  | 2-3                        |                              |             |
| Isoniazid and ethambutol (streptomycin)            | Rifampicin  | 3                          | rifampicin                   | 6           |
|  | Aminoglycoside <sup>c</sup>                                     | 3                          | Ethionamide <sup>d</sup>     | 6           |
|  | Pyrazinamide  | 3                          |                              |             |
|  | Ethionamide <sup>d</sup>  | 3                          |                              |             |
| Isoniazid rifampicin                               | Aminoglycoside <sup>c</sup>                                     | 6                          | ethionamide                  | 12-18       |
|  | ethionamide   | 6                          | fluoroquinolone <sup>f</sup> | 12-18       |
|  | fluoroquinolone   | 6                          | pyrazinamide                 | 12-18       |
|  | pyrazinamide  | 6                          | ethambutol +/-               | 12-18       |
|  | ethambutol +/-  | 6                          |                              |             |
| Isoniazid, rifampicin, streptomycin and ethambutol | Aminoglycoside <sup>c</sup>                                     | 6                          | ethionamide                  | 18          |
|  | Ethionamide   | 6                          | fluoroquinolone <sup>f</sup> | 18          |
|  | Pyrazinamide  | 6                          | Cycloserine                  | 18          |
|  | Cycloserine <sup>g</sup>  | 6                          |                              |             |
| Resistance to all drugs                            | Aminoglycoside <sup>c</sup>                                     | 6                          | fluoroquinolone <sup>f</sup> | 18          |
|  | fluoroquinolone <sup>f</sup>                                    | 6                          | 2 of these Ethionamide       | 18          |
|  | 2 of these Ethionamide  | 6                          | PAS                          | 18          |
|  | PAS   | 6                          | Cycloserine <sup>g</sup>     | 18          |
|  | Cycloserine <sup>g</sup>  | 6                          |                              |             |
| Susceptibility test to reserve drugs available     | Tailor regimen according to susceptibility pattern <sup>h</sup> |                            |                              |             |

1. Streptomycin, if still active, if resistance to streptomycin, use kanamycin or capreomycin.

1. If ethionamide is not available or poorly tolerated (even at a dose of 500 mg day) use ofloxacin.

1. Kanamycin or mikacin, or capreomycin

1. Ciprofloxacin or Ofloxacin.

1. PAS if cycloserine is not available or too toxic.

1. Individualized regimen is feasible in designated centers of excellence.

3. Use of first line drugs is preferred because they are most effective and less toxic. INH should be included in all regimens, unless it can not be used due to resistance to it.

4. A previous history of treatment with a particular drug, leads to reduced efficacy of that drug, regardless of "in-vitro" sensitivity.

Table 2 : The regimen is modified as recommended in table 2.

5. Never add a single drug to a failing regimen.

6. It is ineffective to combine two drugs of the same group or to combine a drug, potentially ineffective because of cross-resistance. Cross resistance occurs between thioamides and thioacetazone; kanamycin/amikacin with streptomycin; rifampicin with rifapentine and rifabutin (> 70% strains) and among various derivatives of fluoroquinolones. Cross resistance has also been reported between ethionamide and INH; Viomycin and kanamycin; viomycin<sup>f</sup> and capreomycin. Strains resistant to streptomycin/kanamycin and amikacin are still sensitive to capreomycin.

7. All the drugs should preferably be given in a single daily

dose, except PAS which is usually given in two divided doses in order to avoid problems of intolerance.

8. Intermittent therapy is usually not effective and should be avoided in the treatment of MDR-TB.

9. No drug should be kept in reserve and like most powerful drugs (bactericidal) should be used initially and in maximum combination so as to ensure that the first battle is won and won permanently.

10. Therapy should be initiated in the hospital to permit monitoring of toxicity and drug intolerance. Direct observation therapy (DOT) should be preferably for 3 to 4 months or till the sputum conversion.

11. The treatment may be initiated with a small dose of each drug and gradually increased to the planned dose over 3 to 10 days.

12. All the patients should be monitored by repeated culture and sensitivity tests, monthly during intensive phase and "once in 3 months till the end of therapy. If culture remains positive after 4 months of therapy, the strategy must be changed.

Table 2 : Suggested regimen for resistant/Multidrug Resistant Tuberculosis with Various patterns of past history of treatment.

| Group | Past Treatment                      | Intensive Phase   |                    | Continuation Phase  |                    |  |
|-------|-------------------------------------|---|--------------------|---|--------------------|--|
|       |                                     | Drugs   | Duration in months | Drugs   | Duration in months | Non Responders   |
| I     | Misused drugs like SHE and TZN      | Rifampicin<br>Isoniazid<br>ethambutol<br>Pyrazinamide+<br>Streptomycin  | 2-3*               | Rifampicin<br>Isoniazid<br>Ethambutol+<br>Pyrazinamide  | 9                  | Treat as Group II or Take help of sensitivity result                   |
| I     | Misused drugs like SHREZ TZN        | Streptomycin<br>Isoniazid <del>q</del><br>Rifampicin<br>Ethambutol<br>Pyrazinamide  | 2-3*               | Rifampicin<br>Isoniazid<br>Ethambutol+<br>Pyrazinamide  | 9                  | Treat as Group III Or Take help of Sensitivity result.                 |
| III   | Failed after adequate 5 drugs SHREZ | Aminoglycoside <sup>a</sup><br>Ethionamide<br>Fluoro-quinolone <sup>b</sup><br>Pyrazinamide<br>Ethambutol+<br><b>O R</b><br>Kanyamycin<br>PAS<br>Ethionamide<br>Cycloserine<br>+<br>Isoniazid | 6*                 | Ethionamide<br>Fluoro-quinolone <sup>b</sup><br>Pyrazinamide<br>Ethambutol+                       |                    | Treat Group IV Or Take help of Sensitivity result and consider surgery |
|       |                                     |   | 6*                 | PAS<br>Ethionamide<br>Cycloserine<br>Pyrazinamide<br>+<br>Isoniazid                               |                    |  |
| IV    | Failed on group III treatment       | Aminoglycoside <sup>a</sup><br>Fluoro-quinolone <sup>b</sup><br>Clofazimine<br>Ethio/PAS/Cyclo<br>+<br>Newer ATT <sup>c</sup>   | 6*                 | Fluro-quinolone <sup>b</sup><br>Clofazimine<br>Ethio/Cycle/<br>PAS<br>+<br>Newer ATT <sup>c</sup> | 18                 | Consider surgery   |

\* Amikacin/Kanamycin/Capreomycin

\* Ciprofloxacin/Ofloxacin/Sparfloxacin

\* Clarithro/Azithro/Rifabutin/Coamoxyclav

\* Depending on sputum conversion can be used for 3-6 months if toxicity does not intervene.

Abbreviation - are as followed - R- rifampicin, H-isoniazid, E-thambutol, Z-pyrazinamide, S-streptomycin, K-kanamycin, C-0capreomycin, TZN-thiacetazone.

13. All measures should be taken to persuade and encourage patients not to stop treatment, despite all its discomforts, as it is the last chance that stands between life and death.
14. The bioavailability of the anti tuberculous drugs may be altered in presence of AIDS (as malabsorption is frequent in them). Serum levels may become necessary to optimize therapy and ensure bioavailability.
15. WHO recommend of ATT drugs in fixed dose combinations of proven bioavailabilities adjusted to body-weight. Reduced bioavailability may lead to difference in choice.
16. Among fluoroquinolones, most active agents are levofloxacin, ofloxacin, sparfloxacin and moxifloxacin<sup>13,14</sup>. Ofloxacin

has a bactericidal action and capable of increasing level of activity of isoniazid - rifampicin in three drug combinations during the exponential growth phase. In contrast, ofloxacin has little bactericidal activity against stationary phase and less active than isoniazid or rifampicin alone. Sparfloxacin is 8 times more potent than ciprofloxacin and almost as potent as rifampicin. Unfortunately, sparfloxacin appears less useful because of relatively high rate of photosensitization. Moxifloxacin, while demonstrating very favourable "in vitro"<sup>15</sup> activity does not have the same extended clinical safety as levofloxacin and ofloxacin<sup>16</sup>. Although fluoroquinolones are usually well-absorbed orally, absorption is reduced by concomitant administration of

Table 3 : Second line drugs used for treatment of resistant/MDR Tuberculosis.

| Drugs  | Average daily dosage                                    | Daily Dosage (mg)         |                            | Type of antimycobacterial activity                  |
|--|---|---------------------------|----------------------------|---|
|  |   | Minimum                   | Maximum                    |   |
| Aminoglycosides<br>- Kanamycin<br>- Amikacin<br>- Capreomycin                        | 15mg/kg   | 750                       | 1000                       | bactericidal against actively multiplying organisms |
| Thioamides<br>- Ethionamide<br>- Prothionamide                                       | 10-20mg/kg  | 500                       | 750                        | bactericidal  |
| Cycloserine  | 10-20mg/kg  | 500                       | 750                        | bacteriostatic                                      |
| PAS acid   | 200-300mg/kg  | 10g                       | 12g                        | bacteriostatic                                      |
| Fluroquinolone<br>- Levofloxacin<br>- Ciprofloxacin<br>- Ofloxacin<br>- Sparfloxacin | 10-15 mg/kg<br>15-20 mg/kg<br>7.5-15 mg/kg<br>6-8 mg/kg | 750<br>1000<br>600<br>400 | 1000<br>1500<br>800<br>600 | weakly bactericidal                                 |
| Macrolide<br>- Clarithromycin<br>- Azithromycin                                      | 10-15 mg/kg<br>10mg/kg                                  | 1000mg/kg<br>500 mg/day   |                            | Bactericidal<br>(pH dependent)                      |
| Clofazimine  | 4-5 mg/kg   | 100                       | 200                        | bacteriostatic                                      |
| Beta Lactam<br>- Coamoxylav  |   | 750                       | 2 gm                       | weakly bactericidal                                 |

antacids. Ofloxacin is better absorbed than ciprofloxacin and has a bioavailability approaching 100%<sup>17</sup>.

17. Surgical treatment may be applied more frequently and aggressively as the overall cure-rate may be much higher (81% vs 56%). Feasibility and success appears to be substantially enhanced by nutritional support.

### Second Line Drugs Used for MDR-TB

The use of the first line drugs for treatment of pulmonary tuberculosis is well established. However, some pharmacological aspects of "secondline" drugs for planning antitubercular therapy are given in Table 3.

**Kanamycin, amikacin, capreomycin** : Kanamycin is a glycoside of 2-deoxy-streptomycin and amikacin is a derivative of kanamycin. The aminoglycosides inhibit protein synthesis by irreversibly binding to the bacterial 30S ribosomal subunit and blocking the aminoacyl-tRNA. Cross-resistance occurs between kanamycin and amikacin because of their structural similarity, but cross-resistance between them and streptomycin is rare. Capreomycin has a similar action and adverse effects to, the aminoglycosides. However, it is a basic polypeptide antibiotic and so cross-resistance with aminoglycosides occurs occasionally. All of these injectable agents are bactericidal against actively multiplying bacilli and have, therefore, become essential agents in treatment of MDR-TB. The major adverse effects of kanamycin include hearing loss, ataxia, nystagmus nephrotoxicity, electrolyte abnormalities and are

contraindicated in pregnancy. Amikacin and capreomycin have similar adverse effects.

The usual daily dose of kanamycin and amikacin is 15 to 30 mg/kg given intramuscularly, with a maximal daily dose of 750mg to 1gm<sup>8</sup>. These drugs can also be given by intravenous infusion through a central line<sup>3</sup>. Following parenteral administration these drugs can be detected in body tissues and fluids. They cross the placenta but their penetration into the cerebrospinal fluid (CSF) is unreliable. Excretion is by glomerular filtration. As, with both agents ototoxicity is more common than nephrotoxicity a monthly audiometry is, therefore, recommended while patients are on treatment. If there is renal impairment, dosage adjustment and careful monitoring of renal function are required. Capreomycin is given by intramuscular injection of the daily dose of 15-30mg/kg to a maximum dose of 1. The dosage should not exceed 20 mg/kg/day for more than 40 to 120 days because of the risk of adverse effects, increases thereafter<sup>8</sup>. If necessary, capreomycin can be continued but given only 2 to 3 times per week. It can also be given intravenously with good tolerability. Capreomycin causes high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs<sup>9</sup>. It is, therefore, recommended to do monthly audiometry with occasional examination of vestibular function. Renal toxicity may also occur, especially in the elderly among whom total daily dose should not exceed 750mg. Electrolyte disturbances, like hypokalemia, hypocalcemia, hypomagnesaemia, possibly result from tubular damage may be observed with

capreomycin (and the aminoglycosides), particularly after 3 to 4 weeks of antituberculosis therapy<sup>9</sup>. It is advisable to monitor renal function and serum biochemistry regularly. Cutaneous reactions and hepatitis may occur rarely. Capreomycin is contraindicated in pregnancy and avoided in children<sup>9</sup>.

**Ethionamide** : Ethionamide (2-ethyl-pyridine-4-carboxylic acid thioamide) is a derivative of isonicotinic acid and exerts a bactericidal effect by inhibiting mycolic acid synthesis. However, isoniazid-resistant isolates of *M.tuberculosis* are susceptible to ethionamide suggesting different sites of action for these two drugs. Ethionamide is also structurally related to thioacetazone. Isolates resistant to thioacetazone are usually sensitive to ethionamide but ethionamide resistance is almost always associated with thioacetazone resistance. Prothionamide is the N-propyl derivative of ethionamide and has similar activity, clinical efficacy and adverse effects<sup>20</sup>. Ethionamide is absorbed from the gastrointestinal tract and distributed widely throughout the body, including CSF. The drug is extensively metabolised in the liver with less than 1% appearing unchanged in urine. The usual daily dose is 15 to 20mg/kg. (500 to 1000mg.) in divided doses with a maximum daily dose of 1g. The main adverse effect of the ethionamide is gastrointestinal intolerance (nausea, metallic taste, epigastric discomfort, and diarrhoea). The drug should be introduced slowly in 250mg increments as tolerated, and can be given with milk or at bed time with a sedative to avoid nausea. Hepatitis with jaundice (4.3%) can occur up to 5 months after commencing therapy<sup>8</sup>. Withdrawal of therapy usually results in resolution. Hepatic enzymes should, therefore, be monitored monthly. Transient elevations in levels may be observed but they usually normalize despite continued administration of the drug. Hence, in absence of symptoms or jaundice, ethionamide administration should only be stopped, if there is a 5-fold elevation of AST or ALT. Other adverse effects include psychotic reactions, convulsions, headache, dizziness, peripheral neuritis, hypoglycaemia (important in patient with diabetes mellitus), hypothyroidism, gynecomastia, acne, menstrual abnormalities, impotence and alopecia and therefore, should be used carefully in patients with diabetes mellitus, liver disease and psychiatric conditions.

**Quinolones** : The newer broad spectrum compounds (sparfloxacin, levofloxacin,<sup>2</sup> moxifloxacin) exhibit greater in vitro activity against *M. tuberculosis* than the narrow spectrum fluoroquinolones (ciprofloxacin, ofloxacin). Ciprofloxacin has an early bactericidal action but neither ciprofloxacin nor ofloxacin have enhanced the sterilising ability of long term regimens containing isoniazid and rifampicin.

The quinolones exert a mycobactericidal effect by binding to the DNA-gyrase and inhibiting DNA-synthesis. There is no recognized cross resistance with other antitubercular drugs but there is complete cross-resistance within the fluoroquinolone group. This resistance develops readily and rapidly, and has been associated with mutations in DNA-gyrase. Fluoroquinolones must be used in combination with other effective drugs when treating MDR-TB. The usual daily dose is 600 to 800mg. (3-4 tablets) of ofloxacin or 1000 to 1500mg (4-6 tablets) of ciprofloxacin during the initial phase. If the dose of 600mg is poorly tolerated the daily dose can be reduced (400mg ofloxacin during the continuation phase. Either

can be given in a single daily dose or the daily dose can be divided in two doses<sup>16,17,18</sup>.

They are well-absorbed orally with bioavailabilities ranging from 60% for ciprofloxacin to 95% for ofloxacin. Their distribution is ideal for treating TB with concentrations in the lung and in macrophages being several times higher than serum concentrations. These drugs also penetrate well into other tissues but not in CSF where levels can be variable. Quinolones are predominantly cleared by glomerular filtration so the dosage should be adjusted in renal failure. Adverse reactions are uncommon but gastrointestinal disturbances like anorexia, nausea, vomiting), neurological symptoms (dizziness, tremors, headaches, insomnia, mood changes, convulsions), hypersensitivity and crystalluria have been associated with quinolone therapy.

Although quinolones are used only for short periods to treat standard bacterial infections, they also appear to be well tolerated when used for 2 years or more in the long treatment of mycobacterial infections<sup>22</sup>. Animal studies have shown that the quinolones may adversely affect growing cartilage. Hence, these drugs should only be used during pregnancy or in children after balancing the potential benefits against this theoretical risk. Quinolones also increase serum theophylline concentrations and hence may increase the adverse effects of theophylline if given in combination. The absorption of quinolones may be reduced by concomitant administration of antacid preparations.

**Cycloserine** : (4-amino-3-iso-oxazolidinone) is a structural analogue of D-alanine that competitively blocks enzymes involved in the synthesis of the dipeptide, D-aryl-D-alanine. By inhibiting synthesis of this dipeptide, which is an essential component of the mycobacterial cell-wall, it limits cell growth and hence has a bacteriostatic effect. This mode of action is unique so cycloserine shares no cross-resistance with other antitubercular drugs<sup>10</sup>.

The drug is rapidly absorbed from the gastrointestinal tract and is widely distributed throughout the body, including the CSF. Clearance is mainly by glomerular filtration. The drug is introduced slowly over several days - starting 250mg daily for a few days, then 250mg twice daily for a few days and finally 750mg daily given as 500mg in morning and 250mg in the evening. Peak-serum concentrations (2 hours post dose) < 10mg/L may be less effective and concentrations > 30-35mg/L are associated with increased toxicity. These concentrations should be checked 1 to 2 weeks after commencing therapy and should be measured following the larger dose if the 500/250 mg regimen is used. Pyridoxine (50 to 100mg daily) has also been given with cycloserine in order to reduce the neurological adverse effects, particularly when given with isoniazid<sup>9</sup>.

Cycloserine administration is associated with significant neurological adverse effects - peripheral neuropathy, dizziness, tremor, headache, convulsions and behavioural complications - confusion, hyperactivity, depression, psychoses, suicidal ideation. Patients must, therefore be closely watched for mood and personality changes. These complications are more common in alcoholics, patients with epilepsy, and patients with renal involvement or previous psychiatric illness. Cycloserine also interferes with the elimination of phenytoin, further complicating its use in epilepsy.

**Para-aminosalicylic Acid** : PAS is a structural analogue of para amino benzoic acid (PABA) that has a bacteriostatic effect by competitively blocking the conversion of PABA into folic acid (an essential burine required for DNA-synthesis). It is readily absorbed from the gastrointestinal tract. It diffuses rapidly into caseous tuberculosis lesions but does not cross uninflamed meninges.<sup>20</sup> PAS is metabolised in the liver to acetyl-PAS and both compounds are excreted in the urine. Hence, PAS is generally avoided in renal failure.

PAS is introduced gradually over several days to a final dose of about 10 to 12 g/day in 3 or 4 divided doses. It is given with food or milk to minimise the gastrointestinal disorders. Few patients can tolerate the gastrointestinal adverse effects produced by combined administration of PAS and ethionamide. PAS may also inhibit the absorption of rifampicin. PAS is an expensive drug and is not readily available<sup>10</sup>.

**Alternative treatment for MDR-TB** : In spite of availability of "second-line" drugs for the treatment of MDR-TB, other alternative treatments may sometimes be required. Several established drugs may also be used for treatment of MDR-TB.

**a High dose isoniazid** : In presence of confirmed MDR-TB isoniazid administration is not recommended<sup>3,10</sup>. But, it has been observed that strains of *M. tuberculosis* identified in the laboratory as isoniazid resistant often contain mixtures of susceptible and resistant organisms. Sometimes isolates resistant to levels just above the critical concentrations for isoniazid (MICs of 0.2 to 5.0 mg/L) may be present. The high dose of isoniazid (16 to 20mg/kg (1 to 1.5 g/day), would eliminate susceptible organisms and those with low level resistance<sup>23,24</sup>. Despite apparent in vitro resistance, isoniazid may retain appreciable residual activity against a particular strain of MDR-TB. No benefit is found in including isoniazid at a regular dosage in a regimen with cycloserine, ethionamide and/or pyrazinamide. However, sputum conversions were found in 69% in patients receiving high dose isoniazid as well as the retreatment regimen without any relapses in comparison to 21% of patients receiving retreatment regimen alone. High dose is associated with hepatotoxicity, peripheral neuropathy and convulsions (which may be prevented by giving higher dose of pyridoxine. Thus high dose isoniazid may be considered as an adjunctive drug in MDR-TB treatment, especially in developing countries unable to afford the expensive secondline drugs.

**b Rifabutin** : It is a derivative of rifampicin-S and may be more active than rifampicin against *M.tuberculosis*. It is rapidly absorbed from the gastrointestinal tract and has a serum half life of 16 hours (which is longer than rifampicin) and achieves higher concentration than rifampicin. The drug is eliminated by the kidney and the liver. Adverse effects include gastrointestinal disorders hypersensitivity, hepatotoxicity and hematological reactions<sup>24,25</sup>. The critical concentration for rifabutin is 0.5 mg/L. The MICs of rifabutin for rifampicin sensitive and resistant strains of *M.tuberculosis* are <0.06 mg/L and 0.25 to 16.0 mg/L respectively. This wide-range of MICs suggest that few MDR-TB strains could be effectively treated with rifabutin<sup>26</sup>. There is cross resistance between rifampicin and rifabutin. Though rifabutin

is equivalent to rifampicin in drug susceptible pulmonary-TB in HIV positive and negative patients, the sustained bacteriological response in MDR-TB was observed in 23 to 47% of patients. The outcome of therapy was independent of the concomitant medications and of resistance patterns, but it showed dose response effect with an 8% response for 150mg/day increasing to 50% response for the and 450 mg/day dosages<sup>27</sup>. In spite of favourable pharmacokinetics and putatively superior activity of rifabutin, experience with this drug has suggested that it does not have a role in the treatment of MDR-TB.

**c Clarithromycin** : It is macrolide antibiotic and is well absorbed orally, attaining peak serum levels of 2 to 4mg/L and concentrates in the tissues. About 30 to 40% is excreted unchanged or as an active metabolite via the kidneys: biliary excretion accounts for the remainder. Adverse effects include nausea, diarrhoea, abdominal pain and bitter taste in mouth.

Though clarithromycin and azithromycin are useful in the treatment of many non-tuberculous mycobacterial infection, including MAC. But has demonstrated poor in vitro activity against *M.tuberculosis*. The MICs and MIC<sub>50</sub> were 16mg/L and 64 mg/L respectively<sup>28,29</sup>. Its addition resulted in 4- to 32 fold reductions in the MICs of isoniazid, ethambutol and rifampin. The utility of clarithromycin as a "second-line" drug in the treatment of MDR-TB remains to be established.

**d Clofazimine** : It is a riminophenazine compound and effective against *Mycobacterium leprae* and MAC infections. After a single dose of 300mg, it attains a peak serum concentration of 1.0mg/L. A substantial portion of the unchanged drug is excreted in the faeces but metabolites are also detected in urine. Adverse effects include gastrointestinal disorders and skin discolouration. Though activity against *M. tuberculosis* has been demonstrated in-vitro and in-vivo, there are only anecdotal reports of successful treatment of MDR-TB<sup>30</sup>.

**e Amoxicillin-Clavulanic Acid** : It is a B-lactam antibiotic and can penetrate the cell-wall of *M.tuberculosis* and bind with high affinity to four penicillin binding proteins (PBP). The resistance is due to presence of B-lactamases (in *M.tub.*) with penicillinase activity and can be inhibited by B-lactamase inhibitors (clavulanic acid, subclavam)<sup>31,32</sup> or circumvented by the use of carbapenems (Imipenem) which are penicillinase resistant. It is bactericidal for *M.tuberculosis* isolates at an amoxicillin concentration of 4mg/L and a clavulanic acid concentration of 2mg/L or less. It is suggested to have an early bactericidal activity but this activity declines rapidly after the third day. This bactericidal activity needs further exploration in the treatment of MDR-TB.

**f Metronidazole** : *M.Tuberculosis* can adapt to low oxygen levels and it is the dormant organisms that undergo orderly metabolic changes to survive anaerobiosis and become susceptible to drugs like metronidazole (generally active against anaerobic organisms). Thus, this drug may have a role in eradicating persistent bacilli during the sterilization phase of treatment and in chemoprophylaxis<sup>33</sup>. It might be useful in the management of drug-susceptible or MDR-TB. This potential role needs to be further studied.

Table 4 : Initial Phase

| Initial Phase   |                         | Continuation Phase |                    |
|-----------------|-------------------------|--------------------|--------------------|
| Drugs           | Minimum duration months | Drugs              | Duration in months |
| Aminoglycoside* | 6                       | Ethionamide        | 12-18              |
| Ethionamide     | 6                       | Fluoroquinolone    | 12-18              |
| Fluoroquinolone | 6                       | Pyrazinamide**     | 12-18              |
| Pyrazinamide    | 6                       | Ethambutol +/-     | 12-18              |
| Ethambutol +/-  |                         |                    |                    |

\* Kanamycin, or amikacin, or capreomycin.

\*\* Ciprofloxacin or Ofloxacin

### Duration of Therapy (Table 4)

The optimal duration has not been clearly established. However, WHO recommend treatment with antitubercular drugs for a period of at least 18-24 months after sputum conversion or 12 months after sputum culture becomes negative to prevent relapse. The injectable drugs are preferably used for 6 months depending upon sputum conversion.

### Monitoring Treatment

The most reliable marker is the bacteriological response<sup>8</sup>. Sputum examinations should be done, for semi quantitative smear and culture monthly, during the intensive phase of therapy<sup>24,3</sup>. After sputum conversion smear examination and culture are obtained once in three months till the end of the therapy. Therapeutic response is judged in order of reliability, by bacteriology of sputum, radiology followed by clinical picture. Once sputum conversion has been obtained some experts recommend with drawing the weaker and more toxic drugs from the regimen<sup>2</sup>. The patient then completes another 18 to 24 months' treatment with the remaining 2 to 3 well tolerated drugs<sup>3</sup>. Other experts would persist with the initial treatment hoping to improve the cure rate. A parenteral drug is given for 4 to 6 months until toxicity develops.

### Outcome of Treatment

In a study - of 134 MDR-TB patients, 47(35%) had no response to therapy and 12 initial respondents relapsed, the overall response rate was 56% for a mean follow up period of 51 months (range 10 to 167)<sup>34</sup>. MDR-TB resulted in a failure of 44% (and TB associated mortality rate of 22%). The median hospital, stay was more than 7 months; One had surgery; the median number of drugs administered per patient was 4 (32 patient had received six or ore drugs. However, in a later study of 25 evaluable patients, 24(96%) had clinical response, and all 17 for whom data on microbiological response were available had documented culture conversions<sup>4</sup>. The median follow up period was 91 weeks (range 41 to 225). However, the patients often had primary MDR-TB, and those with acquired disease had TB for a shorter period (median 2.5 years), had fewer drugs before treatment (median number of drugs, 3.5) and had access to quinolone treatment. In HIV positive patients with MDR-TB (table 5), the earlier reported median survival time for the MDR-TB patients was 2.1 months compared with 14.6 months for the controls. However, later studies reported median survival times reanging between 5.8 and 10 months<sup>35,36,37</sup>. The survival time is prolonged in patients with CD4 + T lymphocyte counts above 200/mL, and in patients

receiving capreomycin and to a lesser extent, a fluoroquinolone and isoniazid<sup>38,39a,39b</sup>.

Table 5 : The Influence of HIV status on Management of MDR-TB.

| Influence           | HIV Negative             | HIV Positive  |
|---------------------|--------------------------|---|
| Treatment Failure   | 63 times                 | 172 to 89% died   |
| Relapse             | 2 times                  | within 4-19 week, 38 to 70% to TB                       |
| Resistance to       | 5.8 drugs                | 1 Median survival AIDS-1.5mths.<br>1 No AIDS 14.8 mths. |
| Each received       | 5.7 drugs                | 1 8%of contacts developed TB in 2 years                 |
| Duration Conversion | 24 mths after conversion |   |
| Long Term           | Initial 65%<br>56%       |   |

### Chemoprophylaxis For Contacts of MDR-TB

The CDC has recommended three levels of control :

- The use of *administrative measures* to reduce the risk of exposure (early recognition of potential TB patients, prompt laboratory diagnosis and immediate implementation of effective chemotherapy).
- The use of *engineering controls* to prevent the spread of TB bacilli (ventilated rooms, air-filtration and ultraviolet air disinfection) and
- The use of personal respiratory protective equipment such as high efficiency particulate air filter (HEPA)<sup>40</sup>. However, these are expensive and cumbersome and therefore remain unproven.

Observation without preventive therapy has been recommended for most people exposed to MDR-TB. However, in those who are at high risk of progressing to active disease (HIV+ve), the potential regimens are pyrazinamide and ethambutol, or pyrazinamide and a quinolone and the proposed duration of therapy was 6 to 12 months. Patient's preference and any adverse effects become major factors as the benefit of MDR-TB prophylaxis is small. Treatment with pyrazinamide 1500 mg daily plus ciprofloxacin 750mg twice daily for 4 months do have some support from different experts<sup>41,42</sup>.

BCG vaccination proved marginally "superior to screening and preventive treatment with post-infection prophylaxis with ciprofloxacin-pyrazinamide. Overall, BCG is only recommended for infants and children at continued risk of TB infection. However, BCG vaccination may now be considered for health care workers who remain exposed to MDR-TB despite the institution of comprehensive infection control programme<sup>43</sup>.

## Role of Surgery in Management of MDR-TB

Though medical therapy is the cornerstone of management of MDR-TB, but in best circumstances success rate is only in 40-50% of cases. However, combined with surgery the success rate may be 90-95%. The preoperative and postoperative medical therapy should be given for 24 months or 18 months after sputum conversion<sup>44,45</sup>.

*The aims of surgery in MDR-TB include :*

- 1 Extensive drug resistance resulting in likely or proven failure of chemotherapy.
- 1 Presence of localized disease allowing successful debulking of abnormal lung without compromising lung functions.
- 1 Removal or closure of the cavity.
- 1 Bacteriological conversion
- 1 For the control of disease process, complications and sequelae.
- 1 Rehabilitation of the patient in his social & economic environment.

However majority of MDR- patients have too extensive a disease and/or too poor pulmonary functions to be considered suitable for surgery.

*The indications for surgery in MDR-TB are :*

- 1 Positive sputum with localised disease; negative sputum with significant pulmonary lesions and unstable lesion/cavity may also be considered for surgery.
- 1 Massive hemoptysis (600ml in 24 hours) or recurrent hemoptysis.
- 1 Chronic empyema
- 1 Bronchopleural fistula

*The contraindications are :*

- 1 Extensive diseases
- 1 Poor cardiopulmonary reserve
- 1 Active endobronchial disease

*Success of Surgery :*

- 1 It depends upon availability of medical therapy with susceptible/partially susceptible drugs; resulting in success rate of 90-95%. However, if the bacilli are resistant to all drugs, success rate drops to 50%.
- 1 It depends upon residual lung lesions; when there are no remaining lung lesions and susceptible drugs are available the success rate is nearly 90-95% but in presents remaining lung lesions because of bilateral involvement or poor lung function success drops to 60%.
- 1 It depends upon surgery being performed after three months of treatment with reserve/second line drugs since at this point of time, bacteria are still likely to be sensitive and the bacillary population is likely to be at its lowest.

*Preoperative assessment :*

- 1 Whether unilateral/localised disease. The contralateral lung should be healthy but minimal healed lesion is, also, acceptable for resection.
- 2 Patient should be fit for major surgery or pneumonectomy.
- 3 Bronchoscopy should be done in all cases to rule out any endobronchial disease at the site of section of the bronchus.
- 4 Best results are seen when two or more susceptible drugs including one injectable drug is available.
- 5 Presence of uncontrolled diabetes-mellitus increases the chances of life threatening complications.
- 6 Pulmonary functions assessed clinically and by spirometry. The criteria for fitness require:-

- a FEV<sub>1</sub> of 1.5L or > in males & 1.3L or more in females or > 50% of predicted value.
- b The post operative FVC (by ventilation scan) should be > 800-1000ml.
- c The MV should be more than 50% of the predicted value. For thoracoplasty, FEV<sub>1</sub> upto 1 ltr. is enough.

## Surgical Procedures for MDR-TB

- a Resection of lung: It is the surgery of choice as it takes away the disease bodily. Pneumonectomy, lobectomy, segmental resection or wedge resection may be as per the requirement of the case.
- b Thoracoplasty : If the resection is not feasible, due to extensive disease or poor lung function, thoracoplasty may be performed the specific indications are : (1) apical Cavity, (2) apical cavity with disease in contralateral lung, (3) apical cavity with disease in the same lung.  
Though good results are reported after thoracoplasty but the main drawback is unpredictability of results.
- c Cavemostomy : In a very few selected case, tube drainage of the a cavity with abundant bacilli, may be carried out.
- d Artificial pneumoperitoneum may be helpful in a highly selected case but usually not perform<sup>46</sup>.

## Morbidity or major complications after surgery

The complication rate in MDR-TB is 20-25%. The major ones being haemorrhage residual apical space, bronchopleural fistula or chronic empyema. The complications may be managed conservatively or if required surgically. The overall mortality from these procedure is 1.5 to 2%, but in "salvage" patients, this may be higher. Post surgically, sputum positivity is observed in 18-25% of patients, but with combined medical therapy or reoperation like "Completion pneumonectomy" Sputum - Status at the end (18-24months) of therapy is 3 to 5%. It is essential for the success of surgery and final cure that aggressive chemotherapy as in preoperative period is continued for 18 months after surgery. Over all cure rate after surgery is 90%. Overall complications like BPF is 10%; post operative empyema in 8% "The surgery in salvage" cases is not as optimistic because it is performed as a "last resort" Salvage cases have morbidity/mortality in 35% as against 7% in properly selected cases. This group includes patients with. (a) Destroyed lung with extensive pleural involvement; (b) Chronic empyema with disease in opposite lung; (c) Hemoptysis with bilateral disease; (d) Sputum positive or relapse in spite of best available drugs.

Tuberculosis with complications like diabetes, and uncontrolled extrapulmonary tuberculosis<sup>46</sup>. In a study of 29 patients selected for surgery 23(79%) of the 29 patients remain sputum culture negative for 9 to 69 months (mean 39 months). However surgery was associated with some morbidity in this debilitated population: 2 post operative death; 1 relapsed and died; 1 patient developed pulmonary hypertension and another had respiratory insufficiency Appropriate drug therapy nutritional support and certain operative techniques may lead to cure rate over 90% in MDR-TB<sup>47</sup>.

## Adjuvant Therapies

In addition to the administration of antimicrobial drug therapy and surgery, various other modalities have been proposed but they remain experimental and of uncertain utility at present. They may provide some direction and hope for the development of novel antituberculous agents that are required for treating patients with MDR-TB. These include immunomodulation therapy, laser therapy

gene therapy and some novel chemo-therapeutics.

### Immunotherapy or Immunomodulation

Immune modulation can be affected either by enhancing proinflammatory cytokines like IL-2, IL-12, IFN- $\gamma$ , TNF-L or inhibiting the anti-inflammatory cytokines like IL-4, IL-5, IL-10, addition of serum to enhance humoral factors and diverting the harmful TH2 immune pathway to the beneficial Th1 response by vaccination utilizing *M. vaccae*. However, these are only experimental and controlled trails have failed to confirm utility of therapy.

Aerosolised, interferon- $\gamma$  in conjunction with other second line drugs may be given to treat MDR-TB<sup>48</sup>. The aim of this treatment was to activate pulmonary macrophages into effective phagocytic cells. It was well tolerated and resulted in temporary sputum smear (but not culture) conversions<sup>49</sup>. *M. Vaccae* has been used as immunotherapy in combination with ciprofloxacin, cycloserine and pyrazinamide, in the treatment of a patient with abdominal MDR-TB. The potential role of transfer factor, indomethasone, and Livanasole is still experimental. Ievamisole as an adjunct to drug treatment was reported to cause more rapid radiological clearing without affecting the clinical outcome.

### Gene Therapy

The decoding of the human genome provides another fascinating aspect in the future therapeutic intervention of tuberculosis by identifying resistance genes, it will be possible to detect drug resistance before start of therapy and also to develop drugs that target these specific genes and thereby reducing the duration of therapy. A mutant *rpo B* gene has been produced that effectively mimics the mode of action of rifampicin and inhibits transcription<sup>50</sup>. This mutant gene represents a potential suicide gene for MDR-TB if a delivery strategy can be developed.

### Laser therapy :

This has been experimented in some countries like Russia and is effective in multicavitary disease with heavy bacterial loads, particularly, when there is an increased chance of failure of medical treatment. This, probably kills bacteria rapidly, increases and improves penetration of antitubercular drugs in walled off lesions and helps in early closure of cavities and is of proven benefit in tracheal and bronchial stenosis due to endobronchial growth. It also reduces the trauma of surgery and post operative complications<sup>51</sup>.

### Novel Chemotherapeutics

A recently reported drug *ABT-255*, a 2-pyridone inhibits the bacterial DNA-gyrase and has MICs ranging between 0.016 to 0.031 mg/L for drug susceptible and drug resistant isolates of *M. tuberculosis*<sup>52</sup>. Similarly, branched-chain amino acid biosynthesis (*sulphoneturamethyl-a commercial herbicide*) had shown promising antitubercular activity<sup>53</sup>. *OPU-100480* and *Linezolid* have been found to have activities similar to that of isoniazid and/or rifampicin. *PA-824 (introzimidazopyran)* has shown potent bactericidal activity against MDR-T and promising oral activity. The understanding of the cell-wall synthesis through the use of mycolic acid synthesis,

inhibitors such as thiolactamycin or the thiourea isoxyl may lead to the development of new specific antimicrobial agents. *Non-antibiotics* include chlorpromazine and thioridazine, which are antipsychotic the growth of *M. tuberculosis*<sup>54</sup>. Hence, these phenothiazines and the related antihistaminics may need the attention of researchers.

### What do we do Now?

- (a) Primary aim is to control the development of drug resistant tuberculosis which can be done by revision of "National Guidelines" based on levels of resistance, training of professionals in private sector, strengthening existing national tuberculosis control programme, restricting use of Rifampicin (for TB and Leprosy only)
- (b) Taking logistic measures to ensure regular supply of drugs at all levels of National tuberculosis control programmes and by ensuring measure like providing free/subsidized antitubercular drugs.
- (c) DOT is essential and therefore, supervised treatment with fixed drug combination and health education are integral to success. Strict drug quality control is also essential.
- (d) Providing widespread susceptibility testing with quality control laboratories.
- (e) WHO has proposed the work plan known as *DOTS-PLUS*<sup>55</sup> and established Green Light Committee<sup>56</sup> to implement it. Main focal point are to :- Ensure adherence to full course of treatment, cure MDR-TB with second line drug. Provide DOT-PLUS in areas where MDR-TB has emerged due to previous inadequate TB-control programmes; Provide DOT-PLUS in settings where the DOTS-strategy is fully in place to protect against the drug resistance; Implementation of DOTS-PLUS will minimize the risks of creating drug resistance to second line Anti TB Drugs; If possible, National Control Programme may apply "Molecular epidemiology detect virulent clones of MDR-TB; The support to drug discovery programme should be a priority.

### References

- 1a. Edward D. Chan, V Laurel, Mathew J et al. Treatment and outcome Analysis of 205 patient with MDR-Tuberculosis *Am J Respir Crit Care Med* 2004;169:1103-9.
- 1b. Multidrug resistant tuberculosis *ICMR* 1999;29(10&11):105-114.
2. Treatment of tuberculosis guidelines for national programmes. Geneva WHO 2003 (WHO CDS/TB 2003;313).
3. Isenan MD Treatment of multidrug resistance tuberculosis *New Engl J Med* 1993;329:784-91.
4. Telzak EE, Sepkowitz K Alpert P et al [of 205 patients with MDR-Tub. *Am J respir crit care Med* 2004;169:1103-9]. Multidrug resistance tuberculosis in patients without HIV infection. *N Engl J Med* 1995;333:907-11.
5. Barnes PF the influence of epidemiological factors on drug resistance rates in tuberculosis *Am Rev Respir Dis* 1987;136:325-8.
6. Salomon N. Peman DC. Priednran P, et al Predictors and outcome of MDR tuberculosis *Clin Infect Dis* 1995;21:1245-52.

7. Fischl MA, Daikos GL, Uttamchandani RB et al. Clinical presentation and outcome of patients with HIV infection and tuberculosis caused, by multidrug resistant bacilli. *Ann Intern Med* 1992;117:184-90.
8. Crofton J, Chaulet P, Maher D et al Guidelines for the management of Drug resistant tuberculosis Geneva, WHO 1997;Publication no WHO/TB 96.210.
9. Combs DL O'Brien PJ Geiter LJ USPHS tuberculosis short course chemotherapy trial 21: Effectiveness, toxicity and acceptability: the report of final results. *Ann Intern Med* 1990;112:397-406.
10. American Thoracic Society/Centers for disease control. Treatment of Tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994;149:1359-74.
11. Kim TC, Blackman RS Heatwole KM et al. Acid fast bacilli in sputum smears of patients with pulmonary tuberculosis. Prevalence and significance of negative smears pretreatment and positive smears post treatment. *Am Rev Respir Dis* 1984;129:264-8.
12. Espinal MA, Laszlo A, Simonsen L et al Global trends in resistance to anti tuberculosis drugs *N Engl J Med* 2001;344:1294-1303.
13. Tmkoka H, Saito H, Saito K, Comparative antimycobacterial activities of the newly synthesized quinolone AM-1155, sparfloxacin and ofloxacin. *Antimicrob Agents Chemother* 1993;37:1259-63.
14. Alangaden GJ, Lerner SA. The clinical use of fluoroquinolones for the treatment of mycobacterial infections. *Clin Infect Dis* 1997;25:1213-21.
15. Ji B, Lounis N Maslo C, et al. In vitro and in vivo activities of moxifloxacin and ciprofloxacin against *M. tuberculosis*. *Antimicrob Agents, Chemother* 1998;42:2006-9.
16. Yew WW, Chan CK Chau CH et al. Outcomes of patients with Multiresistant pulmonary tuberculosis treated with ofloxacin, levofloxacin-containing regimens. *Chest* 2000;117:744-51.
17. Jacobs MR Activity of quinolones against mycobacteria *Drugs* 1999;55 Suppl 2:19-22.
18. Herbert D, Paramasivan CN, Ventkatesan et al. Bactericidal action of ofloxacin, sulbactam ampicillin rifampin, and isoniazid. *Antimicrob Agents chemother* 1996;40:2296-9.
19. Peloquin CA Pharmacology of the antimycobacterial drugs *Med Clin North Am* 1993;77:1253-62.
20. Aranda CP-Second line agents: p-aminosalicylic acid, ethionamide, cycloserine, and thiacetazone. In: Rom WN, Gray SM editors. *Tuberculosis*: New York: Little brown & Company (Inc.), 1996:811-6.
21. Saito H, Sato K, Torioka H et al, In-vivo antibacterial activity of a new quinolone. Levofloxacin (DR-3355). *Tuber Lung Dis* 1995;76:377-80.
22. Berning SE, Madsen L, Iseman MD et al. Long term safety of ofloxacin and ciprofloxacin in the treatment of mycobacterial infections. *Am J Respir Crit Care Med*. 1995;151:2006-9.
23. Moulding TS, should isoniazid be used in retreatment of tuberculosis despite acquired isoniazid resistance. *Am Rev Respir Dis* 1981;123:262-4.
24. Victor TC, Warren R, Butt JL et al Genome and MIC stability in *M. tuberculosis* and indications for continuation of use of isoniazid in multi drug resistance tuberculosis. *J Med Microbiol* 1997;46:847-57.
25. De Cian Sassella D Wynne BA Clinical experience with rifabutin in the treatment of mycobacterial infections. *Scand J Infect Dis* 1995;Suppl. 98:22-6.
26. Heifets LB, Lindholm-Levy PJ, Iseman MD Rifabutin minimal inhibitory concentrations for mycobacterium tuberculosis. *Am Rev Respir Dis* 1998;137:719-21.
27. Mc Gregor MM, Olliaro P Wolmarans L. et al. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am J respir Crit Care Med* 1996;154:1462-7.
28. Hardy DJ, Guay DRP, Jones RN. Clarithromycin, a unique macrolide: a pharmacokinetic, microbiological and clinical overview. *Diagn Microbiol Infect Dis*. 1992;15:39-53.
29. Luna Herrera J, Reddy VM, Deneluzzi D. et al Antitubercular activity of clarithromycin. *Antimicrob Agent chemother*. 1995;2692-5.
30. Reddy VM, Nadadur G, Deneluzzi D. et al Antituberculous activities of Clofazimine and its analogs B 4154 and B 4157 *Antimicrob Agents Chemother* 1996;40:633-6.
31. Nadler JP, Nerger J Nord Ja. et al Amoxicillin-clavulanic acid for treating drug resistant *M.tuberculosis*. *Chest*. 1991;99:1025-6.
32. Yew WW, Wong CF Lee J. et al. Do B-lactam, B-lactamase inhibitors combination have a place in the treatment of multidrug resistance, tuberculosis. *Tub Lung Dis* 1995;76:90-2
33. Wayne LG, Sramek HA Metronidazole is bactericidal to dormant cells of *Myobacterium tuberculosis* *Antimicrob Agents chemother* 1994;38:2054-8.
34. Goble M, Iseman M Madsen LA et al., Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N. Engl J Med*. 1993;328:527-32.
35. Park MM Davis AL Schluger. NW et al. Outcome of MDR-TB patients, 1983-1993: prolonged survival with appropriate therapy. *AM J Respir Crit Care Med* 1996;153:317-24.
36. Salomon N, Perlman DC Friedmann P et al. Predictors and outcome of multidrug resistant tuberculosis. *Clin Infect Dis* 1995;21:1245-52.
37. Mannheim SB, Sepkowitz KA, Stoeckle M et al. Risk factors and outcome of HIV infected patients with sporadic MDR tuberculosis in New York City. *Int J Tuberc Lung Dis* - 1997;1:319-25.
38. Fischl MA, Daikos GL, Uttamchandani RB et al Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multi drug resistant bacilli. *Am Intern Med* 1992;117:184-90.
- 39a. Frieden TR, Sherman LF, Maw KL et al. A multi institutional outbreak of highly drug resistant tuberculosis: epidemiology and clinical outcomes. *JAMA* 1996;276:1229-35 (396).
- 39b. Sharma SK, Mohan A. Confection of HIV and Tuberculosis (Indian perspective) *Indian J Tuberc* 2004;51:5-16.
40. Adal KA, Anglim AM, Palumbo CL et al. The use of high efficiency particulate air filter respirators to protect hospital workers from tuberculosis: a cost effectiveness analysis. *N Engl J Med* 1994;331:169-73.
41. American Thoracic Society/Centers for disease control. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994;149:1359-74.
42. Centers for disease control. Management of persons exposed to MDR-TB. *MMWR Morb Mortal Wkly Rep*. 1992;41(RR-II):61-71.
43. Centers for disease control. The role of BCG vaccine in the prevention and control of tuberculosis in United-States. *MMWR Morb Mortal Wkly Rep* 1996;45(RR-4)1-18.
44. Pomerantz M, Madsen L, Goble M, Iseman MD Surgical Management of resistant mycobacterial tuberculosis and other

- mycooacterial pulmonary infections. Am Thorac Surg 1991;52:1108-1112.
45. Nitta AT Iseman MD, Newell JD, Madsen LA, Goble M. Ten Year experience with artificial pneumopentoneum for end stage, drug resistant pulmonary tuberculosis Clin Infect Dis 1993;16:219-222.
  46. Iseman MD, Madsen L, Goble M, et al Surgical Intervention in the treatment of pulmonary disease caused by drug resistant M tuberculosis. Am Rev Respir Dis 1990;141:623-5.
  47. Pomerantz M, Brown JM. Surgery in the treatment of multidrug resistant tuberculosis. Clin Chest Med. 1997;18:123-30.
  48. Condos R, Rom WN, Schiuger NW. Treatment of multidrug resistant pulmonary tuberculosis with interferon gamma via aerosol. Lancet. 1997;349:1513-5.
  49. Prior JG, Khan AA Cart Wright KAV. et al. Immunotherapy with M. Vacce Combined with second line chemotherapy in drug resistant abdominal tuberculosis. J Infection. 1995;31:59-61.
  50. Rom WN, Yie T-A, Tchou-Wong KM. Development of a suicide gene as a novel approach to killing M tuberculosis Am J Respir Crit Care Med 1997;156:1993-8.
  51. Puri MM Arora VK Role of Gallium Arsenide Laser Irradiation at 890 nm. as an adjunctive to Antituberculosis drugs in treatment of PULmonary tuberculosis Ind J Chest Dis Allied Sci. 2003;45:19-23.
  52. Grandoni JA, Marta PT, Schloss JV Inhibitors of branched chain aminoacid biosynthesis as ptoential antituberculosis agents. J Antimicrob Chemother 1998;42:475-82.
  53. Oleksijew A, Muellbroek J, Ewing P. et al In-vivo efficacy of ABT-255 against drug sensitive and drug resistant M tuberculosis strain. Antimicrob agents chemother 1998;412:2674-7.
  54. Amaral L, Kristiansen JE, Abebe LS et al. Inhibition of the respiration of multidrug-resistant clinical isolates of M. tuberculosis by thioridazine: potential use for initial therapy of freshly diagnosed tuberculosis. J. Antimicrob Chemother 1996;38:1049-53.
  55. Farmer P, Kim JY Community based approaches to the control of multidrug resistant tuberculosis: Introducing "DOTS-plus" BMJ 1998;317:671-4.
  56. DOTS-plus and Green Light Committee. www.who.int/gtb/policyrd/dotplus.htm.

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**Special Issue : ENVIRONMENTAL POLLUTION & HUMAN HEALTH - Guest Editor Dr. I.P.S. Kalra & Prof. S.K. Bhargava**

- 1 Environment & Health
- 1 Respiratory Function Tests in Rubber Factory Workers.
- 1 Corrolation of lung Function Tests with Nutritional and Socio-Economic Status in Male Children.
- 1 Fluoride distribution and Fluorosis in Some Rural Areas of Udaipur, Rajasthan.
- 1 Natural Protection from Environmental Pollution.
- 1 Changing quality of urban air "Future of Indian Air quality" and its impact on Health.
- 1 Asbestos : Disquieting tale goes on.
- 1 Environmental Pollution and Unborn Child.
- 1 Effect of indoor Air Pollution during cooking in Woman belonging to Rural, Urban and Slum Areas of Delhi.

1 Altitude related disorders.

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### Abbreviated Prescribing Information :

Therapeutic Category: Phosphate binder. Composition: Each film-coated ablet contains Sevelamer hydrochloride 400mg or 800mg. Indication: Sevelamer is indicated for the control of serum phosphorus in patients with chronic kidney disease on hemodialysis. Dosage and Administration: Patients not taking a Phosphate binder: The recommended starting dose of Sevelamer is based on serum phosphorus level. For a serum phosphorus level of >5.5 and <7.5 mg/dl: 1 tablet of 800mg or 2 tablets of 400mg of Sevelamer thrice daily with meals; for a serum phosphorus level of >7.5 and < 9mg/dl: 2 tablets of 800 mg or 3 tablets of 400mg of Sevelamer thrice daily with meals; for a serum phosphorus level of >9mg/dl: 2 tablets of 800mg or 4 tablets of 400mg of Sevelamer thrice daily with meals. Patients Switching From Calcium Acetate: for patients taking 1 tablet of 667mg of calcium acetate per meal: 1 tablet of 800mg or 2 tablets of 400mg of Sevelamer per meal; for patients taking 2 tablets of 667mg of calcium acetate per meal: 2 tablets of 800mg or 3 tablets of 400mg of Sevelamer per meal; for patients taking 3 tablets of 667 mg of calcium acetate per meal: 3 tablets of 800mg or 5 tablets of 400mg of Sevelamer per meal. Dose Titration for All Patients Taking Sevelamer: Dosage should be adjusted based on the serum phosphorus concentration with a goal of lowering serum phosphorus to 5.5mg/dl or less. The dose may be increased or decreased by oen tablet per meal at two week intervals as necessary. Warnings & Precautions: Caution should be exercised when Sevelamer is used in aptients with GI disorders or dysphagia. Serum calcium, bicarbonate, and chloride levels should be monitored. Drug Interactions: Sevelamer does not alter the pharmacokinetics of digoxin, warfarin,alpril, metoprolol and iron. Special precautions should be taken when presecriving sevelamer to patients taking anti-arrhythmic and anti-seizure medications. Pregnancy: Category C, Pediatric Use: Safety and efficacy has not be established. Adverse Reactions: Nausea, dyspepsia, flatulence, diarrhea, vomiting, hypertension, thrombosis, infection, headache, hypotension, constipation, cough, pruritis, rash and abdominal pain have been reported. Contraindications: Sevelamer is contraindicated in patients with hypophosphatemia or bowel obstruction and in patients known to be hypersensitive to Sevelamer hydrochloride or any of its constituents. Overdosage: There is not reported over dosage of Sevelamer in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low. Storage: Store at 25°C: Excursion permitted to 15-30°C.

- 1. Maurizio Gallieni, et al. J Nephrol. 2001;14:176-183. (2) Block GA, et al. Am J Kidney Dis 1998;31:607-617. (3) Bleyer AG, et al. Am J Kidney Dis. 1999;33:694-701. (4) NKF. Clinical Practice Guidelines for bone metabolism and disease in CKD. Am J Kidney Dis. 2003;42(Suppl 3):S1-S201. (5) Chertow GM, et al. Kidney Int. 2002;62:245-252. (6) Klemmer PJ. Blood Purif. 2005;23 Suppl 1:12-9. (7) Chertow GM. J Am Soc Nephrol. 2003;14:S310-S314. (8) Collins AJ. Clin Nephrol. 2000;54:334-341. (9) Rosenbaum DP. Nephrology Dial Transplant. 1997;12:961-964.

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