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# JOURNAL of the INDIAN MEDICAL ASSOCIATION

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Editorial

# Tropical Fever — Tropical or Global Challenge ?

**Prof. (Dr.) Jyotirmoy Pal**
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Tropical fever means fever due to infections which are more prevalent in tropics and subtropics. Characteristics of weather of the Tropics consists of excess of rainfall,prolonged summer, higher average temperature through out year, higher humidity, presence of rain forest with rich biodiversity – making ecology of tropics favorable for proliferation and survival of different organisms, vectors and living creatures. Unfortunately most of the poor countries are in tropics – having less nutrition, health care, education and hygiene. So in one hand there is emergence and proliferation of organisms and other hand, lesser preventive and curative medical care with huge population burden – putting challenges in diagnosis and treatment of Tropical fever. Infections in tropics have more overlapping clinical features, atypical clinical presentations , diagnostic dilemma, quickly changing clinical profile , concomitant infections - posing challenges to physicians.

Disease of tropics and subtropics have been known from the ancient period of Roman and Egyptian Civilization. Molecular analysis of the "Mummies"revealed the presence of malarial antigen. Tropical diseases drew attention in 19th century when Europeans due to exploration and colonial expansion moved to tropical countries like Asia including India, Latin America, Africa. They suffered from fever due to different tropical infections. Research and discovery of drugs started actually for the need of rulers of tropical countries. One of the Pioneer in this field **Sir Leonard Rogers** in his book 'Fevers in the Tropics. 2nd Ed, London: Oxford University Press, 1908: 1'. written "The vast and complicated subject of fevers in the tropics has specially attracted the attention of physicians in India, a study of whose writings is of great interest to workers of the present day in the same far-from exhausted field, as they contain remarkably accurate descriptions of fevers, whose pathology and causation are only now becoming clearly understood". Literature of 19th century primarily discussed malaria, yellow fever, enteric fever and filariasis. With the dawn 20th century, focus shifted on to typhus fever and influenza. Relation of vectors like mosquitoes, fleas, lice and tick with those tropical disease were established.

Among tropical diseases, some had been present for centuries , some have emerged & some reemerged. The Emerging Tropical diseases are HIV infections, SARS, H1N1, hantavirus, West Nile Virus, Ebola, Zika Virus & Corona Virus etc. Reemerging diseases are Malaria, Pertussis, Influenza , Pneumococcal disease etc. Some diseases that had been present since the dawn of Mankind like Filariasis, tuberculosis and enteric fever. A few of the tropical diseases that we have successfully controlled are–Bubonic Plague, Yellow fever and Cholera.

Tropical disease usually present with Fever. Fever can occur due to infectious or noninfectious causes. Infection can be tropical or nontropical. In our part of world,clinical approach and empirical treatment to disease have immense importance due to paucity of laboratory facility, less infrastructure and Human Resources. Among tropical infections, few are prevalent throughout the year, while some are seasonal or have geographical preferences. Some of these infections may even have chronic presentation or even present with recurrent complaints. Though autoimmune disease or malignancy can present with Fever but infections in Tropics are so common that whenever any patient from this part of world presents with pyrexia, infectious etiology should be sought first. In approaching patient with Fever detailed medical history, comorbid conditions ,history of any arthropod bite, sexual exposure, immunization history , occupational risk, contact history with animal and patient as well as travel history within and outside country recent and past should be considered. Often classical picture may be absent due to comorbid and concomitant infections and may be due to antipyretics and injudicious use of antibiotics . Examination findings like rash, lymphadenopathy, hepatosplenomegaly, neck rigidity, jaundice, anaemia etc are important clues in reaching clinical diagnosis . Epidemiological history , history of recent outbreak, knowledge of incubation period, possible exposure, seasonal trend may help in empirical diagnosis. Most challenging is Acute undifferentiated Febrile illness – oral temperature >101°F for less than 14 days with no localizing signs and symptoms. Again diagnostic facilities to reach definite diagnosis are often not available or not affordable in diverse socioeconomic population in tropics. Considering all these facts it is practical to approach Tropical infection in Syndromic fashion. There may be argument that syndromic approach may not cover atypical presentation , but resource limiting settings this approach can cover most of the organisms and prompt initiation of therapy can save lot of patients.

So tropical infections can be classified in following groups like a)Acute undifferentiated fever without localizing signs and symptoms – Malaria, Dengue, influenza, typhoid fever etc. b) Fever with rash – Measles, chickenpox, scrub typhus etc. c) fever with thrombocytopenia – dengue, Malaria, leptospirosis etc. d) fever with ARDS – Malaria, scrub typhus, H1N1 infections, Dengue etc. e) Acute Encephalitis Syndrome – scrub typhus, Dengue, HSV, Japanese Encephalitis infection, N meningitides infection. f) Fever with jaundice – malaria, scrub typhus, leptospiral infection, viral Hepatitis g) Fever with hepatosplenomegaly – Enteric fever, Viral hepatitis, Viral Fever, Malaria, Kala-azar etc. i) fever with lymphadenopathy – tuberculosis, filariasis, Plague, HIV, brucellosis etc. j) fever with pulmonary renal involvement – Falciparum Malaria, Leptospira, scrub typhus k) Fever with hepatorenal involvement – Viral Hepatitis, Falciparum Malaria, Leptospirsis, scrub typhus Laboratory diagnosis may not be possible often at presentation due to different reasons. Again rapid diagnostic test available only for malaria and dengue (which is again controversial). ELISA and PCR technology is often not available and affordable. Considering these facts infections in Tropics should be treated empirically and it is rational for population of a particular geographic area (except for Malaria for which rapid kit test is available). Without waiting for definitive diagnosis physician should start therapy and definitive diagnosis to help in scaling down burden of medicines . Primary aim is to stabilize patient and to do baseline laboratory investigations for Syndromic Classification. As rapid diagnostic kit available there should be noempirical therapy should be given for Malaria. Otherwise based on epidemiological , Outbreak history and Syndromic classification empiric therapy may be started,even with more than one drug if required. Although, previously suggested in various articles- not to start any antibiotics unless the diagnosis of Tropical Disease is confirmed; considering the changing pattern of tropical infection it may be suggested to start therapy with Doxycycline and Ceftriaxone – that will cover many of the organisms like Leptospirosis, Typhus, enteric fever, acute pyogenic meningitis. If no response is found even after 48 hrs, alternate diagnosis or complications should be thought of. Thrombocytopenia or coagulopathy is often found in patients suffering from tropical Infections. Thus, invasive procedure should be minimized unless indicated.

Tropical infection is challenge not only to Tropical Physicians , also to World Health authorities. As poorer part of world is involved there is less research on drugs or vaccine of these infections. Because of deforestations, rising immigration, increased international travel infections are not confined to the tropics any more. With Global warming, temperature of temperate countries have risen significantly making them vulnerable to so called tropical infections . So, these infections are gradually transforming into Global threat. In 1975, Special programme on research and training on Tropical disease was undertaken by WHO with help of UNESCO, UNDP and the World Bank. But unfortunately, there is still lack in political will. Poverty and pollution are two key issue – in control of vectors and tropical infections. Uneducated people hardly maintain personal hygiene and all vector control programme will fail unless spontaneous involvement of people occur. In first Global Conference on human environment (UNCHE) in Sweden, Indian Prime Minister Mrs Indira Gandhi made history by her famous quote "Poverty is Greatest Polluter". Population control, control of green house Gas emission, prevention of deforestation and more spending in Health and education by Government with motivation of Pharmaceuticals to develop Drug and Vaccine towards eradication of these diseases can be long term strategy for controlling tropical disease. Otherwise there will be emergence and reemergence of Diseases and its huge impact on economy will make poor to poorer. So Politicians, bureaucrats, Physicians, organizations , pharmaceuticals should take a positive steps so that "Tropical Infections" should not emerge as "Global Infections".

**Further Readings :**


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diseases which take an epidemic form, and are the most influenced by sanitary improvements.

When Sir William Gull tells us that there are 20,000 deaths annually from typhoid fever, and that these form but a small part of the deaths caused by infectious fevers, we cannot doubt that the necessity for strenuous effort is very great, and that any failure on the part of the nation and the Government to adopt all such measures as may most effectually narrow the area of infection, would lay both open to the gravest reproach. Above all, it is essential that hospitals for the isolation of all infectious cases should be provided in all our towns.

## A TROPICAL FEVER.

By G. SHERMAN-BIGG, Allahabad, India,
Surgeon, Army Medical Department.

THERE is a fever in the tropics (for want of a better name, I call it tropical fever) which possesses certain characteristics of its own. Akin to malarial fever, and also to enteric, it cannot correctly be designated by either name. It is certainly sporadic, and usually attacks adults. That it is not due to the germs of malaria there is every reason to conclude, as neither quinine, arsenic, nor any other antifebrifuges exert any influence on the course of the disease. The great weakness, the dry raw-beef appearance of the tongue, the expistaxis, the sordes on the mouth and lips, the persistent headache, the indomitable thirst, and the loss of appetite, at first lead one to suspect enteric fever; but the obstinate constipation throughout the disease, the absence of tympanites and of gurgling in the right iliac region, the want of any eruption, and the clear intellect the patient maintains throughout, upset the theory of suppuration. It cannot be classed as a fever of continued type, as there are decided remissions; nor can it be said to be relapsing fever, since it is not epidemic, and the attacks are irregular.

The disease runs its course in twenty-one days; and there is often a relapse, which resembles in severity and duration the primary attack. The temperature from the commencement of the illness resembles that of convalescence from true enteric fever, the difference between the morning and evening temperatures being as much as three, four, and even five degrees. It is usual for one of the internal organs to be principally affected. It may be the stomach, as shown by vomiting and nausea; or the lungs may be considerably congested, and in some cases pneumonic; or the liver may be enlarged and tender, accompanied occasionally with jaundice; or the spleen may be the seat of hyperæmia.

The disease is not usually fatal; but troublesome sequelæ generally result, the most common being thrombi, producing swelling, and œdema of one limb, with painful, tender, and enlarged iliac glands. The necropsy, when death has occurred in the early stage, shows congestion of the internal organ affected, with extensive congestion of the mucous membrane of the ileum. The jejunum and duodenum are also, though in a less degree, congested. In cases in which death has occurred later on in the disease, the special organ affected during life shows more marked evidence of congestion. For instance, the spleen may be enlarged to three or four times its natural size; it may be soft and friable, and of a dark red colour; or the liver may have a nutmeg appearance; or even the smallest bronchi may be considerably congested. The most important changes, however, take place in the small intestines; the congestion extends from the ileum to the lower part of the duodenum, and the mucous membrane is studded with patches of ulceration. The solitary glands and Peyer's patches are also the seats of ulceration; but they do not seem to be more especially selected than any other part of the lining membrane.

REMARKS.—Malaria is an important factor in the production of ague; but what part it plays in fevers of a continued and remittent type is a matter open to serious argument. It is true, that fevers of this latter class occur nearly exclusively in malarious districts; but may this not be a coincidence? People who have lived in the tropics must have noticed the carelessness, the want of thought and attention to the atmospheric changes. At one time, the weather may be warm and genial; and in half an hour's time, raw and damp. Anglo-Indians dance, indulge in violent exercise in thin and scanty attire, and then sit down in the open air, without thinking of changing or putting on a warmer covering. This sudden atmospheric change of temperature, acting on an overheated system, produces a severe chill; and, whereas in England we should have a severe influenza, here in India we have a fever, more or less severe, according to the health of our constitution. I see no reason why this chill should attack one organ in prefer-

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The Diagnosis of Tropical Diseases
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## THE DIAGNOSIS OF TROPICAL DISEASES

ANTONIO VALENTI-MESTRE, M.D.* AND B. H. KEAN, M.D.†

ALTHOUGH most of the United States is located in the Temperate Zone, many of the important tropical diseases are encountered in this country. The return of our veterans from overseas, the increase in travel, the movement of large groups of people during the war, the development of commercial aviation and the presence of several important medical institutions have combined to make this country a far more important center for the diagnosis and treatment of certain "tropical" diseases than is generally realized. Especially has there been a tendency for Spanish-speaking peoples of Central and South America to visit the United States for medical reasons. In addition, over half a million Puerto Ricans have moved here; it is estimated that the Spanish-speaking colony in New York City alone consists of almost one million persons.

Unfortunately, because most physicians are neither aware of the frequency of these diseases nor properly advised as to the simplest methods of making accurate diagnoses, many infestations escape recognition. During the past two decades considerable advance has been made in diagnostic methods. The purpose of this paper is to discuss simple laboratory procedures which will help in the recognition of these diseases. Emphasis will be placed upon methods which can be employed by almost any physician and do not require expensive equipment and hospitalization.

It must be realized that the diagnosis of a tropical disease is fundamentally a laboratory diagnosis. Most of the drugs used in the treatment of tropical diseases are toxic and the courses of treatment are often prolonged so that their administration is rarely justified unless clinical impression has been confirmed by laboratory study.

### MALARIA

The only method of making a definite diagnosis of malaria is to find the parasite. Preparation of the thick film is advised, for it can be examined adequately in three minutes. A search for the parasites on a

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Review Article

# Clinical Recommendations on the Management of Seasonal & Acute Febrile Infections

K K Aggarwal[1], K K Pareek[2], Milind Nadkar[3], Mangesh Tiwaskar[4], Agam Vora[5]

**Objective :** Acute fever with multisystem illness is endemic in South Asia and in cases where the cause is unknown; treatment is done with generic antipyretics and antibodies. This has led to compromised clinical decision-making, since evidence-based data on fever is unavailable in the tropical region. There is a dearth of diagnostic facilities, which acts as the precursor to delayed response or inaccurate diagnosis of the patient eventually resulting in poor patient outcome or even fatality in patients with acute fever and associated symptoms.

To overcome the gap in diagnosis and management, the objective of this review is to assess the prevalence and seasonal implications of acute febrile illness and provide evidence-based clinical practice recommendations for these conditions.

**Method :** The review process followed for formulating the clinical recommendations was systematic review of available evidence in the form of published literature followed by deliberations among the members of the expert panel. Where there was little or no evidence, the panel relied on logical empiricism and consensus to generate recommendations about the rational method of therapy and management of acute febrile illnesses and the role of broad spectrum antibiotics.

**Conclusion :** Six acute febrile illnesses with high prevalence and burden in India were identified; Typhus, Dengue, Chikungunya, Influenza, Upper Respiratory Infections (URIs) and Malaria. The authors have provided clinical practice recommendations for all the 6 febrile illnesses.

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***Key words*** **: Fever, Chikungunya, Malaria, Respiratory tract disease, Influenza, Typhus, Dengue.**

Acute febrile illness involving multiple systems is a common characteristic of many endemic infectious diseases in South East Asia and includes diseases such as malaria, dengue, scrub typhus etc[1]. In most cases of febrile illness of unknown etiology, a generalized treatment approach using antibiotics and antipyretics is followed. Hence, it is also suggested that unavailability of epidemiological or evidence-based information on febrile illness in tropical region becomes a prominent reason for compromised clinical judgment and treatment[2].

It is the need of the hour that general physicians have easy access to clinical guidelines on the treatment and management of seasonal febrile illness of known etiology. This will help them in taking informed and improved clinical decisions.

In this paper, we discuss some of the prevalent febrile seasonal infections in India, their current management and give clinical practice recommendations for the same.

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***Editor's Comment :***

- **In scurb typhus, treatment with doxycycline should be initiated before referring the patient for assessment of complication**
- **Scrub typhus is one important cause of Acute Encephalitis Syndrome (AES).**
- **Patients with simple fever without any danger signs or complications may be managed with symptomatic approach**
- **In case of chikungunya, treatment is entirely symptomatic**
- **In case of H1N1 influenza, use of antiviral medication oseltamivir is recommended**
- **In case of URTI, except for streptococcal infections presenting with fever and sore throat, antibiotics are not recommended**
- **In all fever cases diagnosed as malaria by RDT or microscopy should promptly be given effective treatment.**
- **Dengue fever may be diagnosed on day one by NS1 test by Elisa method.**

## Methodology

The present paper assesses the recent evidence on seasonal and acute febrile illnesses and their management.

In order to impart the highest possible evidence base for the management of acute febrile illness, a systematic review of literature was conducted. Existing guidelines, meta-analyses, systematic reviews, reports, white papers and key cited articles on prevalence, epidemiology, seasonal implications and management of acute febrile illnesses were reviewed and recommendations were framed.

As a result of the review, 6 acute febrile illnesses with high prevalence and burden in India were identified; Typhus, Dengue, Chikungunya, Influenza, Upper Respiratory Infections (URIs) and Malaria. Recommendations for each disease were discussed by the expert panel and where there was little or no evidence the panel relied on logical empiricism and consensus to generate recommendations about the rational method of therapy and management of acute febrile illnesses and the role of antibiotics.

## Discussion

### Acute febrile Illness Definition :

Fever of rapid onset & lasting less than 21 days (14 days in some definition) with no identified source.

Fever with no localising signs is called Acute Undifferentiatiated Febrile Illness (AUFI).

The febrile response is supervised and coordinated by the central nervous system through endocrine, neurological, immunological and behavioral mechanisms. Therefore, it is marked by a regulated increase in temperature accompanied by various sickness behaviors, alterations in metabolic and physiological characteristics of body systems and alterations in immune responses. Fever and the febrile response are important contributors to the pathogenesis, clinical presentation and outcome of many illnesses and diseases[3]. As a result of the literature search, 6 febrile illnesses with significant prevalence in India were selected. This review highlights their clinical manifestations, management and expert recommendations.

No antibiotics are generally recommended till reports are available in case of acute febrile illness, but if there is a compelling indication to start an empirical antibiotic, then less resistance-prone; older, broad spectral antibiotics like oral or IV doxycycline should be used. Antibiotics should be started early in immunocompromised or high-risk patients with acute febrile illness including those with associated disease conditions such as suspected sepsis, deep-seated abscess, pneumonia, meningitis, typhus encephalitis, bacterial pansinusitis, bacterial otitis media, osteomyelitis and streptococcal sore throat. In fact, doxycycline and cephalexin are the only broad-spectrum antibiotics approved by the Drug Controller General of India (DCGI) as per the Central Drugs Standard Control Organization (CDSCO). Oral or IV doxycycline (200 mg) is approved as broad-spectrum antibiotic of choice in acute undifferentiated fever with suspected typhus fever, leptospirosis, malaria, typhoid, dengue or respiratory tract infections.

### Typhus

Scrub typhus is a serious public health problem in the Asia-Pacific region including, but not limited to, Korea, Japan, China, Taiwan, India, Indonesia, Thailand, Sri Lanka and the Philippines. It was observed that maximum cases of Typhus occurred in seasons with cooler temperature[4]. In India, the peak of the disease is between August and October[5].

**Clinical manifestations :**

Typhus is caused by mite infection. The clinical symptoms include high temperature, severe generalized headache, diffuse myalgia, presence of rash and an eschar at the site of the chigger bite in many patients. If typhus is not treated in time, it may cause encephalitis[6]. Eschar can be seen early in patients depicting local tissue necrosis at the site of chigger bite. Care should be observed while examining moist intertriginous surfaces such as axilla, scrotum or perianal region so that the clinician does not miss the eschar[6].

**Management :**

The disease persists for 14 to 21 days in absence of treatment. Patients treated with appropriate antibiotics

Table 1 — *Treatment of Typhus*

| Drug | Dose | Duration | Treatment |
|---|---|---|---|
| **Doxycycline :** | | | |
| Adults | 200 mg/day in two divided doses | 7 days (IV or oral) | Treatment of choice |
| Children | 4.5 mg/Kg body weight/day in two divided doses | 5 days | |
| Pregnant women | Contraindicated | | |
| **Azithromycin :** | | | |
| Adults | 500 mg in a single dose | 5 days | |
| Children | Azithromycin in the dose 10mg/kg body weight | 5 days | |
| Pregnant women | 500mg in single dose | 5 days | Drug of choice |
| **Chloramphenicol :** | | | |
| | 50-100 mg/Kg/day divided every 6h IV OR 500mg qid orally | 7-14 days (oral) | In adults |
| **Rifampicin :** | 600 to 900 mg/day | | Should be used where there is poor response to doxycycline |

typically become afebrile within 48 hours of starting therapy[7]. DHR-ICMR guidelines endorse the use of doxycycline 200 mg/day in two divided doses for patients above 45 Kg for a period of seven days or a single dose of azithromycin 500 mg for five days when the fever has persisted for five or more days and other febrile illnesses such as malaria, dengue and typhoid have already been ruled out. Alternative diagnosis should be considered, if clinical signs and symptoms persist even after the first line of treatment. Table 1 describes the different medicines used in the treatment of Typhus[8-10]. Even though South Asia has seen the presence of Doxycycline or chloramphenicol resistant strains, these strains have shown susceptibility towards azithromycin[11].

**Expert Clinical recommendations :**

If the patient presents to the primary care clinician or general physician with suspected typhus infection, it is recommended to initiate treatment with doxycycline even before the patient gets examined for presence of associated complications. If the patient shows signs of complications such as Acute respiratory distress syndrome, acute renal failure, meningoencephalitis, multi-organ dysfunction, it is recommended to prescribe doxycycline for managing typhus along with a treatment regimen for pneumonia.

## Dengue

Currently prevalent in over 100 countries across the globe, dengue attributes to probably 50 million infections occurring annually. From 1998 to 2014, the highest dengue incidence was reported in Pondicherry, followed by Dadra Nagar Haveli and Delhi. Similarly, high dengue incidence, ranging between 21 and 50 per million was reported for the states of Punjab, Gujarat, Karnataka, Kerala, Tamil Nadu and Orissa[12].

**Clinical manifestations :**

WHO reviewed the classification of dengue cases in 2009, wherein the traditional dengue fever and dengue hemorrhagic fever or dengue shock syndrome was replaced with dengue with and without warning signs and severe dengue[13].

**Management :**

No therapeutic agents exist for dengue infections; the key to successful management is timely and judicious use of supportive care[14].

While treating dengue, the management strategy is dependent on the severity of condition; ranging from mild, moderate to aggressive. NVBDCP & World Health Organization (WHO) have published Indian National Guidelines for dengue management which recommends that clinical supportive and symptomatic therapy should be given to patients based on the severity of the condition. Simple approach of management should be adopted for patients with fever but without any danger signs or associated complications. In case of patients with warning signs, the management should be accompanied with close observation of the patient to check and control progression of DHF/DSS or severe bleeding. Symptomatic and supportive management is provided in dengue fever. Antipyretics may be considered for lowering body temperature. Oral fluid and electrolyte therapy are recommended for patients experiencing rigorous sweating, vomiting or low blood pressure. Continuous monitoring for a period of 24-48 hours is recommended in case of DHF in endemic areas until the patients stops getting fever without the use of antipyretic drugs and once the hematocrit values stabilize, platelet count is >50,000/mm$^3$ or improving. Another recommendation is for the clinician to be watchful for detecting anyred flags for signs of fluid overload as the patient is prone to developing complications in the later stages of fever or in the afebrile phase of the disease[15,16]. In a study including dengue hemorrhagic fever patients (n=231), the results suggested that doxycycline offers clinical advantages to patients who are highly susceptible to complications. It is suggested that this effect may occur via the reduction in the pro-inflammatory cytokine levels[17]. In another study, doxycycline was evaluated with regard to changing serum levels of IL-6, IL-1B, and TNF. The results showed that treatment with tetracycline or doxycycline significantly brought down cytokine levels, with doxycycline demonstrating better cytokine modulating activity and cytokine receptor/antagonist levels compared with tetracycline[18].

**Expert Clinical recommendations :**

We recommend that patients with simple fever without any red flags or associated complications should be simply managed by providing symptomatic treatment. Rigorous treatment should only be given to patients who have grade III and IV Dengue Hemorrhagic Fever, substantial bleeding or are experiencing multi-organ dysfunction. A simple rule of 20 may be followed in the management of dengue; "*in a patient with dengue fever; if there is acute rise in pulse by 20, acute fall in blood pressure by 20 mm Hg, pulse pressure lower than 20, rapid rise in hematocrit by 20% with rapid fall in platelet count to less than 20, 000 or more than 20 petechiae in the tourniquet test, give 20ml/Kg fluid immediately and shift the patient to the nearest medical center for observations and treatment.*" It is recommended that doxycycline may be considered in Dengue Hemorrhagic Fever patients.

## Chikungunya

Chikungunya fever is one of the most important public health problems in India[19].

**Clinical manifestations :**

When an epidemic occurs with characteristic pattern

of abrupt onset of fever accompanied with arthralgia, myalgia, with/without rash, chikungunya is suspected. Fever and arthralgia are the hallmark of chikungunya fever. As the clinical manifestations of chikungunya fever resemble those of dengue and other fevers caused by arthropod borne viruses, lab diagnosis is critical to establish the cause of diagnosis[20].

**Management :**

Management is mostly symptomatic for this self-limiting illness. During an epidemic, every patient clinically suspected does not need to undergo serological testing. Systemic manifestation is rare, relapse or reinfection is not seen. Co-infection with dengue and malaria can occur concurrently. No specific treatment or antiviral drug is currently available for managing chikungunya[21].

Indian guidelines on chikungunya management have suggested that the treatment should be initiated in all suspected cases of chikungunya, even before the serological or viral presence is confirmed in the diagnostic tests. All control measures including mosquito nets should be provided to all suspected fever cases. Treatment recommendations include paracetamol 1 g administered 3 to 4 times a day for the management of fever, headache and other pain; and antihistamines for itching. The recommended dose for children is 50-60 mg per Kg body weight administered in multiple doses. Lukewarm water sponging may be considered. Another important recommendation is that if paracetamol or other analgesics have already been given to the patient with no response, Nonsteroidal anti-inflammatory drugs may be considered. Topical or systemic drugs can be used for topical manifestations of the disease[22,23].

Patients who are non-responders or have obstinate joint pain or incapacitating arthritis even after treatment duration of 3 days, patients aged above 60 years or below 1 year also require immediate hospitalization. Serious complications should be treated; bleeding disorders with blood components, hypotension with fluids/inotropics, acute renal failure with dialysis, contractures and deformities with physiotherapy/surgery, cutaneous manifestations with topical or systemic drugs, neuropsychiatric problems with specialist care and drugs[22,23]. When the patient is in the recovery phase, recommend mild exercise and physiotherapy to them. If effective, cold compress may also be considered in recovering patients[22,23].

**Expert Clinical recommendations :**

Symptomatic approach should be followed for treatment. Initiate treatment in all suspected cases. The drug of choice is paracetamol; however other pain relieving medications or NSAIDs may be considered if the patient is not responding to paracetamol. Steroids should be avoided in the acute stage of the disease because they may be associated with side effects. Aspirin should also be avoided in these patients as it may lead to gastrointestinal side effects like Reye's syndrome.

Single dose of steroids or hydroxychloroquine 200 mg may be considered to be administered orally for duration of 4 weeks in patients who have acute fever associated with 'chikun' flexion posture due to painful arthritis or persistent inflammatory arthritis.

## Influenza

There are no estimates of influenza-associated mortality existing for India and the exact burden of influenza in India is also not known[24].

**Clinical manifestations :**

The hallmark of influenza is the sudden, rapid onset of symptoms which include fever, chills, body aches, sore throat, non-productive cough, runny nose and headache[25].

**Management :**

The recommended treatment is oseltamivir. The recommended dose for treatment is provided in Table 2. Supportive therapy includes IV fluids, parenteral nutrition, oxygen therapy, antibiotics for secondary infection, vasopressors for shock, paracetamol or ibuprofen for fever, myalgia and headache. The suspected patients should be constantly monitored[25]. Patients should increase their intake of fluids. Oxygen therapy should be considered in patients experiencing symptoms of tachypnea, dyspnea, respiratory distress or less than 90 per cent oxygen saturation[26].

**Expert Clinical recommendations :**

We recommend considering the disease severity and progression, age of the patient, other comorbid conditions, probability of progression to severe stage of influenza and time elapsed since the onset of symptoms before initiating them on antiviral medication, oseltamivir.

Other recommendations include use of topical decongestants, saline nasal drops, throat lozenges and steam inhalation for symptomatic relief. Complete cessation

Table 2 — *Oseltamivir dose and duration for the treatment of seasonal influenza*

| **Oseltamivir dose and duration :** | | | |
|---|---|---|---|
| By weight | Dose | For infants | Dose |
| <15 Kg | 30 mg BD for 5 days | <3 months | 12 mg BD for 5 days |
| 15-23 Kg | 45 mg BD for 5 days | 3-5 months | 20 mg BD for 5 days |
| 24-<40 Kg | 60 mg BD for 5 days | 6-11 months | 25 mg BD for 5 days |
| >40 Kg | 75 mg BD for 5 days | | It is also available as syrup 12 mg per mlIf required dose and duration can be changed based n clinical situation |

of smoking is recommended to abort disease progression or worsening of the symptoms. Avoid aspirin in all influenza patients. It is recommended to closely monitor the patient to detect clinical or radiological signs of lower respiratory tract infection or hypoxia.

For prevention of influenza, we recommend respiratory hygiene (maintaining a distance of 3 feet from an infected person), encouraging cough etiquette (coughing on the sleeve or tissue paper) and timely annual influenza vaccination.

### Upper Respiratory Infection

Acute respiratory infection (ARI) is the largest single disease category for India, accounting for about one-ninth of the national burden[27]. The incidence of acute Upper Respiratory Tract Viral Infections (URTI) is directly correlated to air temperature with most URTI occurring seasonally in cold weather[28].

**Clinical manifestations :**

The most common symptoms of upper respiratory tract infections include sore throat, congestion, rhinorrhea, pain & fever and cough[29].

**Management :**

As per the ICMR guidelines, the upper respiratory tract infections are mostly due to viral infections. Hence, role of empirical antibiotics is limited. In most immunocompetent adult patients, the URI treatment is based on providing symptomatic relief. However, in certain patients antimicrobial or antiviral treatment may be warranted depending on the symptoms and cause[28]. Table 3 discusses the treatment based on guidelines in different upper respiratory tract infections[28].

A multi-center trial including patients with infections of respiratory tract who were treated with doxycycline, the results clearly demonstrated that treatment with 200 mg doxycycline given on the first day followed by 100 mg daily resulted in effective results and rapid onset of action (in 87% of patients)[30-32]. In a survey conducted among general practitioners, a statistically significant better response was seen in acute and acute-on-chronic bronchitis patients who were given doxycycline as compared with amoxicillin[33,34].

Table 3 — *General upper respiratory infections with their diagnostic findings and treatment approach*

| Condition | ICMR guidelines | AFP guidelines |
|---|---|---|
| Acute bronchitis and tracheitis | Viral, antibiotics not required | Symptomatic treatment; antibiotics not recommended |
| Acute otitis media | Amoxicillin clavulanate 1 gm oral BD for 7 days<br>Azithromycin 500 mg OD for 5 days OR<br>ciprofloxacin 500 mg BD for 7 days | Amoxicillin, 80 to 90 mg per Kg per day,<br>in two divided doses: first line treatment |
| Acute rhinosinusitis | Amoxicillin clavulanate 1 gm oral BD for 7 days<br>Azithromycin 500 mg OD for 5 days OR<br>Ciprofloxacin 500 mg BD for 7 days | Observe in mild cases;<br>Amoxicillin (80 to 90 mg per Kg per day in two divided does) as first line therapy<br>Doxycycline as alternative therapy |
| Common cold | No antibiotics | Symptomatic treatment; antibiotics are not recommended<br>Consider antibiotics |
| Epiglottis | | A third-generation cephalosporin and an antistaphylococcal agent active against methicillin-resistant *Staphylococcus aureus*(IV) or ceftriaxone, cefotaxime or ampicillin/sulbactam (IV). |
| Influenza | No antibiotics | Influenza vaccination; supportive care; initiation of antiviral therapy within 48 hours of symptom onset<br>Symptomatic treatment; antibiotics not required |
| Laryngitis | No antibiotics | Treatment based on modified Centor score<br>In patients with a score of 1 or less, no further treatment is indicated. |
| Pharyngitis and tonsillitis | Commonly viral, no antibiotics.<br><br>If bacterial, oral Penicillin V 500 mg BD or amoxicillin 500 mg oral TDS for 7 days.<br><br>In case of Penicillin allergy, azithromycin 500 mg OD for 5 days. | In those with score of 2 or 3, streptococcal rapid antigen detection testing recommended and antibiotic treatment if test results are positive.<br>Antibiotic treatment is recommended for patients with a score of 4 or 5.<br>The recommended first line treatment is a 10-day course of Penicillin. Erythromycin can be used in patients who are allergic to penicillin.<br>Amoxicillin, azithromycin and first generation cephalosporins are other alternatives. |

**Expert Clinical recommendations :**

We recommend except for streptococcal infections presenting with fever and sore throat and absent cough and cold, antibiotics are not recommended in viral infections. However, presumptive antibiotic therapy may be initiated in bacterial cases. Based on the results of trials and survey among general practitioners, doxycycline can be considered in the management of upper respiratory tract infections.

## Malaria

Over the past two decades, India has made immense progress in malaria control[35]. It has been noted that malaria cases start increasing in April and peak during the monsoon period (ie, June and July) and then steadily drop from August onward[36].

**Clinical manifestations :**

Malaria has non-specific clinical manifestations. Fever or a history of fever forms the primary basis of clinically suspecting malaria. There are no distinguishing features of malaria; making the specific diagnosis difficult and increased chances of over treatment. In regions with endemic malaria, malaria is suspected in all patients with a history of fever or temperature ≥37.5°C without any other prominent cause. It is suggested that in places where malaria transmission is stable, it should be suspected in children who present with palmar pallor or hemoglobin level <8gdL[37].

**Management :**

The treatment of malaria should be refrained till laboratory investigations have established the diagnosis. "Presumptive treatment" without a confirmed diagnosis should only be considered in extreme cases[38].

A parasitological test to confirm diagnosis is a must in all suspected malaria cases. The WHO recommendations suggest that all confirmed cases in children and adults with uncomplicated *P falciparum* malaria (excluding pregnant women in their first trimester) should be treated with any artemisinin-based combination therapies (ACT); artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine, artesunate + sulfadoxine-pyrimethamine. The treatment duration for Artemisinin derivative based therapy is recommended to be 3 days. In low-transmission areas, one dose of primaquine with ACT is recommended in patients with *P. falciparum* malaria (excluding pregnant women, infants below 6 months of age and women breastfeeding infants aged <6 months) to lower the rate of disease spread. In the first trimester of pregnancy, quinine + clindamycin is recommended to treat uncomplicated cases of *P falciparum* malaria[39].

*Plasmodium falciparum* isolates with reduced sensitivity to quinine have been isolated from various regions of the world; hence either doxycycline or clindamycin (for instance in children and pregnant women where doxycycline is contraindicated) may be given for 7 days alongside quinine[40].

**Expert Clinical recommendations :**

We recommend that confirmed cases of malaria (Rapid diagnostic test or Microscopy) should be immediately started on treatment. Recommended treatment is chloroquine 25 mg/Kg in confirmed *P. vivax* cases. Primaquine 0.25 mg/Kg body weight should be given for 14 days under close observation to prevent relapse of the disease. Artemisinin combination therapy is recommended in all confirmed *P falciparum* cases. Doxycycline 100 mg/day (1.5 mg/Kg of body weight) is recommended for short-term prophylaxis and mefloquine 250 mg weekly (5 mg/Kg of body weight/week) for long-term prophylaxis. Doxycycline is note recommended in pregnant and lactating women and in children younger than 8 years.

## Conclusion

Acute fever is related with multi-system dysfunction and may be viral or bacterial in nature. In this article, 6 such febrile infections were discussed and recommendations for their management have been discussed. Most of the diseases were viral infections and did not require the use of an antibiotic in the management of the disease conditions. In many cases where there is no anti-viral treatment available so far, symptomatic treatment as well as vector prevention has been recommended.

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Review Article

# Coronavirus Disease 2019 (COVID-19) due to Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV2) Infections – An update

**Rajesh Purushothaman[1], Sribiju MK[2], Martin Joseph[3], Priya Radhakrishnan[4]**

**An outbreak of severe acute respiratory disease due to a novel corona virus was reported from the city of Wuhan, Hubei Province, China in December 2019. Initially named as novel coronavirus 2019 (2019-nCoV), the virus was later officially named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). The disease caused by it was officially named by the World Health Organization as Corona Virus Disease 2019 (COVID-19). Within a short span of time the epidemic spread to all provinces of China and 88 other countries and caused more than 80,000 confirmed infections and over 3000 (as on 6th March, 2020) deaths. 33 cases were confirmed in India and several suspected cases quarantined. In this review article, the origin of the virus, its genetic make-up, and how the epidemic evolved are discussed. The spectrum of clinical features, important laboratory and imaging findings as per early clinical studies are described in detail. The current treatment principles along with the future prospects of treatment are outlined. Preventive measures taken are narrated. The possible future scenarios of the epidemic are depicted.**

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***Key words*** **: SARS-CoV2, COVID-19.**

The 2019 novel corona virus (2019-nCoV), now known as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2) epidemic originated in the Wuhan city, Hubei Province, Peoples Republic of China in December 2019 and as of March, 6th, 2020 there were 98,192 confirmed cases and 3,381 deaths reported from 88 countries including China. At the time of submission of this article, majority of cases and deaths (80,711 confirmed cases and 3,045 deaths) have been in China. Inside China, Hubei province borne the brunt with 67,592 confirmed cases and 2,931 deaths. Outside of China, cases have been confirmed in 88 countries accounting for 17,487 confirmed cases and 335 deaths. In India, there were 33 confirmed cases of which first three were from the state of Kerala[1]. Rest of the cases were reported after 16 Italian National tested positive for virus on 4th March, 2020. Bengaluru, New Delhi, Gurugram & Ghaziabad had each reported one/two people with travel history of Italy have tested positive on case on 7th March, 2020. On February 11, 2020, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses

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***Editor's Comment :***

- **Coronavirus Disease 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV2), a novel corona virus that emerged in Wuhan, China in December 2019.**
- **It causes severe acute respiratory distress in some patients, especially in older patients with comorbidities.**
- **It should be suspected in patients with fever, radiographic evidence of pneumonia, reduced lymphocyte count with no response to 3 days of antimicrobial treatment especially those with history of travel to China or having history of contact with travelers who visited China recently.**
- **Confirmation of diagnosis is by identification of specific sequences of SARS-CoV2 in the throat secretions of patients using RT-PCR.**
- **Patients are treated by isolation and by supportive treatment. No specific antiviral treatment or vaccine is available at this point of time.**
- **Patients should be watched for features of respiratory distress, cardiac arrhythmias and multiorgan dysfunction especially from the second week onwards.**
- **On serial estimation,progressive elevation of total WBC count, d-dimer, lactate dehydrogenase and creatine kinase associated with decreasing total lymphocyte count indicate worsening of prognosis.**

officially named the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the World Health Organization officially named the clinical disease caused by SARS-CoV-2 as Corona Virus Disease-2019 (COVID-19).

**What is Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2) ?**

The SARS-CoV2 virus, belonging to the Coronaviridae family, is composed of positive-sense single-stranded RNA viruses. Prior to 2002 this viral family was considered mostly inconsequential as it rarely led to severe illness. In 2002, SARS (Severe Acute Respiratory Syndrome) due a corona virus called SARS-CoVwas identified in the Guangdong province of China, that ultimately spread to 29 countries, infected over 8096 individuals, and caused 774 deaths (WHO News 2003; **81(5):** 384).

This was followed by the emergence in 2012, in the Arabian Peninsula, of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Although the clinical manifestations of MERS resembled that of SARS, the case fatality rate (CFR) of MERS was much higher (37.1% *versus* 9.6%). MERS-CoV lead to 2494 infections and 858 deaths (Zaki AM, 2012). While both SARS-CoV and MERS-CoV caused severe respiratory diseases in humans, four other previously documented human corona viruses (HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-HKU1) were responsible for 10-30% of minor upper respiratory tract infections worldwide.

**COVID 19**

***(Update 10/03/2020)***

- **Global cases : 113702**
- **Global death : 4012**
- **No of countries affected : 109**
- **WHO risk assessment : Very high (Global)**
- **Total no cases in India : 52**
- **Most affected region : Kerala, Uttar pradesh**

In 2019, the newest member of the corona virus, SARS-CoV2 infection has been identified as the causal virus in the exponentially increasing current epidemic, prompting the World Health Organization to classify the event as a Public Health Emergencyof International Concern (PHEIC) on 30-1-2020. Starting in the Wuhan District of Hubei province of China in December 2019, it is estimated that this novel coronavirus has caused over 98,192 confirmed cases and a current death toll of 3,381 as on February 20, 2020. The situation is dynamic and it is clear that the true magnitude of the problem is yet to be determined.

**Genetic build-up of SARS-CoV2 :**

Coronaviruses (order *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae)* are enveloped viruses with single-stranded, positive sense RNA genome having a genome size between 26 to 32 kilobases. The genome codes for four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein. The sequenced genome of SARS-CoV2(NCBI Reference Sequence NC_045512.2) was 88% identical to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses called bat-SL-CoVZC45 and bat-SL-CoVZXC21. It was 79% identical to SARS-CoV and 50% identical to MERS-CoV (Roujian Lu, 2020). Phylogenetic analysis showed that it belonged to the subgenus Sarbecovirus of the genus Betacoronavirus. SARS-CoV2 was found to have 96.3% sequence similarity throughout the genome to BatCoV RaTG13 viruses found in bats from Yunnan province of China, but SARS-CoV2 showed discordant clustering with the Bat_SARS-like coronavirus sequences (D Paraskevis, 2020). Though bat coronavirus RaTG13 remains the closest relative of SARS-CoV 2 across the whole genome, a coronavirus found in Malaysian Pangolins (*Manis javanica*), the most common illegally traded endangered mammal in the world, was found to be identical to SARS-CoV 2 at all six key receptor binding domain (RBD) residues (Wong 2020).

**Timeline :**

Chronologically, this global health emergency began on December 8, 2019 in Wuhan, China, a city with a population of 11 million, when the first patient was brought into the emergency room with pneumonia of unknown etiology. Thereafter, the emergency department noticed a multitude of similar presentations, and by December 30, 2019, the total number of cases locally rose to 41. The surveillance mechanism for "pneumonia of unknown aetiology": a system created and implemented to aid in timely identification of novel pathogens causing pneumonia after SARS epidemic, was activated. All subsequent cases were notified to the Chinese National Health Commission (Chaolin Huang, 2020).

On January 7, 2020, the China-CDC identified the causative organism as a novel coronavirus which was phylogenetically in the SARS-CoV clade. Despite measures to counter the illness, the first fatality occurred

on January 11, 2020 in a 61-year-old patient with multiple comorbidities. Around the same time, the full viral genome was sequenced, and shared with the World Health Organization on January 12, 2020. This was subsequently made available on the Global Initiative on Sharing All Influenza Data [GISAID] platform, which currently has 103 SARS-CoV-2 genomes uploaded from worldwide. The availability of the full viral genomic data lead to rapid development of point-of-care real-time PCR diagnostic testing. Ongoing analysis of subsequent genomes received from worldwide will help in early detection of mutations in the SARS-CoV-2 genome.

**Origin :**

Epidemiological investigations into the first 41 cases found that many of the patients had exposure to a large seafood and live animal market in Wuhan, suggesting an animal-to-person spread. As ongoing investigations occurred, an increasing number of those affected reported no exposure to the market, indicating a person-to-person transmission (Chaolin Huang, 2020). As discussed earlier, current data on the viral genome has suggested bats as a possible reservoir for the virus, propagated by their propensity to inhabit small, enclosed, ill-ventilated spaces in large colonies. Bat-borne viruses generally lack the capability to adhere onto human cell surface receptors, and may need an intermediary host such as dromedary camels in the case of MERS for the cross-species jump enabled by mutations and recombinations. These claims require further scientific investigation before any conclusions could be made. Nevertheless, the SARS-CoV2 has 96.3% sequence similarity throughout the genome to BatCoV RaTG13 viruses(D. Paraskevis, 2020) and share six key receptor binding domain (RBD) residues with a coronavirus isolated from Malaysian pangolins (Wong 2020).

**Global picture :**

As per WHO situation report dated March 6th, 2020, globally there are 98,192 confirmed cases. In China, there are 80,711 confirmed cases (146 new), and 3,045 deaths (30 new). It has spread to all provinces of China including Hongkong, Macau and Taiwan and to 88 countries including India. As diagnostic facilities become available in more countries, the number of countries affected is expected to escalate. In addition to China, human-to-human transmission have been identified in Germany, Vietnam, Japan, USA and France. Italy has been hit hard since the outbreak with more than 4,600 confirmed cases & over 200 deaths.

**How is it transmitted ?**

The virus probably spreads by airborne transmission via large droplets, aerosols, faecal-oral routeor by fomites. A reproduction number or R0 of 1.8 to 3.5 is the current estimation. This means that overall, each patient infected with the virus will spread the infection to 1.8 to 3.5 other people. Preventive measures aimed at reducing the R0 are being implemented, and this will help to curb the epidemic. This can be done with early diagnosis, contact tracing and surveillance, social distancing, personal hygienic measures, appropriate personal protective gear and isolation of known/suspected cases. As a comparison, R0 for various common illnesses are as follows: measles 12-18, mumps 4-7, AIDS 2-5, SARS 2-5, MERS less than 1 and Spanish flu (1918) 2-3. Due to the ongoing nature of SARS-CoV2 epidemic, all estimations are likely to change.

**Clinical Features :**

From the data on first 425 patients, the meanincubation period was estimated to be 5.2 days (95% confidence interval [CI], 4.1 to 7.0) and the 95th percentile ofthe distribution was 12.5 days (95% CI, 9.2 to 18). Serial interval between infective cycles is reported to have a mean (±SD) of 7.5±3.4 days(95% CI, 5.3 to 19). Epidemic growth rate was found to be 0.10 per day (95%CI, 0.050 to 0.16). Doubling time for the number of cases reported as 7.4days (95% CI, 4.2 to 14)(Qun Li, 2020).

According to clinical features of first 41 cases reported in *The Lancet* on January 24$^{th}$, symptoms during prodromal phase including fever and dry cough were nonspecific and upper respiratory tract symptoms such as running nose and sore throat were notably infrequent(Chaolin Huang, 2020). Similar to SARS-CoV, SARS-CoV2 also binds to hACE-2 receptors (Human Angiotensin converting enzyme-2). hACE-2 receptors are predominantly seen in the lower respiratory tract which may explain the predominance of lower respiratory tract symptoms. Intestinal symptoms in contrast to SARS (Severe Acute Respiratory Syndrome) infections and MERS (Middle East Respiratory Syndrome) were uncommon. 22 patients (55%) developed severe respiratory distress, 13 (32%) needed intensive care and 6 patients (14.6%) died. Blood investigations showed relative reduction of lymphocytes (lymphopenia) and chest x-rays showed bilateral lung field opacities suggestive of viral pneumonia.

A study based on 99 patients with RT-PCR proven SARS-CoV2 infection treated at the Jinyintan Hospital, Wuhan from 2020 January 1$^{st}$ to 20$^{th}$, published in *The Lancet* on January 29, 2020, the clinical manifestations were

fever (83%), cough (82%), shortness of breath (31%), muscle ache(11%), confusion (9%), headache (8%), sore throat (5%),rhinorrhoea (4%), chest pain (2%), diarrhoea (2%), and nausea and vomiting(1%)(Nanshan Chen, 2020). Average age was 55.5 years and 51% had comorbidities. 17% developed acute respiratory distress syndrome (ARDS) and 11% died of multiple organ failure.

A study CT scans of chest of 21 patients, showed bilateral pulmonary parenchymal ground-glass and peripherally distributed consolidative pulmonary patches with a notable absence of cavitation, pleural effusion, discrete nodules and lymphadenopathy (Michael Chung, 2020).

In a retrospective study submitted to the Lancet based on 52 critically ill patients out of 710 confirmed cases at Wuhan Jinyintan Hospital, the authors found that the average age was 59.7±13.3 years (mean±standard deviation), 35 (67.3%) were male, 21 (40.4%) had chronic illness, 51 (98.1%)had fever, 35 (67.3%) developed ARDS and 37 (71.2%) required mechanical ventilation(Xiaobo Yang, 2020).Thirty-three (57.7%) patients deceased, and theduration from hospital admission to death was 7 [3 - 11] days.

In an article under consideration for publication in *The Lancet*, a team of authors reported on 9 patients with known exposure to confirmed or suspected cases, who presented with gastrointestinal symptoms and no fever (Ping An, 2020). Five patients subsequently developed fever and respiratory symptoms, but 4 patients did not develop respiratory symptoms or fever. Multifocal patchy ground-glass pulmonary opacities were found in all 9 patients on CT scan of chest done during the first clinical visit. Hence those with history of exposure to confirmed or suspected cases of SARS-CoV2 infection, presenting with gastrointestinal symptoms should be evaluated for the disease even in the absence of fever and respiratory symptoms.

In a single-centre, retrospective consecutive case series of the 138 hospitalized patients with confirmed SARS-CoV2 pneumonia at Zhongnan Hospital of Wuhan University in Wuhan, China, from January 1 to January 28, 2020, authors reported fever (98.6%), fatigue (69.6%)dry cough (59.4%), myalgia (34.8%) and dyspnoea (31.2%) as the most common symptoms (Dawei Wang, 2020). Hospital associated transmission was suspected in 57 (41.3%) of patients, of this 40 were health care workers and 17 were already admitted patients. Of the 40 health care workers infected, 31 worked on general wards, 7 in the emergency department and 2 in the intensive care unit. Median interval from onset of symptoms to dyspnoea was 5 days, to hospital admission was 7 days and to ARDS was 8 days. Lymphopenia (70.3%), prolonged prothrombin time (59%) and elevated lactate dehydrogenase (39.9%) were observed on lab investigations. Computed tomography showed bilateral opacities or patches in all patients. Transfer to intensive care unit was needed in 36 patients (26.1%) either due to ARDS in 22 patients (61.1%), arrhythmia in 16 patients (44.4%) and shock 11 patients (30.6%). Patients admitted to ICU were older and were more likely to have comorbidities. At admission, patients who later required ICU care showed statistically significant elevated levels of neutrophil count, D-dimer, procalcitonin, blood urea nitrogen, aspartate aminotransferase, creatine kinase and lactate dehydrogenase. As of February 3, 6 patients died (4.7%), 85 patients (62.6%) remains hospitalised and 47 patients (34.1%) were discharged. Nonsurvivors had higher total WBC counts, elevated neutrophil count, lower lymphocyte count and elevated D-dimer levels on serial investigations after admission to the hospital mainly seen from the second week onwards.

As per the epidemiology report by SARS-CoV2 National Incident Room Surveillance Team of Australia for the week from 26 January to 1 February, there were 12 confirmed cases of SARS-CoV2 infections in Australia and all had history of travel to China. Of the 12 patients, 11 had mild to moderate symptoms, one was admitted in the ICU and there were no deaths. All had fever and 83% had cough(2019-nCoV National Incident Room Surveillance Team. Australia., 2020).

**When to suspect Coronavirus Disease 2019 (COVID-19)?**

SARS-CoV2 caused pneumonia now officially termed Coronavirus Disease 2019 (COVID-19) should be suspected if it meets all the four criteria below fever >38$^0$C, radiographic evidence of pneumonia; low or normal white-cell count or low leucocyte count; and no reduction in symptoms with antimicrobial treatment of 3 days duration or any of the three criteria with history of contact with an infected person or infectious place with or without recorded fever;radiographic evidence of pneumonia, low or normal white-cell count or low lymphocyte count, and no reduction in symptoms with antimicrobial treatment of 3 days duration.

**How to confirm Coronavirus Disease 2019 (COVID-19)?**

Throat swabs are collected and send with virus preservation solution. SARS-CoV2 infection confirmation may be done by next-generation sequencing, real-time RT-PCR, cell culture, or electron microscopy. Isolation of the virus from specimens is not advised for diagnosis.

Diagnosis is confirmed if RT-PCR (real-time polymerase chain reaction) with SARS-CoV2 specific primers and probes for the targets or the genetic sequence that matches SARS-CoV2 is found in the collected sample. In the laboratory, total RNA is extracted within 2 hours and real-time reverse transcriptase polymerase chain reaction done by amplifying for two target genes of SARS-CoV2: open reading frame 1ab(*ORF1ab*) and nucleocapsidprotein(*N*) (Dawei Wang, 2020). RT-PCR is considered positive if 2 targets (open reading frame 1a or 1b(*ORF1ab*), nucleocapsid protein(N) were positive at a cycle threshold value (Ct-value) less than 37, values more than 40 was considered negative and for values between 37 and 40, retesting should be done. Genetic sequencing done using either Sanger sequencing, Illumina sequencing, or nanopore sequencing (Nanshan Chen, 2020).

Supportive laboratory investigation results are as per *The Lancet* article dated January 29, 2019 about the clinical features of first 99 patients are as follows: decreased haemoglobin in 51%, leucocytosis in 24%, neutrophilia in 38%, lymphopenia in 35%, raised erythrocyte sedimentation rate in 85%, increased C-reactive protein in 86%, raised serum ferritin in 63%, raised interlekin-6 in 51%, D-dimer increase in 36%, hypoalbuminemia in 98%, elevated liver enzymes in 35% and increased lactate dehydrogenase in 76%. On imaging studies, 75% had bilateral pneumonia and 14% had multiple mottling and ground-glass opacity.(Nanshan Chen, 2020)

**Treatment at present :**

This section is based on the reported treatments in the published articles and online reports of leading journals. The cornerstone of treatment is supportive. Patients should be treated in isolation. Medical history, exposure history, comorbidities, symptoms and physical findings should be recorded. In sick patients, Glasgow Coma Scale, Sequential Organ Failure Assessment (SOFA) Score and Acute Physiology and Chronic Health Evaluation II (APACHE II) Scores should be recorded at ICU admission and serially. Observe the patients for acute respiratory distress syndrome, renal failure and cardiac injury as these are cardinal events that influence the outcome. ARDS is diagnosed as per 2012 Berlin definition (Ranieri VM, 2012). Acute kidney injury diagnosed as per 2012 Acute Kidney Injury Work Group recommendations (KDIGO, 2012). Cardiac injury should be looked for using serum biomarkers such as troponin I and lactate dehydrogenase, serial electrocardiograms and echocardiography. Total WBC count and differential count should be done every 2 days as serially increasing total count, increasing neutrophil count and decreasing lymphocyte counts suggest poor prognosis. Raised D-dimer, elevated lactic dehydrogenase levels, elevated liver enzymes, elevated creatine kinase, deranged renal function also should be looked for as they indicate worsening. As worsening generally develops in the second week, patients should be more stringently observed during the second week.

Scientifically proven antiviral treatment or specific vaccines are not available at present. Case reports of successful use of antiviral agents along with protease inhibitors have been described. Antiviral agents that have been used include oseltamivir (75 mg every 12 h, orally), ganciclovir (0·25 g every 12 h,intravenously), in combination with protease inhibitors: lopinavir and ritonavir tablets (500 mg twice daily, orally). The duration of antiviraltreatment is 14 days. Antibiotics such as cephalosporins, quinolones, carbapenems, tigecycline, linezolid against methicillin-resistant Staphylococcus aureus and antifungal drugs are given for secondary bacterial infections. Steroids (methylprednisolone1–2 mg/kg per day) are recommended for patients withARDS, for as short a duration of treatment as possible. Non-invasive or invasive mechanical ventilation may be needed if the oxygenation levels are not maintained. Dialysis may be needed if there is associated renal failure.

**Future prospects of treatment :**

As the event has been classified as a global health emergency, transparency as well as data sharing are essential for a successful outcome. The current trend has shown leading journals publishing articles with real-time peer review, freely available to all. Genomes sequenced so far has been made available to researchers, which allows an international, collaborative effort to evaluate and scrutinize the data. Governmental agencies and private companies are working against time to develop an effective vaccine. Coalition for Epidemic Preparedness Innovations (CEPI), a non-profit formed in 2016 announced on 23 January, 2020 that it will provide 12.5 million dollars to 3 companies (Moderna, Inovio and University of Queensland) to develop and test SARS-CoV2 vaccines faster than any previous effort (Cohen, 2020). Vaccines are expected to be available for phase 1 trials soon.Virologists in Australia have successfully grown the virus in vitro, improving the chances of rapid vaccine and antiviral drug development. Moving forward, it is imperative that the healthcare community and general public work collaboratively to overcome the SARS-CoV2 epidemic rapidly progressing to become a pandemic.

**What is being done now to control the disease?**

The Chinese government has taken significant steps to contain the disease. A public health emergency has been declared, entire Hubei Province has been declared as *cordon sanitaire* (a quarantined area preventing anyone fromleaving) and vehicular transport have been banned. The effectiveness and its impact on human rights of *cordon sanitaire* is controversial. As a reported number of 5 million people have already left the area prior to the enforcement of quarantine of the entire region, the effectiveness of this method remains to be determined (Shih G, 2020). In addition, as animal reservoir of the virus is not yet known, further spill over to human beings cannot be ruled out. The SARS-CoV2 epidemic has been declared as Public Health Emergencyof International Concern (PHEIC) by the WHO on 30-1-2020 due to sustained disease transmission in China and human-to-human transmission has been reported in Germany, Japan, Vietnam and USA. Flights to China are being stopped and the borders with neighbouring countries are being closed. But how long these measures may have to be continued and how long it can be maintained is not yet known. Different countries including India have repatriated their nationals from the epidemic zone including Wuhan. Once repatriated, these individuals are being quarantined for 14 days. Entry of the virus into low income countries which may not have the resources for preventive measures is a global concern.

In India, the Ministry of Health and Family Welfare has issued guidance statements for the surveillance of cases and is developing laboratory testing capability in case of spread of the disease. The government of Kerala had declared emergency status which was subsequently revoked following no new cases.

In Indian response : The Government of India has made 52 more labs functional across India in wake of 33 confirm cases of Coronavirus in India.

**Practical Considerations :**

Physicians encountering patients with new onset acute respiratory or flu like syndromes must get a detailed travel history that includes a personal travel history and exposure to individuals who might have returned from China. All high risk cases, at this time, should be quarantined and admitted to designated hospitals (usually medical college hospitals, large government or private hospitals) and appropriate infection prevention and treatment protocols must be initiated. (Guidelines on Clinical management of severe acute respiratory illness (SARI) in, 2020). In busy out-patient departments, signage for infection control and triage must be instituted in order to prevent person to person transmission. Physicians, and other healthcare workers, including nurses, ambulance workers and staff must follow universal infection control and hand hygiene precautions. (WHO)

**Future projections :**

The emergence of SARS-CoV2 has raised concerns and fears that it is the beginning of a global pandemic due to a highly contagious novel virus with a significant mortality and morbidity. The exponential rise in the number of new cases, suspected cases and deaths has led the WHO to declare the epidemic as a public health emergency of international concern (PHEIC) as of January 30, 2020. Inherently RNA viruses have a higher mutation rate, though coronavirus has a lower than normal mutation rate than other RNA viruses due to the presence of a genome-coded error-detection capable exonuclease. Nevertheless, the exponential increase in new cases, deaths, reported transmissions while asymptomatic, and widening geographic spread are elements which should elevate the level of significance.

Along with this, it is important to understand the cultural context and significance to timing. The entire event is unfolding amid the largest annual human migration event on Earth, the Chinese New Year also known as Chunyun. Over the 40 days long Chunyun period, roughly 400 million Chinese workers and students travel home to have reunion dinner with their families on the new year eve and then back resulting in 3 billion passenger-travels. The Chinese authorities have taken unprecedented measures to contain the spread of the virus by restricting travel to affected areas, by extending the new year vacations and by closing down public spaces and work spaces.

In a manuscript submitted to *The Lancet*, a team of investigators used a SEIR (Susceptible, Exposed, Infected and Resistant) model with an assumed R0 of 0.5, 0.25 and 0.125 predicted that the estimated numbers of cumulative cases would reach the peak on 3rd, 4th and 5th of February, 2020, which were 11,116, 11,373, 11,966, respectively, in Chinese Mainland. (Huwen Wang). Another team of researchers have estimated the reproduction number (R0) based on number of confirmed cases on January 23, 2020 as 2·90 (95%CI: 2·32-3·63) using exponential growth model and 2·92 (95%CI: 2·28-3·67) using maximum likelihood model for future projections. (Tao Liu, 2020). As per the WHO situation report dated February 8, 2020 the cumulated figures were 34,886 confirmed cases, 6101 severe cases and 723 deaths in the Mainland China. The majority of the cases have been restricted to China.

Will these preventative measures succeed? Will the virus become an endemic that spreads at lower rates of transmission much like Chikungunya, Dengue, and others? Or will the event evolve into a global pandemic similar swine flu which occurred in 2009, going on to kill more than 200,000? We will be cautiously optimistic, while working collaboratively to prevent transmission and treat those infected.

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## FAQs :

**(1) Does Vaccination against Pneumonia and Influenzae protect against Coronavirus infection?**

No.

**(2) Is it safe to receive a package /article made in China ?**

Yes absolutely safe .Virus survive only for 3 hr in vitro.

**(3) Does antibiotics effective in coronavirus infection?**

No. it is viral infection, antibiotics not effective

**(4) Who are more Susceptible ?**

All age group may be affected , but in older , children and in persons with comorbid conditions morbidity and mortality higher .

**(5) Can Pets at Home can spread Corona infection ?**

At present no such evidence . But it is good practice to wash hands properly after handing pets.

**(6) Can Coronavirus can spread by faeces ?**

Yes like other coronavirus it can be present in Faeces. So after using toilet, after changing diper hands should be properly cleaned.

**(7) Does corona Virus infection transmitted by mosquito ?**

No such evidence till now.

**(8) Any thing that should not Do**

Smoking, taking multiple antibiotics , wearing multiple masks

## PREVENTIVE MEASURES

- **Keeping a distance of at least one metre from persons showing symptoms remain particularly important for all travellers.**
- **Perform hand hygiene frequently, particularly after contact with respiratory secretions. Hand hygiene includes either cleaning hands with soap and water or with an alcohol-based hand rub.**
- **Cover your nose and mouth with a flexed elbow or paper tissue when coughing or sneezing and disposing immediately of the tissue and performing hand hygiene;**
- **Refrain from touching mouth and nose;**
- **A medical mask is not required if exhibiting no symptoms, as there is no evidence that wearing a mask – of any type – protects non-sick persons.**

## RESPONSE FROM INTERNATIONAL COMMUNITY

- **The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020.**
- **Since WHO declaration of a public health emergency of international concern in relation to COVID-19, and as of 6th march 2020, 88 countries have been affected as per WHO report. WHO declared it an Pandemic on 12th March, 2020.**
- **UN, Humanitarian Chief Mark Lowcock released US$15 million from the Central Emergency Response Fund (CERF) to help global efforts to contain the COVID-19 virus on March, 2020.**
- **WHO has shipped nearly half a million sets of personal protective equipment to 47 countries, but the global supply is rapidly depleting. To meet rising global demand, WHO estimates that industry must increase manufacturing by 40 per cent.**
- **The international community has asked for US$675 million to help protect states with weaker health systems as part of its Strategic Preparedness and Response Plan.**
- **All Journal articles on COVID 19 to be made open access.**
- **Entire Cities and Regions in lockdown. International travel ban for affected regions.**
- **Many factories closed; conferences & sports events cancelled.**

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## USE OF MASKS

### INDICATIONS

**(a) Healthy workers or caretakers who are coming in contact with proven or suspected patients.**

**(b) Any persons who are suffering from Cough and Cold**

**(c) Otherwise healthy persons should not use Masks**

**(d) Use of Mask is effective if only associated with proper handwashing with alcohol based handrub or soap with water.**

### HOW to USE

**(a) Wash hand properly before putting masks**

**(b) Cover mouth and nose with mash in a fashion that there should be no gap between mask and skin.**

**(c) Avoid touching mask while using particularly front side.**

**(d) Identify proper side of masks- front , back , top – buttomans sides. Observe any holes in Mask.**

**(e) During removing mask remove from back , immediately discard in bin , clean hands with alcohol based rub or soap water.**

**(f) Do not reuse masks.**

## FUTURE RESEARCH

- **Gilead's remdesivir, an intravenous treatment, has already been used to treat one infected patient in the U.S. and will soon be deployed in a pair of large, late-stage studies in Asia. (Stage 3)**
- **mRNA-1273, a vaccine candidate identified just 42 days after the novel coronavirus was sequenced. (still in phase 1)**
- **An intranasal Covid-19 vaccine is being developed by US-based clinical-stage biopharmaceutical company, Altimmune**
- **The National Medical Products Administration of China has approved the use of Favilavir, an anti-viral drug, as a treatment for coronavirus.**
- **Indian Council of Medical Research (ICMR) got approval from the Drug Controller General of India (DCGI) to use Lopinavir & Ritonavir in Corona virus infection if it turn into a Public Health Emergency in India.**

Review Article

# Food Allergies in Clinical Practice

Rajiv Dhall[1], Arjun Dhall[2]

**Food allergies constitute an important component of the disease burden encountered in the community and their incidence is steadily on the rise. Food anaphylaxis is a particularly serious condition warranting prompt action. This article presents a review of the literature exploring various facets including the modern management of this largely neglected but potentially serious clinical problem. Attention has been drawn to the common food items which may contain food allergens and to a stepwise approach to a correct diagnosis. Management strategies including emergency measures (which may even require self administration of epinephrine), immunomodulation, immunotherapy and nutritional safeguarding have been discussed.** [*J Indian Med Assoc* 2020; **118(3):** 28-30]

***Key words*** **: Food allergy, immunomodulation, immunotherapy, eosinophilic esophagitis, omalizumab.**

Food allergies have profound clinical implications and may present either as the primary disease or as an association with another disease presentation.

A variety of immune-mediated adverse reactions to certain foods may present as allergies, the underlying mechanism being Immunoglobulin E (IgE)-mediated, cell-mediated or mixed[1]. Various organ systems may be involved and the presentation may range from itching and a slight skin rash to severe life threatening anaphylaxis. A clear distinction must, however, be made from non-immunological adverse reactions such as food intolerance and food poisoning.

## Pathophysiology and Epidemiology :

Development of food allergy depends on heredity, intestinal permeability, immune responsiveness and, of course, exposure to the particular food[2]. Food allergen exposure, though usually by ingestion, may occur by inhalation also. The reaction can develop within seconds to several hours and the symptoms can last for days or even weeks. In some cases the symptoms of food anaphylaxis are not seen unless the patient exercises within a few hours of food ingestion[3]. Foods known to be associated with allergic reactions are crustaceans (such as shrimps, crabs and lobsters), eggs, fish, shellfish, peanuts, tree nuts (such as walnuts and cashew nuts), soybeans, milk and cereals containing gluten (such as wheat and barley).

The incidence is higher in children and decreases to about 1-3% in adults[2]. More than 90% of acute systemic reactions to food in children are from eggs, milk, soy, wheat or peanuts and in adults from crustaceans, tree nuts, peanuts or fish[4]. Hidden allergens may be present not only in the food item but also in additives, preservatives and contaminants.

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***Editor's Comment :***

- **Allergies to various food items are frequently encountered and may sometimes be dangerous.**
- **If there is a known allergy, one must be cautious about offending agent.**
- **Immediate medical attention must be sought when an allergy occurs.**

Food allergens have certain biochemical and physicochemical properties which include thermal stability and resistance to proteolysis[5]. Human studies strongly suggest that microbial inhabitants of the human body may play either a pathogenic or protective role in allergies[6].

Allergies to milk, wheat and eggs tend to abate in late childhood but those to peanuts, tree nuts and seafood are most likely to continue lifelong. Allergies to fruits and vegetables are most commonly encountered in adults and may develop because of homologous proteins shared with airborne allergens. In coeliac disease, extensive enteropathy secondary to immunologic reaction to gliadin (a component of gluten) causing a severe form of malabsorption is seen[7]. There also seems to be a definite relationship between food allergy and both allergic rhinitis and bronchial asthma.

Non IgE mediated food allergy may be acute e.g. Food Protein Induced Enterocolitis Syndrome or chronic e.g. coeliac disease and Eosinophilic Esophagitis[8].

## Clinical Presentation :

The clinical picture may include skin features (urticaria, angioedema or atopic dermatitis), respiratory features (allergic rhinitis, asthma or laryngeal oedema), gastrointestinal features (itching and swelling of oral cavity, nausea, vomiting, abdominal pain or diarrhoea), eye

features (itching and swelling) or cardiovascular features (chest pain or severe hypotension and unconsciousness).

Non-IgE mediated food reactions may present as enterocolitis, coeliac disease and allergic contact dermatitis.

Anaphylactic shock is a life threatening condition encountered in certain food allergies and may present with laryngeal oedema, bronchospasm and hypotension.

## Diagnosis :

A proper history should enquire about suspected food items, the quantity of the particular food which may bring about a reaction, whether the reaction is reproducible with the same food and whether avoiding the food brings relief.

On clinical examination, the concomitant presence of atopic disorders such as asthma and atopic dermatitis increases the likelihood of a food allergy. Conversely, a thorough physical examination may rule out the possibility of a food allergy. Skin prick tests are often useful. A positive test shows up as a wheal. Intradermal testing may be potentially dangerous and also has an unacceptably high false positive rate. Skin prick and radio allergosorbent tests which involve testing for IgE antibodies in the blood for particular foods have about 85% sensitivity and 30 – 60% specificity[4]. Dietary manipulations are also used for food allergy testing. An elimination diet beginning with items not likely to cause a reaction and progressing with stepwise addition of other food items over a period of time may incriminate a specific food item. An Oral Food Challenge remains the diagnostic standard for food allergy[1] but should always be carried out under close medical supervision and should be conducted in a double-blind placebo-controlled fashion.

## Awareness and Prevention :

The only certain way to avoid food allergies is to avoid exposure to the specific food allergen. This requires awareness on the part of the individual and also the family, caregivers, health care providers and catering services in restaurants, schools, hospitals, airlines, railways and public gatherings. Education regarding strict avoidance of food allergens, the early recognition of anaphylactic symptoms and the early use of self injectable epinephrine remains the mainstay of therapy[9]. It should be ensured that food labels clearly declare ingredients known to be important food allergens.

The role of breast feeding in the prevention of allergic diseases needs to be examined. It has been reported that, in general, studies reveal that infants fed formulae of intact cow's milk or soy protein compared with breast milk have a higher incidence of atopic dermatitis and wheezing illnesses in early childhood[10]. Breast feeding mothers should avoid highly allergenic foods if a family history of allergies is present.

## Management :

Management focuses on three broad areas namely, avoidance of the offending food, nutritional support to guard against nutritional deficiencies and prompt recognition and treatment of acute food anaphylaxis. Assessing the nutritional status of the food allergic person and assuring nutritional adequacy during treatment and maintenance highlights the importance of the dietician's expertise[2]. Probiotics improve the intestinal immunological barrier function and reduce the generation of proinflammatory cytokines and therefore appear to be useful in the treatment of food allergy[11]. An elimination diet may be beneficial in patients with chronic symptoms where the offending food remains unidentified[7].

For acute food anaphylaxis management must be prompt and correct. This includes life saving measures like epinephrine (adrenaline) injection, securing the airway, cardiopulmonary resuscitation and assisted respiration if necessary, oxygen administration and intravenous fluids. Epinephrine reverses laryngeal oedema, bronchospasm and hypotension and should be given intramuscularly (preferably in the anterolateral thigh), the dose being 500 micrograms (0.5 ml of 1 in 1000 solution) in the adult. Repeated doses may be required at 5 minute intervals according to response. The onset of action is more rapid with the intramuscular route as compared to the subcutaneous route. Epinephrine in the form of properly labelled pre-assembled syringes fitted with a needle (auto-injectors) should be carried by patients with severe allergy at all times.A dose of 300 micrograms in the adult may be appropriate for self administration intramuscularly. In severe circulatory collapse, a dilute (1 in 10000) solution of epinephrine may be given by slow intravenous injection (under close medical supervision) in the dose of 0.5 ml (50 micrograms) in the adult, repeated as per response. Additionally, antihistamines like chlorpheniramine and corticosteroids like hydrocortisone sodium succinate may be given and continued for 24 to 48 hours in accordance with clinical response. Anaphylactic reactions may be prolonged or biphasic. Therefore, medical supervision should continue for an appropriate period.

Drug therapy in the form of steroids and proton pump inhibitors may be required in Eosinophilic Esophagitis[8]. Omalizumab, a humanised monoclonal antibody against IgE used in allergic asthma has been shown to reduce concomitant IgE mediated food allergy symptoms[12].

## Newer Frontiers :

Recent advances in the field of immunology have opened up newer frontiers in the management of food allergies. Many food allergens have been characterized at the molecular level leading to novel diagnostic and immunotherapeutic approaches[13]. Novel diagnostic methods including ones that focus on immune responses to specific proteins or epitopes of specific proteins are under study[14]. More recently, specific IgE to particular protein components have provided additional diagnostic value[15]. A study on the treatment of peanut allergy with rush immunotherapy (a method of rapid desensitisation) provided preliminary data demonstrating the efficacy of

injection therapy with peanut extract[16]. Immunomodulation via diet (with special emphasis on pro- and prebiotics, beta-glucans and fungal immunomodulatory proteins) appears to have advantages for managing allergies[17].

The transfer of food allergy following solid organ transplantation is now well documented. Transfer of peanut IgE sensitisation after combined pancreas-kidney transplant has been reported[18].

## Discussion :

The clinical challenge posed by food allergies lies in the wide range of their presentation. Chronic long standing allergies may cause minor symptoms but may severely impair the nutritional status and (in children) the growth of the individual. On the other hand, acute anaphylactic reactions may have dramatic presentations and may prove fatal. The magnitude of the problem is substantial and is on the rise. However, many studies indicate that the prevalence of actual food allergies is much lower than the number of suspected food allergies[5]. In the absence of a reasonably correct diagnosis, unnecessary food restrictions should, therefore, not be imposed on an individual.

It should also be realised that complete avoidance of the offending food may not always be possible particularly if it is widely present as an ingredient in many food items and is a part of safe and healthy diet for the population in general. With increasing awareness on all fronts, it should be possible to harness knowledge and effort towards mitigating food allergies in an effective way.

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## Relevance of Allergy Test

- **In clinical practice, a proper history pertaining to the suspected food item is very important with particular reference to whether the reaction is reproducible with the same food item and whether avoiding the item brings relief.**
- **A thorough clinical examination looking for concomitant presence of atopic disorders is also very crucial.**
- **Skin prick tests and radio allergosorbent tests are available for Allergy Testing .. They have high sensitivity but low specificity and must be interpreted judiciously.**
- **Intradermal testing may be potentially dangerous and has an unacceptably high false positive rate.**
- **The detection of specific IgE to particular protein components is of additional diagnostic importance but this is not universally available.**
- **Clinically, an elimination diet with stepwise addition of food items over a period of time may incriminate a specific food tem.**
- **An oral food challenge test may clinch the diagnosis but must be carried out under close medical supervision.**

Original Article

# A Study of Association between High Sensitivity C-reactive Protein and Diastolic Dysfunction in Patients with Cardiac Risk Factors

**Swapan Sarkar[1], Joydeep Biswas[2]**

**Background : Diastolic dysfunction (DD) is considered to be associated with inflammatory fibrosis of myocardium. So, this cross-sectional, observational study was done to test the hypothesis that hsCRP, an inflammatory biomarker is associated with diastolic dysfunction and is a predictor of incipient diastolic heart failure in patients with cardiac risk factors.**

**Methods : 84 patients were selected. hsCRP level was measured and echocardiogram was done to assess ratio of transmitral flow velocity and annular velocity (E/E') and left ventricular end-diastolic pressure (LVEDP). Correlation coefficient was calculated to quantify strength of association between hsCRP and numerical variables. Linear regression was performed to evaluate the association between hsCRP and numerical variables.**

**Results : The mean age was 59±7years. 40(48%) were men and 44(52%) were female. 27(32.14%) had mild DD(DD1) with normal LVEDP and 29(34.52%) had DD with elevated LVEDP(DD2). E/E´, a parameter of LV diastolic function showed the strongest positive correlation to hsCRP (r=0.653, p<0.001). Linear regression showed that only E/E'(b-coefficient=0.845, p<0.001) was significantly associated with hsCRP.**

**Conclusion : The data shows that hsCRP is significantly increased in patients with diastolic dysfunction and establishes a close association between hsCRP levels and diastolic dysfunction in patients with diabetes and hypertension.**

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***Key words*** **: Diastolic dysfunction, high-sensitivity C-reactive protein, cardiac risk factors.**

The underlying pathophysiological mechanism in more than half of patients of heart failure (HF) is diastolic dysfunction(DD)[1,2]. Diastolic dysfunction is considered to be associated with inflammatory fibrosis and stiffening of myocardium caused by increased collagen deposition in interstitium[1,3]. Studies have shown that low grade systemic inflammation is associated with arterial and ventricular stiffness, which again is associated with diastolic heart failure[4-6]. So, pro-inflammatory conditions like hypertension (HTN) and diabetes (DM) may predispose to myocardial stiffness and diastolic dysfunction, which ultimately leads to heart failure[7,8].

On the other hand, high-sensitivity C-reactive protein (hsCRP), produced by liver in response to inflammatory conditions has been also shown to predict cardio-vascular events[9,10]. So, hsCRP has been used recently as a therapeutic target for preventing heart disease[11].

Although some data is available about the relationships between hsCRP and echocardiographic parameters[12], but there is few data between hsCRP and left ventricular (LV) diastolic function. Studies have shown an association between hsCRP and diastolic dysfunction in patients with symptomatic heart failure. But very limited data is available about the relationship between hsCRP and diastolic dysfunction in patients with risk factors who are asymptomatic. A study found association between hsCRP and diastolic dysfunction in young African American asymptomatic patients but not much data was found in Indian population where diabetes and hypertension are quite prevalent and have higher level of inflammation as suggested by the raised inflammatory marker levels.

So, this cross sectional, observational study was done to test a hypothesis that hsCRP, an inflammatory biomarker

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***Editor's Comment :***

- **hs-CRP level is found to be significantly associated with presence of diastolic dysfunction in asymptomatic patients with cardiovascular risk factors.**
- **It is recommended to measure hs-CRP in these patients to identify the population at risk of diastolic heart failure and to diagnose diastolic dysfunction at an early stage.**
- **hs-CRP may be used as a possible predictor of incipient diastolic heart failure in these patients.**

is associated with diastolic dysfunction and is a predictor of incipient diastolic heart failure in patients with cardiac risk factors.

## Materials and Methods

The study population were the patients visiting outpatient department (OPD) of MR Bangur Hospital, a district hospital in Kolkata from November 2011 to October 2013, for their medical problems. Sample size was 84 patients between 30 to 90 years both male and female.

The patient selection was based on history taking, clinical examination, laboratory investigations and echocardiogram.

**Inclusion Criteria :**

(1) Hypertension ie, systolic BP ≥140mmHg and/or diastolic BP ≥90mmHg or receiving antihypertensives;

(2) Diabetes ie, history of type 2 diabetes based on American Diabetic Association criteria or on antidiabetic medications.

**Exclusion Criteria :**

(1) Heart failure signs and symptoms or other cardiac symptoms (chest pain or shortness of breath);

(2) History of cardiac diseases (heart failure, coronary artery disease, myocardial infarction, valvular heart disease, bundle branch block, arrhythmias, wall motion abnormalities, peripheral vascular diseases, stroke);

(3) Digoxin use;

(4) Recently diagnosed (<1 year) DM or HTN;

(5) Pre-existing renal disease (serum creatinine ≥1.6mg/dl);

(6) History of heroine or cocaine use;

(7) History of alcoholism;

(8) Body mass index (BMI)≤18.5 or ≥40;

(9) Situations associated with acute hsCRP elevation (signs of acute systemic infection like fever, collagen diseases like rheumatoid arthritis, lupus,etc.);

(10) Estrogen use.

All patients satisfying the inclusion criteria were interviewed with a standardized proforma. Physical examination was performed. Venous blood was drawn for measurement of routine blood investigations. Latex particle immunoassay with nephelometry was used to measure plasma high-sensitivity C-reactive protein (hsCRP).

Transthoracic echocardiogram was done with M-mode, 2D (two-dimensional), Doppler and tissue Doppler imaging. At first following parameters were measured by M-mode: Interventricular septal thickness (IVST), left ventricular posterior wall thickness (PWT), end-systolic dimension of left atrium (LAD) and left ventricular internal diameter (LVID) at end-diastole (LVIDd) and end-systole(LVIDs). Calculation of left ventricular mass index (LVMI) was done (left ventricular mass)$^{2.7}$ to minimize errors due to overweight. Left ventricular ejection fraction (LVEF) was calculated and wall motion abnormalities noted.

Next, LV diastolic function was estimated by transmitral flow velocity using Doppler. Peak early-diastolic(E) and late-diastolic(A) transmitral flow velocity, deceleration time (DT) and E/A ratio was noted.

Lastly tissue doppler was performed at medial mitral annulus. Peak early(E') and late(A') diastolic mitral annular velocities and ratio(E'/A') was measured. Ratio of transmitral flow velocity and annular velocity(E/E') was calculated to assess LV end-diastolic pressure (LVEDP) that was used as the parameter of LV diastolic dysfunction. Elevated filling pressure was based on E/E' ratio>10. Diastolic function was categorised into : normal(DD0), diastolic dysfunction with normal LVEDP(DD1)(impaired relaxation, grade-1 DD), diastolic dysfunction with high LVEDP(DD2) which includes - impaired relaxation with elevated LVEDP(Grade-1B DD), pseudonormal filling pattern (Grade-2 DD), advanced diastolic dysfunction (Grade-3 DD, restrictive filling pattern).

Written informed consent was taken from all patients. Approval was taken from the Institutional Ethical Committee and Scientific Research Committee.

**Statistical analysis :**

Data was summarised by descriptive statistics ie, Mean±Standard Deviation for numerical variables and proportions and percentages for categorical variables. Correlation coefficient was calculated to quantify strength of association between hsCRP and different numerical variables. Multiple linear regression analysis was performed to evaluate the association between hsCRP and other numerical variables. $p<0.05$ indicated statistical significance.

**Software used :** SPSS Statistics version1 [Illinois, Chicago: SPSS Inc, 2008]

## Results

A total of 84 patients between 30 to 90 years both male and female were selected by simple random sampling. Majority belonged to age group of 50-60 years with mean age 59±7 years (Table 1). 40(48%) were men and 44(52%) were female. Diabetes was present in 59(70.24%) and hypertension in 49(58.33%) patients. The mean hsCRP level was high (0.782±0.471). Majority had ejection fraction between 60-70% and mean was 65.3±5.3%; all had normal systolic function. Raised mean LVMI indicated LV hypertrophy and decreased mean E/A indicated diastolic dysfunction. Mean E/E' was 9.78±4.4. All variables were normally distributed by Kolmogorov-Smirnov goodness-of-fit test other than LVEF, E/A, E'/A', E/E'.

Grade-2(DD2) diastolic dysfunction patients were maximum in number (29). Echocardiogram showed any DD in 56(66.66%) patients, 27(32.14%) had mild DD(DD1) with normal LVEDP(E/E' ratio≤10) and 29(34.52%) had DD with elevated LVEDP(DD2)[E/E ratio>10 and a decrease in E/A ratio by 0.5 with Valsalva maneuver]. The mean hsCRP level progressively increased across the 3 diastolic dysfunction grades and gradually increased as the E/E' increased (Fig 1).

**Association between hsCRP and other variables :**

Correlation coefficient was calculated to quantify

Table 1 — *Clinical and Echocardiographic Features*

| *Characteristics* | *Participants (mean±SD)* |
|---|---|
| Number (male/female) | 84 (40/44) |
| Age (years) | 58.6 ± 7.4 |
| BMI (kg/m$^2$) | 23.5 ± 1.7 |
| Hypertension (*n* (%)) | 49 (58.3) |
| Diabetes mellitus (*n* (%)) | 59 (70.2) |
| Pulse (beats/min) | 78.9 ± 4.4 |
| Systolic BP (mmHg) | 136.5 ± 10 |
| Diastolic BP (mmHg) | 85.3 ± 5.8 |
| FBS (mg/dL) | 152 ± 46.4 |
| PPBS (mg/dL) | 240 ± 63.9 |
| HbA1c (%) | 6.9 ± 0.57 |
| Urea | 28.2 ± 6.7 |
| Creatinine | 1.09 ± 0.26 |
| hsCRP (mg/dL) | 0.78 ± 0.47 |
| LV structural parameters : | |
| LAD (mm) | 35.4 ± 5.9 |
| LVMI (g/m$^{2.7}$) | 37.5± 7.8 |
| LV functional parameters : | |
| LVEF (%) | 65 ± 5 |
| E/A | 1.19 ± 0.36 |
| E´/A´ | 1.13± 0.38 |
| E/E´ | 9.78 ± 4.39 |

LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAD, left atrial dimension;E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; peak early diastolic annular velocity; A´, peak late diastolic annular velocity.

strength of association between hsCRP and different numerical variables. hsCRP was correlated with age, hypertension, diabetes, HbA1c, creatinine, LAD, LVMI, LVEF, E/A, and E/E´ (Table 2). E/E´, a parameter of LV diastolic function showed the strongest positive correlation to hsCRP among all variables (r=0.653, p<0.001)(Fig 2). These results indicate that elevated hsCRP reflects LV diastolic dysfunction rather than LV hypertrophy. Age and BMI may be confounding variables in the association between hsCRP and E/E'. So the correlation coefficient was calculated between hsCRP with age and BMI. But there was poor correlation between hsCRP levels with both age (0.257) and BMI (0.170).

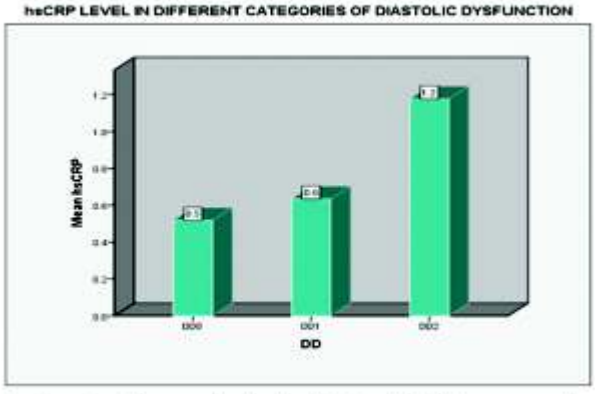


Fig 1 — Bar Diagram showing hsCRP level in different categories of Diastolic Dysfunction

**Assessment of the factors related to hsCRP :**

Multiple linear regression analysis was performed to evaluate the association between hsCRP and other numerical variables in all subjects. Only E/E'(β coefficient=0.845, p<0.001) was significantly associated with hsCRP (Table 3).

## Discussion

In our study, there was high prevalence of DD with high LVEDP(34.5%). The most significant finding was the strong association between diastolic dysfunction ie, E/E' and elevated hsCRP levels, which was much greater than with DM, HTN, LV hypertrophy, and BMI. Patients having higher hsCRP levels were shown to have advanced DD with elevated LVEDP. Our study shows that there is a strong association between hsCRP level, a marker of inflammation and LVEDP in asymptomatic DD patients. This indicates that inflammation has a prominent role in development of

Table 2 — *Correlation of hsCRP levels with numerical variables for entire study sample (n=84)–Pearson correlation coefficient*

| Variables | Pearson correlation (r) | P value |
|---|---|---|
| Age | 0.257 | 0.009 |
| BMI | 0.170 | 0.061 |
| Pulse | 0.126 | 0.127 |
| Systolic BP | 0.238 | 0.015 |
| Diastolic BP | 0.218 | 0.023 |
| FBS | 0.303 | 0.003 |
| PPBS | 0.297 | 0.003 |
| HbA1c | 0.300 | 0.003 |
| Urea | 0.210 | 0.028 |
| Creatinine | 0.283 | 0.005 |
| LAD | 0.221 | 0.022 |
| LVMI | 0.289 | 0.004 |
| LVEF | -0.326 | 0.001 |
| E/A | 0.222 | 0.021 |
| E´/A´ | 0.150 | 0.086 |
| E/E´ | 0.653 | 0.000 |

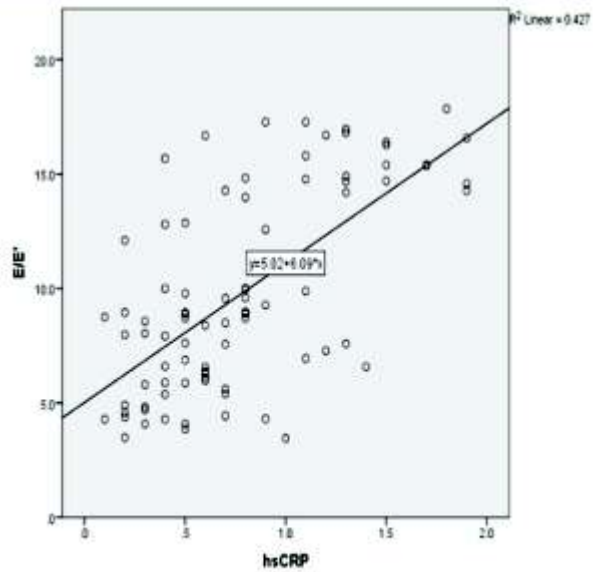


Fig 2 — Scatter Plot showing Correlation between hsCRP and E/E'

diastolic dysfuncton.

HsCRP appeared to be a stronger clinical predictor of DD than age, HTN and DM. DM and HTN leads to ventricular stiffness and diastolic dysfuncton and ultimately to heart failure by a common pathway of inflammation. If this association between diastolic dysfunction and inflammation is confirmed by further prospective long term observational studies, inflammation control may become a target for diastolic dysfunction therapy and heart failure prevention. HsCRP level could be useful in finding patients at risk for diastolic dysfunction and predict the likelihood of progression to heart failure.

The strong association between hsCRP and diastolic dysfunction in our study may be due to the high prevalence of hypertension (58.3%) and diabetes(70.2%). In our study, hsCRP is associated with presence of hypertension (p=0.029) and diabetes (p=0.005)(Table 2). Earlier studies have shown that in diabetic and hypertensive patients, there is an association between hsCRP and microvascular complications like retinopathy and nephropathy. Diastolic dysfunction being also produced by microvascular complication in hypertension and diabetes, is likely to be associated with raised hsCRP.

**Study Limitations :**

E/E´ was measured at septal mitral annulus. But some studies recommended measuring velocities of lateral mitral annulus or averaged velocities of septal and lateral mitral annulus.

There was no information regarding insulin resistance and atherosclerosis which are microvascular complications and have a common inflammatory background.

The variability of hsCRP levels produced by alcohol intake, medications and exercise were not included. Other markers of inflammation and some non inflammatory causes may be more strongly associated with diastolic dysfunction. So, a prospective longitudinal study with serial measurements of hsCRP along with other inflammatory markers will be needed.

The patients were not investigated for coronary artery disease, which can have inflammatory origin and present as diastolic dysfunction, as further invasive testing was considered unnecessary.

Lastly, a multicenter trial with larger population is needed to further investigate the role and clinical significance of hsCRP in diastolic dysfunction.

Table 3 — *Linear regression analysis to evaluate association between hsCRP and other numerical variables*

Model Summary

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | 0.709[a] | 0.503 | 0.384 | 0.3698 |

a. Predictors: (Constant), E/E', Pulse, E'/A', LAD, Urea, DBP, LVMI, PPBS, Cr, BMI, AGE, LVEF, FBS, SBP, HBA1c, E/A

ANOVA[a]

| Model | | Sum of Squares | df | Mean Square |
|---|---|---|---|---|
| 1 | Regression | 9.263 | 16 | 0.579 |
| | Residual | 9.160 | 67 | 0.137 |
| | Total | 18.423 | 83 | |

a. Dependent Variable : hsCRP

b. Predictors:(Constant)E/E', Pulse,E'/A', LAD, Urea, DBP, LVMI, PPBS, Cr,BMI, AGE, LVEF, FBS, SBP, HBA1c, E/A

Coefficients[a]

| Model | | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.744 | 1.842 | | 0.947 | 0.347 |
| | AGE | -0.004 | 0.008 | -0.065 | -0.502 | 0.617 |
| | BMI | -0.060 | 0.031 | -0.217 | -1.959 | 0.054 |
| | Pulse | 0.013 | 0.010 | 0.119 | 1.244 | 0.218 |
| | SBP | -0.001 | 0.010 | -0.025 | -0.118 | 0.906 |
| | DBP | -0.004 | 0.017 | -0.055 | -0.267 | 0.790 |
| | FBS | 0.001 | 0.002 | 0.144 | 0.922 | 0.360 |
| | PPBS | 0.000 | 0.001 | -0.015 | -0.085 | 0.933 |
| | HBA1c | -0.139 | 0.173 | -0.169 | -0.804 | 0.424 |
| | Urea | -0.004 | 0.008 | -0.063 | -0.560 | 0.577 |
| | Cr | 0.093 | 0.200 | 0.052 | 0.465 | 0.643 |
| | LAD | 0.001 | 0.009 | 0.012 | 0.114 | 0.910 |
| | LVMI | 0.000 | 0.006 | -0.003 | -0.025 | 0.980 |
| | LVEF | 2.737E-005 | 0.012 | 0.000 | 0.002 | 0.998 |
| | E/A | 0.088 | 0.300 | 0.068 | 0.292 | 0.772 |
| | E'/A' | 0.002 | 0.301 | 0.002 | 0.008 | 0.994 |
| | E/E' | 0.091 | 0.019 | 0.845 | 4.748 | 0.000 |

a. Dependent Variable: hsCRP

## Conclusion

The data obtained shows that hsCRP is significantly elevated in patients with diastolic dysfunction and establishes a close association between hsCRP levels and diastolic dysfunction in asymptomatic patients with diabetes and hypertension. This provides evidence that systemic inflammation is a cause of myocardial fibrosis and LV dysfunction. HsCRP is more strongly related to diastolic dysfunction which is assessed by E/E' than to LV hypertrophy, assessed by LVMI. This finding suggests that hsCRP may be a possible marker of subclinical diastolic dysfunction in patients with cardiac risk factors, like hypertension and diabetes. If this is supported by further multicenter, longitudinal, prospective studies it may be used to identify the people at risk for heart failure and to establish new targets for management of diastolic dysfunction and prevention of heart failure. HsCRP levels may also be used to detect patients with advanced diastolic dysfunction without symptomatic heart failure.

**Funding : None**

**Conflict of Interest : None**

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## Learning Points on CRP :

- **CRP was first discovered in 1930 by William Tillet and Thomas Francis at the Rockefeller Institute for Medical Research, in New York.**
- **Inflammation plays an important role in the initiation and progression of atherosclerosis and the development of atherosclerotic events.**
- **The C-reactive protein (CRP) is one of the most reliable biomarker of underlying systemic inflammation.**
- **CRP an acute phase protein is synthesized by hepatocytes in response to proinflammatory cytokines, in particular interleukin-6.**
- **CRP plays a pivotal role in many aspects of atherogenesis including, activation of complement pathway, lipids uptake by macrophage and release of proinflammatory cytokines. It induces the expression of tissue factor in monocytes, promotes the endothelial dysfunction and inhibits nitric oxide production.**
- **Unlike other markers of inflammation, CRP levels are stable over long periods, have no diurnal variation. It can be measured with high-sensitivity assays and it can predict the risk of cardiovascular events.**
- **Many large-scale prospective studies demonstrate that CRP strongly and independently predicts adverse cardiovascular events, including myocardial infarction, ischemic stroke, peripheral arterial disease and sudden cardiac death in individuals both with and without overt CHD**
- **Significance of elevated hs-CRP levels is as follows :**
  - **< 1 mg/L Low risk**
  - **1-3 mg/L Moderate risk**
  - **>3 mg/L High risk**
- **Stable plaque shows modest elevation and there is marked elevation in hs-CRP in ruptured plaque.**
- **Elevated hs-CRP levels in stable patients after myocardial infarction can predict recurrent infarction and cardiovascular death.**
- **Determination of hs-CRP can assist physicians to evaluate cardiovascular risk and to monitor therapeutic interventions.**
- **The measurement of plasma CRP is reasonable for assessing absolute risk for coronary artery disease in primary prevention - particularly in intermediate risk individuals.**
- **Elevated hs-CRP has been recognized as moderate risk in the recent ESC/EAS Guidelines for management of dyslipidemia and Canadian cholesterol guidelines.**
- **In the prospective Physicians' Health Study, Men in the quartile with the highest CRP values had three times more risk of myocardial infarction compared with men in the lowest quartile, and the risk of stroke was approximately also doubled.**
- **In women also hs-CRP levels have been found to be highly predictive of future CVD risk.**
- **In the JUPITER, TIMI 22 and the REVERSAL (reversal of Atherosclerosis with Lipitor) trials. The greatest clinical benefit of statin therapy occurred among patients who had lowering of both LDL-C and hs-CRP**
- **Determination of CRP may provide additional information regarding which patients may benefit from statin treatment irrespective of cholesterol level.**

***— DR GURPREET SINGH WANDER,***
***Prof. & Head, Dept of Cardiology, Dayanand Medical College, Ludhiana***

Original Article

# Randomized Study to Evaluate the Effectiveness of the Injection Sclerotherapy for Bleeding Grade I Hemorrhoids on Outpatient Basis

Tapan A Shah[1], Yogendra S Modi[2], Rajesh H Parmar[3], Chetan Sharma[4]

**Objective : Polidocanol 3% is a novel agent used in sclerotherapy for hemorrhoids, and used for treatment of internal haemorrhoids without surgery. In our study we checked for the safety and postsclerotherapy results of polidocanol 3% using proctoscope.**

**Materials and Methods : Subjects comprised 90 internal hemorrhoid patients (67 males and 23 females). An anoscope was inserted injection was applied to submucosally to the hemorrhoids. The outcome post injection anooscopicsclero therapy were decided by examination of hemorrhoids after detailed questionnaire to the patient 1month after the treatment.**

**Results : A complete resolution, some improvement, and no improvement were observed in 72,9 and 9 patients, treated with Polidocanol 3%. We found complications in 9 patients (pain in 9 in 3 and blood in urine in 6). 9 patients came with recurrence.**

**Conclusions : Our study concluded that Polidocanol 3% is a very useful and out patient minimally invasive procedure.**

[*J Indian Med Assoc* 2020; **118(3):** 36-8]

***Key words*** **: Polidocanol, Sclerotherapy.**

Hemorrhoids are a very common proctological disease and it is classified as internal haemorrhoids when above dentate line and external when below the dentate line. Bleeding per rectum and prolapse piles are most common presentation of internal haemorrhoids.

Conservative therapies like stool softners, local ointments, lifestyle modifications and increase liquid intake (to avoid constipation) are primarily helpful in resolving Internal hemorroids; though sometimes active bleeding per rectum, pain which may interfere daily routine, subsequent therapies may needed. Non-surgical therapies are desirable as haemorrhoids are benign condition[1,2].

When conservation therapies don't change symptoms other modalities which are useful are Injection sclerotherapy and Rubber Band Ligation for hemorroids, which are non-surgical methods and used by clinicians since many decades. Some researchers did an analysis of some studies and compared various treatment therapies for hemorrhoids which mentioned that rubber band ligation was more useful sclerotherapy and also that patients who underwent ligation needed further modality. Injection sclerotherapy is a simpler and safer treatment for bleeding hemorrhoids where 5% phenol in almond oil was commonest sclerosing agent used in the past mostly for haemorrhage but for prolapse its effects are not proven.

Patients with hemorrhoidal disease experience varying degrees of the following symptoms, bleeding, anal swelling, pain, discomfort, discharge, hygiene problems and pruritis. Usually, but not invariably, the larger the cushions and the more they prolapse the more troublesome are the symptoms[2,3].

In this study all the cases of Hemorrhoids in OPD under Surgery Department has been studied and diagnosed, graded and treated with Injection Sclerotherapy to assess

***Editor's Comment :***

- Bleeding haemorrhoids are most commonly ignored by common people
- Injection sclerotherapy is an OPD procedure which is easy and handy procedure
- Postsclerotherapy patient compliance is also good
- If surgeons want to plan for surgery then by releasing patient from bleeding, it will give window period for improving haemoglobin.

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its effectiveness.

Polidocanol 3% (Sclerosing agent) is successfully used in the treatment for the bleeding oesophageal varices, since years. Here we have used the same agent in cases of bleeding Internal Hemorrhoids to check its efficacy in the patients on OPD bases.

Polidocanol 3% has very less complications and it stops hemorrhage after defecation and has many pros over surgery, and it is out patient period so hospitalization is avoided. So, Polidocanol 3% has become a striking sclerosing agent as a new hemorrhoid treatment method without surgery.

## Materials and Methods

Subjects comprised of 90 patients (67 males and 23 females) who required treatment for hemorrhage between June 2018 to June 2019 and were not satisfied with conservative supportive treatment methods.

Polidocanol 3% Sclerotherapy is indicated for only bleeding internal hemorrhoids so external piles and thrombosed piles were excluded.

With the proctoscope with attached light source, internal haemorrhoids are visualised and prepared polidocanol 3% is injected into the submucosal layer, appx 3-4 ml/injection and 2-3 injections.

## Results and Discussion

In our study out of 90 patients 51 were of age less than 40 years, 13 patients were of age group 41-50 and 26 were of age group above 50 years. Mean age was found of 42.24 ± 17.65 years (Table 1).

In our study out of our 90 patients we checked for the complications and post procedural interview of the patient for the symptomatic relief after 1 month and 3 months. Where we found 72 patients with complete symptomatic relief while 9 patients had rebleeding and 9 patients found some complication like hematuria and pain (Table 2).

Hematuria was found in 6 and 8-9 Patients have post procedural pain reported.

Table 1 — *Age Incidence*

| Age | No of Patients | Percentage | $\chi^2$-value |
|---|---|---|---|
| ≤40 Years | 51 | 56.67% | 24.86 |
| 41-50 years | 13 | 14.44% | Significant |
| > 50 Years | 26 | 28.89% | |
| Total | 90 | 100% | |
| Mean ± SD | | 42.24 ± 17.65 years | |

Table 2 — *Agent and Effects*

| Sclerosant | Total Patients | Symptomatic Relief | Recurrence | Complications |
|---|---|---|---|---|
| Ask 3% | 90 | 72 | 9 | 9 |
| $\chi^2$-value | | 7.53 | | |
| p-value | | 0.11, NS, p>0.05 | | |

Table 3 — *Postoperative Sequel*

| Complications | Injection sclerotherapy |
|---|---|
| | Ask 3% |
| Hemeturia | 6 |
| Pain | 9 |
| Anal Stenosis | 0 |
| $\chi^2$-value | 1.41 |
| p-value | 0.49, NS, p>0.05 |

Table 4 — *Effect of Treatment*[4,5,6,7]

| Study | Asymptomatic | No relief | Complications |
|---|---|---|---|
| Present series | 95% | 5% | 6% |
| Gartell *et al* | 35% | 45% | 20% |
| Sim *et al* | 50% | 30% | 20% |
| Khan *et al* | 82.6% | 17.3% | - |
| Majid *et al* | 76% | - | 24% |
| Santi *et al* | 50% | 19% | 31% |

None of the patients have anal stenosis or stricture in our series (Tables 3&4).

Hemorrhoids are the most commonly found disease of anal region. For internal hemorroids resection of hemorroids – Hemorroidectomy is most common performed method. but pain, longer duration of morbidity and complications such as bleeding and stricture formation are some associated fears. Therefore, Minimallyinvasive methods are required for the treatment of Hemorroids without surgery. Suturing hemorroids by the Farag method has traditionally been employed as a nonsurgical method for haemorrhoids. Now a days MIPH and transanal-hemorrhoidal dearterialization, are method of choice for haemorrhoids due to lesser pain and lesser stay. Rubber band ligation and injection sclerotherapy are found to be effective treatments and have been the mainstay of nonsurgical treatments many decades. Though Previous studies mentioned less effectiveness and higher recurrence rate with injection sclerotherapy to rubber band ligation. But our findings for Injection Sclerotherapy are different[8-10].

Polidocanol 3% induces aseptic acute inflammation followed by Fibrosis followed by haemorrhoid scleroses and recesses. Immidietly after injection, vascular constriction occurs. By which blood flow is reduced and stops bleeding[10,11].

## Conclusion

For Large or prolapsed haemorrhoids or failed conservative supportive methods, only surgical therapies are recommended.Our study suggested that the post sclerotherapy effects of Polidocanol 3% were sucessful for bleeding hemorroids on OPD basis and also that it has the potential to become a mainstay treatment method for bleeding internal hemorrhoids without surgery. Therefore, Polidocanol has the potential to become a minimally invasive and useful approach for sclerotherapy.

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**Conflict of Interest : None**

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Original Article

# A study to know the reason of highest Multi Drug Resistant Tuberculosis in Mandi District of Himachal Pradesh as compared to other Districts of the Himachal Pradesh

Sudhansu Parida[1]

**As per the Revised National TB Control Programme (RNTCP) report of the stateout of 11 Districts of Himachal Pradesh MANDI District has the highest incidence of MDR TB cases continuously from 2010 to 2014 as compared to other districts.Although the population of KANGRA district (1.6 Million) is much higher than the MANDI district (1.1 million), but the incidence of Multi Drug Resistance Tuberculosis (MDR TB) is higher in MANDI district as compared to KANGRA district.By the end of 2014, a total of 567 MDR TB cases were diagnosed in 11 districts of Himachal Pradesh out of which 130(23 %) MDR cases were detected only in Mandi District. The objective of this study was to know the reason of high number of MDR TB in Mandi District of Himachal Pradesh as compared to other districts of the State.**

**Private sector in India, has unfortunately, been a source of mismanagement of TB cases and hence of drug resistance. This includes the use of incorrect diagnostics, incorrect regimes and a lack of supervision to ensure all TB patients complete their TB treatment. The Methodology of this study adopted was to establish Designated Microscopic Centers (DMC) with different private Health Providers (ie, private hospitals, private Laboratories and in the clinic of qualified Private Practitioners) as per the guidelines of RNTCP with logistic support by District TB office. All the TB cases diagnosed by these private health providers were notified to District TB office. Strict supervision wasmade by RNTCP consultant, WHO Consultant and District TB Officer (DTO).**

**Results of TB cases notified from these private health providersfrom 2013 to 2015 were analyzed. It was observed that out of 3518 sputum of different TB suspects were examined in these private DMCs in Mandi District a total of532 (15 %) TB suspects were found to be positive for TB. These 532 TB patients were not given Directly Observed Treatment (DOT) instead were prescribed anti TB drugs by the Private hospitals and PPs and handed over the prescription to the patients.**

**Conclusion and Lessons Learned : Any District of India with high number MDR and XDR TB, it is likely that there are high number of Private health providers are treating TB cases who are not completing the full course of treatment. So those Districts of India with high number MDR / XDR TB should be line listed and extensive efforts should be made to open up DMCs and DOT center with Private health providers as per the guidelines of RNTCP.**

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***Key words*** **: RNTCP, TB, MDR TB, XDR TB, DMC, DOTS, DTO, CME.**

In 2016 WHO estimated 10.4 million new TB cases worldwide,10% of which were people living with HIV. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat[1]. WHO estimates that there were 600 000 new cases with resistance to rifampicin - the most effective first-line drug, of which 490 000 had MDR-TB. Almost half of these cases were in India, China and the Russian Federation. Drug resistance TB can occur when the drugs used to treat TB are mismanaged (ie, People do not complete full course of TBtreatment)[2]. Private sector in India, has unfortunately, been a source of mismanagement of TB and hence of drug resistance. This includes the use of incorrect diagnostics (eg, blood tests), incorrect regimes and a lack of supervision to ensure all TB patients complete their TB treatment. As per the report

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***Editor's Comment :***

- **There is increasing trend of MDR Tuberculosis all over world.**
- **Noncompliance is key factor in developing MDR Tuberculosis.**
- **Early Detection of drug resistance by CBNAAT is another crucial issue in controlling MDR tuberculosis.**
- **Significant number of patients are diagnosed and treated by Private Practitioners.**
- **Govt Sector and Private sector should work hand in hand to eliminate TB.**
- **GOI launched END TB programme to eliminate TB by 2025.**
- **RNTCP renamed as National Tuberculosis Elimination Program (NTEP) from 1st January, 2020.**
- **IMA extended cooperation to GOI and nation to reach the goal.**

of Central TB Division, Ministry of Health, Govt. of India[3], there are large gaps between the burden of MDR TB and the actual number diagnosed and treated till date. Substantial number of MDR TB patients are mis treated in the private sector leading to additional drug resistance and XDR TB. In the private sector, evidence suggests that patients are sent off with their medication without advice or support. As patients feel better within a couple ofweeks, they often stop taking the medication. After default when again the patient become sick, theygo on shopping around with Private Doctors for purchasing the TB treatment and finally end up with MDR TB. Hence completing the course is key to effective treatment.

Global fund for AIDS, TB and Malaria (GFATM) funded Indian Medical Association (IMA) through Ministry of Health, Govt. of India to implement a Public Private Mix (PPM) project in many states of India including Himachal Pradesh State to involve the Private Health Providers (ie, Private Hospitals, Private Practitioners, Private Laboratories etc.) to diagnose and treat TB patients as per the DOTstrategy. The Author was appointed as the Technical Consultant of this Project.

As per the Revised National TB Control Programme (RNTCP) report, out of 11 Districts of Himachal Pradesh Mandi District has the highest incidence of MDR TB cases continuously from the year of 2010 as compared to other districts. Although the population of KANGRA district (1.6 Million) is much higher than the Mandi district (1.1 million), but the incidence of Multi Drug Resistance Tuberculosis (MDR TB) is higher in Mandi district as compared to Kangra district.

## Meterials and Methods

The objective of this study was to know the reason of high number of MDR TB in MANDI District of Himachal Pradesh as compared to other district of the StateThis study is basically aobservationalfield study involving the Private Health providers who are involved in treating TB cases in Mandi District of Himachal Pradesh. The site of study was in Mandi district of Himachal Pradesh State. The duration of this study was from 2012 to 2015.A detailed report on incidence of MDR TBwere collected from state TB office of Himachal Pradeshand was analyzed the incidence of MDR TB. By the end of 2014, a total of 567 MDR TB cases were diagnosed in 11 districts of Himachal Pradesh. Although the population of Kangra District (1.6 Million) is much higher than the Mandi District (1.1 million) but incidence of MDR TB is higher in Mandi Districtas compared to Kangra District. The following table Shows the number of MDR TB in each District of Himachal Pradesh till the end of 2014.

Table 1 — *Total No of MDR TB cases District wise in Himachal Pradesh till December 2014*

| Name of District | Population in Lacks | No of MDR TB |
|---|---|---|
| Kangra District | 16 | 124 |
| Mandi Disrict | 11 | 130 |
| Shimla District | 10 | 65 |
| Solan District | 6 | 53 |
| Bilaspur District | 5 | 35 |
| Hamirpur District | 5 | 33 |
| Chamba District | 5 | 39 |
| Una District | 5 | 29 |
| Kullu District | 4.5 | 53 |
| Kinour District | 1.1 | 6 |
| Lahul Sapti District | 0.4 | - |
| Total | 69 | 567 |

From the above Table 1, it is evident that Mandi district with a population of 11 lacks the number of MDR TB are 130 as compared to Kangra District with a population of 16 Lakhs, the number of MDR TB are 124.

In 2012 initially a State Level CME (continue Medical Education) meeting was conducted where all District Presidents and Secretaries of IMA, all the District TB Officers, WHO consultant and IMA-RNTCP Consultant attended this meeting. This meeting was presided by the State IMAPresident. In this meeting a detail discussion was held on rising trend of MDR TB and to take steps to control it. It was decided that CME meeting will be conducted in each district involving the private health providers. All the District TB officers agreed to give logistic support for opening up of Designated Microscopic Center (DMC) and Directly Observed Treatment (DOT) center with private health providers.All the Doctors working in Private hospitals and individual qualified Medical Private Practicesoners, owner of Private Laboratories should be invited to attend such meeting. District TB Officer (DTO), Technical consultant of IMA and WHO consultant will brief the Private Health Providers about DOTS strategy and also to ensure the completion of TB treatment of 6 to 9 months.

From 2012 to 2015 continuously CME meetings were conducted in different districts by Technical Consultant of IMA, DTO and WHO consultant. Powerpoint presentations were given by the Technical consultant of IMA (i.e. Author of this article)and WHO consultant with an emphasis about compliance of TB treatment for 6 to 9 months.

After the CME was conducted in Mandi District of Himachal Pradesh State in 2012, Private Hospitals and Private Laboratories were requested to join RNTCP by signing MOU as per the guidelines of RNTCP. All the Private Hospitals agreed to open a Designated Microscopic Center (DMC) but did not agree to open a DOTS center. The reason for not opening the DOTS center were mainly due to loss of money which they are getting from the TB patients as their fees for treating TB patient. From 2012 to 2014 many Private Health Institutions after signing MOU with District TB Officeropened DMC in their establishments as per the RNTCP guidelines. After the MOU signed, the District TB officer supplied Laboratory reagents, Sputum cups, Slides etc. free of cost and Rs. 25/- per sputum slide examination were given to these private establishments who signed MOU with District TB Officer. The quality control of these DMC were done by District TB office as per the guidelines of RNTCP.

Table 2 shows the number of Sputum Positive cases detected by these private DMCs.A total of 175 Sputum positive cases were diagnosed and notified to DTO office in the year 2013 by the following private health providers The Name of the Private health providers, date of opening DMC and number sputum positive cases diagnosed in MANDI district are shown in Table 2.

A total of 170 Sputum positive cases were diagnosed and notifiedto DTO office in the year 2014 by the following Private health establishment who signed MOU with District TB Officer. The name of the Private health Providers, date of opening DMC and number sputum positive cases diagnosed by these Private Health institutions in MANDIdistrict are shown in Table 3.

A total of 187 Sputum positive cases were diagnosed and notified to DTO office in the year 2015 by the following Private health establishments who signed MOU with District TB Officer. The Name of the Private health providers,date of opening DMC and number sputum positive cases diagnosed by these Private Health institutions in MANDI are shown in Table 4.

The total Number of TB case Diagnosed and notified year wise by the Private Hospital in Mandi District from 2013 to 2015 (3 Years ) are shown in Table 5.

## Discussion

It is evident from the Tables 2,3 and 4 that a total of 532 Sputum positive cases were diagnosed and notified to District TB Office in 3 years timeby the Private Health Care providers. However all these cases were handed over a prescription of anti TB drugs available in the market (ie, AKT-4 and Fluroquinolone group drugs etc) by the concerned health providers and no effort was made to follow up these cases to know whether they completed the 6 months of TB treatment. In Mandi District of Himachal Pradesh has the highest number of MDR TB may be because of mismanagement of Treatment. As per WHO Multidrug Resistance TB (ie, Resistance to INH and Rifampicin) emerge and spread due to mismanagement of TB treatment. MDR TB infection may be classified as primary or acquired. Primary MDR TB occurs in patients who have not been previously infected with TB but became infected with a strain that is resistant to TB. Acquired MDR TB are due to inappropriate treatment by a medical provider who improperly prescribing ineffective treatment[4]. MDR TB may also occur due to the patient not taking medicine correctly due to a variety reasons including the cost of drug for which he does not have the money to purchase or patient's forgetfulness or patient stopping treatment early because they feel better. Drug resistant TB is a significant problem in India contributing one – fourth of global burden. An estimated one million Tb cases are not reported to Government every year and majority are believed to be in private sector. Additionally the quality of TB care in the private sector are suboptimal[5].

Mandi District which have the highest number of MDR TB (ie, 130 by the end of 2014) and Private Hospitals of this district are just handing over a prescriptionof anti TB Drugs to sputum positiveTB patientsand do not follow up to ensure the completion of TB treatment to those they have prescribed the anti TB drugs.The alarming increase

Table 2 — *Total No of TB Cases Diagnosed by the Private Health Providers in 2013*

| Name of Private Health Institution in Mandi District | Date of Sign of MOU | No of TB Suspects Examined 2015 | No of Found Positite |
|---|---|---|---|
| Mandav Hospital | 1.10.2012 | 695 | 102 |
| Jagruti Hospital | 1.10.2012 | 175 | 42 |
| Niramay Clinic | 1.10.2012 | 28 | 1 |
| H.S. Malhotra Hospital | 1.11.2012 | 18 | 8 |
| Sajivani Hospital (SNR) | 14.12.2012 | 3 | 1 |
| Dr. Aswani Clinic | 1.09.2012 | 5 | 3 |
| Suket Hospital | 14.12.2012 | 14 | 8 |
| Sanjivani Hospital | 23.11.2012 | 2 | 1 |
| Pushakot Clinical Lab. | 29.4.2013 | 48 | 6 |
| Mahamaya Lab. Pangna | 4.6.2013 | 47 | 3 |
| Total | | 1035 | 175(16.9%) |

Table 3 — *Total No of TB Cases Diagnosed by the Private Health Providers in 2014*

| Name of Private Health Institution in Mandi District | Date of Sign of MOU | No of TB Suspects Examined 2015 | No of Found Positite |
|---|---|---|---|
| Mandav Hospital | 1.10.2012 | 753 | 91 |
| Jagruti Hospital | 1.10.2012 | 117 | 21 |
| Niramay Clinic | 1.10.2012 | 2 | 2 |
| H.S. Malhotra Hospital | 1.11.2012 | 19 | 12 |
| Sajivani Hospital (SNR) | 14.12.2012 | 10 | 8 |
| Dr. Aswani Clinic | 1.09.2012 | 24 | 7 |
| Pushakot Clinical Lab | 29.4.2013 | 93 | 8 |
| Harihar Hospital | 1.9.2013 | 92 | 13 |
| Standard Clinical Lab Tihar | 29.8.2013 | 11 | 2 |
| Thakur Lab. Balichauk | 1.11.2013 | 93 | 5 |
| Health Care Medical Center | 14.8.2014 | 1 | 1 |
| Total | | 1215 | 170(14%) |

Table 4 — *Total No of TB Cases Diagnosed by the Private Health Providers in 2015*

| Name of Private Health Institution in Mandi District | Date of Sign of MOU | No of TB Suspects Examined 2015 | No of Found Positite |
|---|---|---|---|
| Mandav Hospital | 1.10.2012 | 776 | 109 |
| Jagruti Hospital | 1.10.2012 | 175 | 38 |
| Niramay Clinic | 1.10.2012 | 2 | 2 |
| H.S. Malhotra Hosp. | 1.11.2012 | 10 | 5 |
| Sajivani Hospital | 23.11.2012 | 3 | 2 |
| Dr. Aswani Clinic | 1.09.2012 | 34 | 9 |
| Pushakot Clinic Lab. | 29.4.2013 | 176 | 10 |
| Super Medical Lab. | 19.8.2014 | 14 | 1 |
| Harihar Hospital | 29.4.2013 | 30 | 5 |
| Thakur Lab. Balichauk | 1.11.2013 | 48 | 6 |
| Total | | 1268 | 187(14.7%) |

Table 5 — *Total No of TB Cases Diagnosed by the Private Health Providers from 2013 to 2015*

| Year | No of TB Suspects Examined | No Found Positive |
|---|---|---|
| 2013 | 1035 | 175 |
| 2014 | 1215 | 170 |
| 2015 | 1268 | 187 |
| Total | 3518 | 532 |

in of anti TB drug resistance in India warrants the need for the structured nation wide surveillance to assist National TB control programme in strengthening the treatment strategy for improved outcomes.

MDR TB have been reported in every country surveyed and is more commonly due to Doctors giving inappropriate treatment or patient missing dosesor failing to complete their treatment. TB strains are often less fit and less transmissible but outbreaks can occur more rapidly with persons having weakened immune system (ie, Persons with HIV infection). However outbreaks among non immune compromised healthy people do occurs but less common. MDR TB was 10.34 times higher previously treated than never treated TB cases. A study in Europe showed previous treatment was the strongest determinant of MDR TB in Europe.

## Conclusion

A field study in Mandi District of Himachal Pradesh was conducted to know reasons of highest number of MDR TB as compared to other Districts of Himachal Pradesh.It was observed in MANDI district from 2013 to 2015 (3 years) a total of 532 TB cases were treated by Private Health Providers.However further study is required to know out of these 532 sputum positive TB casesdiagnosed by the private Health Providershow many of them did not complete the full course of TB treatment and developed MDR TB. Compliance of full course of treatment without interruption is key to reduce MDR TB incidence.Therefore continuous CME and support should be provided to Private Health Providers who are treating TB cases.

## Recommendations

Central TB Division of Ministry of Health, Government of Indiashould take appropriate measures to control MDR and XDR TB. Simply implementing the TB Notifications and counting the number TB patients notified by Private Health Providers is not going to control the occurrence MDR and XDR TB. On the contrary innovative methods on how to involve Private Practitioners and Private Hospitals to treat TB patients through DOTS strategy is important. In all the states of India, the District which have higher incidence of MDR TB should be identified and line listed and a special effort should be made in these District tomotivate Private Health providers either to sign MOU with District TB Officer to open a DMC and a DOT center in their establishment or to refer the TB suspects to the nearest DMC of RNTCP.

IMA should be involved to conduct CME about the DOT strategy. About two hundred thousand qualified Medical Practitioners are members of IMA and many of them are treating TB cases. IMA has a strong infrastructure from District to State to National Level and hold monthly CME meeting. In these CME meetings interaction with the Private Doctorsshould be done and to convince them that although they are prescribing AKT 4 (ie, 4 drugs which include Rifampicin, INH, Ethambutol and Pyrizinamide) are same as 4 drugs given in DOT by RNTCP but the only difference is compliance which is ensured in DOT strategy under direct supervision and Support.By handing over simply a prescription of anti TB drug, the patient is pushed towards MDR TB.

**Funding : None**

**Conflict of Interest : None**

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**Drug Resistance Tuberculosis and Prevention :**

- **Patients develop drug resistant TB as a result of either irregular / inadequate treatment (acquired drug resistance) or direct spread from a person having drug resistant bacilli (primary drug resistance).**
- **Non-compliance (a global and universal phenomenon) is the most important cause of drug resistant TB.**
- **Faulty prescriptions regarding drug regime, doses, timing, duration, poor quality drugs, adding a single drug to a failing regime etc. is accountable in many cases.**
- **Socioeconomic factors (distance from hospital, patients' livelihood, addictions, social belief etc.) and administrative factors (irregular supply of drugs, administrative lacks, lack of motivation and misbehaviour of health workers etc.) are also important.**
- **Contact with drug resistant cases in family members or in close confinement.**
- **Strict adherence to RNTCP guideline is the most important preventive measure.**
- **Early detection by CBNAAT, 1st line LPA and 2nd line LPA (when necessary) followed by proper management of drug resistant TB are essential steps.**
- **Repeated patient education, particularly the danger of irregular treatment, is very important.**
- **Placing handkerchief or a piece of paper in front of mouth during coughing will bring down the spread of respiratory infections as well as TB.**

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Case Report

# Bilateral Breast Cancer

**Snehansu Pan**[1]

**Breast carcinoma is one of the common malignancies encountered in clinical practice. The prevalence is 0.1% of females in any given year. It accounts for 18% of cancer deaths in females. Bilateral breast cancer is very rare. Some author reports an incidence of less than 1%. Here I present a case with bilateral breast cancer.**

[*J Indian Med Assoc* 2020; **118(3):** 43-4]

***Key words*** **: Bilateral breast cancer, Lobular carcinoma, Mammography screening.**

Breast cancer is a reasonably common clinical condition. Perhaps the incidence and prevalence is increasing. The prevalence is 0.1% of females in any given year. The mortality rate is 27% per 100000 females. It accounts for 18% of cancer deaths in females, bilateral breast cancer occurs in up to 10% of patient either simultaneously (less common) or sequentially[1]. Some author reports an incidence of less than 1%[2]. Bilateralism occurs more often in women under age 50 and is more frequent when the tumour in the primary breast is Lobular. The incidence of second breast cancer increases with the length of the patient alive after the first breast cancer- about 0.5% per year.

## Case Report

A 48 years old female came to the clinic with complains of a lump in her right breast for last one year. There was no pain or fever. On examination we found a moderately build patient with a mild pallor. The lump was in the outer and upper quadrant, about 6 cm x 8cm, firm, mobile. There was peau d' orange changes, and doubtful pectoral fixation. Axillary and other nodes were not involved. Abdominal examination was writhen with normal limit.

Though the patient did not complain, examination of the opposite breast revealed a firm lump, 2 cm x 3cm in the outer quadrant with no axillary or muscle involvement.

***Investigations*** — Blood examination revealed Hb 8 gm%, others were reasonably normal. Fine needle aspiration cytology gave the report of lobular carcinoma in both sides. Chest x-ray and USG abdomen was normal.

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***Editor's Comment :***

- **No breast lump should be left alone without tissue diagnosis.**
- **Never forget to examine the contralateral breast & axilla - an age old teaching.**
- **Be sure to consider mammography when in doubt.**

***Treatment*** — Modified Radical mastectomy (Patey's) was done, first on the right side. The other side was operated after an interval of two weeks (Fig 1).

The postoperative period was uneventful. The patient was referred to medical oncology.

## Discussion

***Epidemiology and the Problem*** — Breast cancer is the second leading cause of cancer-related death, second to lung cancer, with approximately 40,000 deaths annually. Breast cancer is also a global health problem, with more than 1 million cases of breast cancer diagnosed worldwide each year. The overall incidence was increasing until approximately 1999 because of increases in average life span. Thereafter it decreased from 1999 to 2006 by approximately 2% per year. This was due to reduction in the use of hormone therapy and reduction in screening mammography.

Survival rates in women with breast cancer have steadily improved over the last several decades, with 5 year survival rates of 63% in the year 1960s, 75% during the year 1975-1977, 79% during 1984-1986 and 90% during 1995-2005. The decreased mortality from breast cancer is thought to be the result of earlier detection via mammography screening, a decreased incidence of breast cancer and improvement in therapy. The current treatment of breast cancer is guided by pathology, staging and more recent insight into breast cancer biology. There is an increased emphasis on defining disease biology and status in individual patients[3].

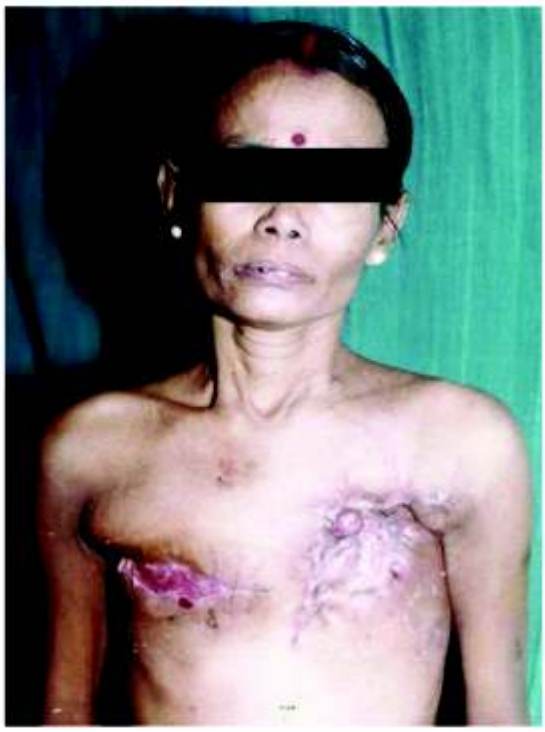

Fig 1 — The Postoperative Patient with Bilateral Breast Cancer

***Bilateral Breast Cancer*** — A bilateral breast cancer (BBC) can be defined as a cancer occurring in both the breast of the same individual. It can be primary, that is developing de novo in both the breasts, or secondary, when the second one develops as a spread from the first one.

Again it can be synchronous (0.2-2% of all breast cancer), meaning second one developing withen six months of first one. Or metachronous (5-6%), when the second one appears after six months.

BBC occurs in less than 5% of cases, but there is as high as a 20%-25% incidence of later occurrence of cancer in the second breast. Bilaterality occurs more often in familial breast cancer, in women under age 50 years and when the tumor in the primary breast is lobular. The incidence of second breast cancer increases directly with the length of time the patient is alive after her first cancer – about 1%-2% per year.

In patient with breast cancer, mammography should be performed before primary treatment and at regular intervals thereafter, to search for occult cancer in opposite or conserved ipsilateral breast. MRI may be useful in the high risk group[4].

***Conclusion*** —BBC represents a small subset of breast cancer. The incidence of BBC is higher in younger premenopausal women as compared with older women. It can be detected in the early stage with a clinical examination at regular intervals. If required mammography or FNAC can be done. These tumor have a poor outcome with standard treatment and should be individualized based on tumor characteristics.

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**Conflict of Interest : None**

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Pictorial CME

# Baby with a Large Head

Rudrajit Paul[1], Jayati Mondal[2]

A newborn child was brought to the paediatrician because of an "abnormal looking head". Above is the picture of the child. The mother had no significant illness or teratogenic drug exposure in the antenatal period. There is no similar history in the family.

**(1) What is the abnormality ?**

**(2) What are the causes ?**

**(3) What is the treatment ?**

**Answers :**

(1) This cephalic abnormality is called trigonocephaly

(2) Trigonocephaly is one type of craniosynostosis (premature fusion of one or more sutures). It can be syndromic or isolated. Syndromes associated with trigonocephaly include Jacobsen syndrome and Opitz syndrome. There is also probable genetic link associated with this anomaly, like mutation in the FGFR1 gene.

(3) Treatment is surgical, from simple suturectomy to frontal bone remodelling. Results are generally very good. Delayed treatment may cause cognitive dysfunction.

***Editor's Comment :***

- **Congenital anomalies like Trigonocephaly needs to be spotted early and surgically repaired to prevent future cognitive impairment and cosmetic effects**
- **Most cases of trigonocephaly are not associated with any syndrome**

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Case Discussion in Medicine

# Lady with A Lump in the Left Upper Abdomen

**Nandini Chatterjee**

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***The Case :***

A nondiabetic non hypertensive 50 year old lady presented with a feeling of heaviness in the left upper abdomen for last few yearsand recent onset exertional dyspnoea. On examination, she had average build, moderate pallor, mild bipedal edema and massive splenomegaly. Her other clinical parameters were normal.

**What are the differential diagnoses ?**

Massive splenomegaly should be approached keeping in mind the following aetiology:

Infections – Kalaazar, hyperreactive splenomegaly syndrome

Haematological disorders – Thalassemia major, hairy cell leukaemia, Non Hodgkin Leukemia, Chronic Lymphoid Leukemia, Chronic Myeloid Leukemia, PolycythemiaVera, Myelofibrosis with myeloid metaplasia.

Portal Hypertension - Cirrhosis of liver, Non Cirrhotic Portal Hypertension (NCPH).

Inherited disorders – Gaucher's Disease

Our patient had no history of fever, recurrent blood transfusion, jaundice, encephalopathy, ascites or hematemesis.

On examination also there was no short stature, jaundice, lymphadenopathy, hepatomegaly, tortuous venous prominence over abdomen.

**What directed investigations are to be ordered ?**

Complete hemogram with peripheral blood smear – it showed moderate microcytic hypochromic anemia, leucopenia without any atypia or morphological abnormality in other cell lines.

Liver function test including P Time was normal ,RK 39 ,Malarial antigen, Hepatites B,C and HIV werenegative.HPLC was also normal.

USG Abdomen with doppler study revealed massive splenomegaly, mild hepatomegaly with normal echotexture, dilated portal vein (18mm) with portalcavernoma.Patent splenoportal axis and hepatic veinwere seen.

Upper GI endoscopy revealed small esophageal varices.

Liver biopsy showed phlebosclerosis in medium sized portal vessels and periportal fibrosis. There was no parenchymal necrosis or regenerative nodule.

A diagnosis of idiopathic noncirrhotic portal fibrosis was made.

**What is non cirrhotic portal Fibrosis ?**

It is an disease of small to medium branches of portal vein leading to portal hypertension in the absence of cirrhosis of liver. The liver function is primarily normal with a normal or mildly raised wedged Hepatic Venous Pressure Gradient (HVPG)[1].

Noncirrhotic Portal hypertension may be of two types namely, Extra Hepatic Portal Venous Obstruction (EHPVO) and Noncirrhotic Portal Fibrosis (NCPF/IPF).

NCPF/IPH is a disorder of young adults or middle aged women, whereas EHPVO is a disorder of childhood. Both disorders present with clinically significant PHT with preserved liver functions.While EHPVO results from an acute infection in neonatal period and affects the main portal vein, NCPF/IPF involves the smaller branches of portal vein.

***Editor's Comment :***

- **The approach to massive splenomegaly should encompass hematological, infectious,vascular and gastrointestinal etiologies.**
- **Patients of cirrhosis of liver will develop portal hypertension but all cases of portal hypertension do not have cirrhosis of liver.**
- **10-30% of variceal bleeding due to Non cirrhotic Portal Hypertension.**

Early age acute or recurrent infections in an individual with thrombotic predisposition constitute the likely pathogenesis. Similar illness is said to be associated with connective tissue disorders HIV infection, schistosomiasis and arsenicosis, drug intake like azathioprine, vinyl chloride or didanosine. Although Idiopathic Noncirrhotic Portal Hypertension (INCPH) has a worldwide distribution, it is particularly prevalent in Asia. It is more frequent in socioeconomically disadvantaged individuals[2,3,4].

Over 95% of patients have splenomegaly and it can cause left upper quadrantabdominal pain or fullness. Commonest presentation is variceal bleeding. Ascites is reported in up to 50 % of cases, and it usually develops in the context of precipitating factors such as variceal bleeding or infections. Generally, it is easily controlled with low dose of diuretics and resolution of the trigger. Features of hypersplenism may be present. Hepatic encephalopathy is a rare complication and it is also related to precipitating factors. There are anecdotic reports of hepatopulmonary syndrome, portopulmonary hypertension and hepatocellular carcinoma.

There is a lack of a specific positive test that leads to an INCPH diagnosis. The diagnosis of INCPH is a diagnosis of exclusion, based on the following previously reported criteria]: (1) presence of unequivocal signs of portal hypertension (eg, gastroesophageal varices, ascites, and/or splenomegaly); (2) absence of cirrhosis, advanced fibrosis or other causes of chronic liver diseases that can cause PH by appropriate serological, biochemical tests and liver biopsy and; (3) absence of thrombosis of the hepatic veins or of the portal vein at imaging studies performed at diagnosis. Histopathology reveals an obliterative portal venopathy, phlebosclerosis and periportal fibrosis[5].

In cirrhosis of liver, on the other hand, there is parenchymal necrosis with fibrosis and regenerative nodules. It is a sinusoidal

**APASL criteria for NCPF/IPH :**

1. **Presence of moderate to massive splenomegaly**
2. **Evidence of portal hypertension, varices, and/or collaterals**
3. **Patent spleno-portal axis and hepatic veins on ultrasound Doppler**
4. **Test results indicating normal or near normal liver functions**
5. **Liver histology - no evidence of cirrhosis or parenchymal injury**

type of portal hypertension with a raised HVPG. There is deranged liver function with progressive decompensation[6].

Management rests on control and prophylaxis of variceal bleeding. Prophylactic beta blocker therapy and endoscopic variceal ligation are the principal modalities of therapy. Surgical shunts are indicated in patients with failure of endotherapy, bleeding from sites not amenable to endotherapy, symptomatic hypersplenism or symptomatic biliopathy. In EHPVO, there are additional concerns of growth faltering, portal biliopathy, minimal hepatic encephalopathy and parenchymal dysfunction.Persistent growth failure, symptomatic and recurrent hepatic encephalopathy, impaired quality of life or massive splenomegaly that interferes with daily activities are other surgical indications[7,8].

Overall, prognosis is generally better than in patients with cirrhosis and a similar degree of portal hypertension. This may be due to the fact that most INCPH patients have well preserved liver function. However, a small subgroup of patients will develop liver failure and will require liver transplantation.

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**Causes of Non cirrhotic Portal Hypertension :**

**Pre Hepatic:**
- i) Extrahepatic portal vein obstruction
- ii) Portal Vein thrombosis
- iii) Splenic Vein thrombosis
- iv) Infiltrative Disorders

**Hepatic:**
- i) Pre-sinusoidal
  - a) Congenital Hepatic Fibrosis
  - b) Primary biliary cirrhosis
  - c) Sclerosing Cholangitis
  - d) Neoplastic occlusion of portal vein
  - e) Granulomatous lesion – schistosomiasis, sarcoidosis
- ii) Sinusoidal
  - a) Drugs (methotrexate, amiodarone)
  - b) Toxins (Vinyl Chloride, copper)
  - c) Metabolic (NASH, Gaucher's)
  - d) Inflammatory (viral hepatits, Q fever)
- iii) Post sinusoidal
  - a) Veno-occlusive disorders

**Post hepatic :**
- i) Inferior Vena cava obstruction
- ii) Tricuspid Regurgitation
- iii) Severe Right sided heart failure
- iv) Constrictive Pericarditis

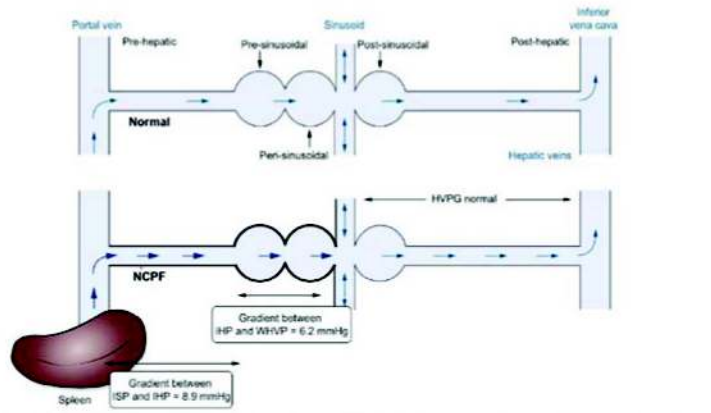


**Fig. 3. Hemodynamics in NCPF/IPH.** Both intrasplenic (ISP) and intravariceal pressures (IVP) are high in NCPF. There are two independent pressure gradients – one between ISP and intrahepatic pressure (IHP) (8.9 mmHg), and another between IHP and wedge hepatic venous pressure (WHVP) (6.2 mmHg), indicating 2 patho-anatomic sites of resistance in these cases – presinusoidal and perisinusoidal. As the vascular resistance in pre- and peri-sinusoidal, HVPG remains nearly normal [79].

**Learning Points :**

- NCPF is an obscure disease of small to medium branches of portal vein
- There is presinusoidal portal hypertension in the absence of cirrhosis of liver.
- The liver function is more or less preserved.
- The HVPG is normal or mildly raised.
- NCPF may idiopathic or secondary to connective tissue disorder, infection, drugs or toxins.
- Common presentation is upper G I bleed and splenomegaly.
- Diagnosis is by exclusion and confirmed by histopathology.
- Control and prophylaxis of variceal bleeding is the mainstay of therapy.
- Decompensation is transient and easily managed.

Drug Corner

# A Prospective, Observational Study to Determine the Demographic Characteristics and Clinical Profile of Indian Patients Presenting with Dry Cough and Effectiveness and Safety of the Fixed-Dose Combination of Codeine Phosphate and Triprolidine Hydrochloride in these Patients

P K Thomas[1], Balamurugan[2], Nimish Shah[3]

**Objective :** Considering the increasing incidence of dry cough in India, this study was intended to evaluate the effectiveness and safety of the fixed-dose combination (FDC) of codeine phosphate and triprolidine hydrochloride.

**Methods :** Demographics, clinico-etiological profile and quality of life (QoL) of adult patients with dry cough, prescribed with the FDC of codeine phosphate and triprolidine hydrochloridewere determined. Standard tools were used for measuring effectiveness and safety during the study.

**Results :** Out of 222 (100.0%) patients, mostaged either ≥55 years (31.08%) or 18-35 years (30.18%). Etiology of dry cough presented by more than 20% patients were allergy (43%), environmental factors (25.23%), and respiratory tract infection (23.42%). Significant ($p<0.0001$) reduction in the mean score of cough frequency, cough severity,and sleep disruption was evident at end of treatment. Approximately 97% patients achieved minimal important differencein a mean (±SD) duration of 5.0 (±0.27) days. Improvement in QoL of patients was also reported withno adverse drug reaction during the study.

**Conclusion :** In Indian set-up, dry cough was demonstrated equally by both the genders with primary presentation among elderly and young adults. The FDC was found to be effective, and safein the management of *dry cough,* with an overall improvement in QoL.

[*J Indian Med Assoc* 2020; **118(3):** 48-53]

***Key words*** **: Dry cough, codeine phosphate, triprolidine hydrochloride, VAS, LCQ score, minimally important difference (MID).**

Cough is a reflex response to mechanical, chemical, or inflammatory irritation of the tracheobronchial tree mediated by sensory neurons in the airways. Cough precipitates as a defence mechanism, however in certain situations, it may exacerbate affecting the airway mucosa.[1] Global prevalence of cough is reported to be 9.6%, while 5%-10% prevalence is reported among Indian population.[2] It is one of the most common complaints among Indians at the primary care setting (30%)[3] and outpatient departments (6.5%).[4] Consequently, it is reported as a 'frequent' symptom according to an Indian population-based survey (Age standardized prevalence: 6.5%; rural: 9.4%; urban: 3.7%).[5] Regardless of the etiology, dry cough incidence may adversely affect the quality of life (QoL), sleep, and work productivity,[6] and in chronic cases may lead to urinary incontinence and depression.[7] Multifactorial etiology of dry cough often hinders with the diagnosis and prognosis of this condition.

Though treatment of cough mainly involves treating the underlying cause, yet symptomatic relief remains an important goal to improve the patients' QoL. In this light, antitussives continue to be the mainstay therapy against

***Editor's Comment :***

- **Dry cough is one of the commonest symptom prevalent equally in both the genders.**
- **Allergy is the most prevalent etiology of dry cough.**
- **Majority of the patients present dry cough with acute severity.**
- **Most Indian physicians prescribe FDC of codeine phosphate and triprolidine hydrochloride due to its effectiveness as a treatment measure.**
- **The FDC is found to be effective, and safe in the management of dry cough, with an overall improvement in QoL.**

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dry cough.[8] A potent antitussive, codeine, is reported as one of the most commonly preferred centrally acting agent, mainly due to its established efficacy through multiple clinical evaluations.[9,10] In addition to the cough suppressant property, codeine also has analgesic and sedative effects, which relieves painful cough experienced during hemoptysis and lung cancer. Number of clinical reports have demonstrated the importance of codeine in the treatment of persistent and painful cough during lung cancer and hemoptysis.[11-13]

The combination of codeine phosphate and triprolidine hydrochloride is commonly used in India. Triprolidine is a first-generation antihistamine that binds to H1 receptor, thereby blocking the actions of endogenous histamines; and hence, used for symptomatic relief of allergy and common cold. Clinical evidences have demonstrated several benefits of codeine in combination with the first-generation antihistamines in relieving cough by virtue of their pharmacodynamic characteristics.[8] Although codeine is proven to be effective in clinical trials, real-world evidence of its utilization in the primary care setting in India is limited. Also, there is paucity of data on the use of codeine and triprolidine combination among patients with dry cough in the Indian setting.

Hence the objective of this prospective, observational study was to explore the clinico-etiological profile and demographic characteristics of adult patients with dry cough recommended with fixed dose combination (FDC) of codeine phosphate and triprolidine hydrochloride as part of routine clinical practice. The effectiveness and safety of this combination was also evaluated in the study patients.

## Material and Methods

### Study design and patient population :

This prospective, observational, multi-centric study was conducted between October 2018 to March 2019 across 15 centers of India (Nagpur, Indore, Pune [3 sites] and 2 sites each in Chennai, Hyderabad, Nasik, Mumbai and Bhopal). Adult patients with dry cough prescribed with codeine phosphate and triprolidine hydrochloride combination (Phensedyl T; Abbott Healthcare Pvt. Ltd) for symptomatic relief of dry cough (either on the same day of enrolment or a day before) in routine clinical practice were enrolled (dose: 5 ml TID, oral route). Patients with dry cough already on FDC codeine phosphate and triprolidine hydrochloride treatment for ≥2 days, or on treatment with anticholinergics, barbiturates, tricyclic antidepressants or other central nervous system depressants, or with any medical condition deemed unacceptable for inclusion based on the investigator's discretion were excluded from the study. Pregnant and/or lactating women were also not included in the study.

The study involved a baseline visit and a follow-up visit at end of treatment (EOT) on Day 7 (± 1 day).

The study protocol was approved by Conscience independent ethics committeeand conducted in accordance with the principles of Declaration of Helsinki, International Council on Harmonization Good Clinical Practice (ICH GCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). All patients provided written consent in the patient authorization form to participate in the study.

### Study endpoints :

Primary endpoints were demographic characteristics that included age, gender, education, and occupation. Clinico-etiological profile comprised of cough classification, mean cough duration, cough etiologies, cough characteristics (cough severity [100-mm Visual Analog Scale (VAS) score], frequency [7-point Likert scale score], night-time awakenings [10-cm VAS score]), concomitant symptoms, co-morbid illness, and rationale for prescribing the FDC of codeine phosphate and triprolidine hydrochloride.

Secondary endpoints included analyzing effectiveness of the study drug as a measure of mean change in cough frequency score using 7-point Likert scale (0: not at all; 6: constant), mean change in cough severity score using a 100-mm VAS (0: no cough to 100: worst cough ever), proportion of patients with minimal important difference (MID) ie, decrease in VAS severity score by ≥17 mm at Day 5 and/or Day 7, time (in days) for achieving MID, and mean change in sleep disturbance by night-time awakenings score based on a 10-cm VAS (0: best possible sleep to 10: worst possible sleep). All assessments were recorded from baseline to EOT; Day 7 [± 1 day].

The QoL was assessed by mean change in Leicester cough questionnaire (LCQ)-acute score (total and domain scores—physical, psychological, and social).

Safety and tolerability of study drug were also assessed (proportion of patients with adverse drug reactions (ADRs), treatment-emergent adverse events, with serious and fatal ADRs and with ADRs leading to discontinuation of the study drug).

### Statistical methods :

No formal sample size calculation was done for this study. Continuous variables were summarized descriptively. Categorical data were summarized as numbers and percentages. Secondary variables were assessed by paired t-test. Statistical tests were performed at 5% level of significance. Statistical analysis was done using Statistical Analysis System® version 9.4 software.

## Results

### Demographic and clinical characteristics :

Of the 222 (100%) enrolled patients, 113 (50.90%) were

Table 1 — *Summary of Socio Demographics- All Enrolled Analysis Set (N=222)*

| Parameter Assessed | Details | n (%) |
|---|---|---|
| Gender : | | |
| | Females | 113 (50.90%) |
| | Males | 109 (49.10%) |
| Age : | | |
| | ≥55 years | 69 (31.08%) |
| | 18-35 years | 67 (30.18%) |
| | 36-45 years | 55 (24.77%) |
| | 46-54 years | 31 (13.96%) |
| Occupation : | | |
| | Unemployed | 118 (53.15%) |
| | Skilled Worker | 72 (32.43%) |
| | Unskilled Worker | 22 (9.91%) |
| | Semi-Professional | 56 (25.22%) |
| | Professional | 28 (12.61%) |
| | Clerical, shop-owner, farmer | 76 (34.23%) |
| | Semi-Skilled Worker | 4 (1.80%) |
| Education : | | |
| | Graduate or Postgraduate | 166 (74.77%) |
| | Intermediate or Post-High School Diploma | 79 (35.59%) |
| | High School Certificate | 59 (26.58%) |
| | Middle School Certificate | 33 (14.87%) |
| | Primary School Certificate | 16 (7.2%) |
| | Profession or Honors | 17 (7.65%) |
| Socio-economic status : | | |
| | Upper Middle Class | 126 (56.76%) |
| | Lower Middle | 50 (22.52%) |
| | Upper Lower | 28 (12.61%) |
| | Upper Class | 17 (7.66%) |
| | Lower Class | 1 (0.45%) |

females and 109 (49.10%) were males (Table 1). The mean ±SD age of study population was 45.76 ± 15.47 years. Most enrolled patients aged ≥55 years (69 [31.08%]), followed by 18-35 years (67 [30.18%]), 36-45 years (55 [24.77%]) and least number of patients were in the age group of 46-54 years (31 [13.96%)]. Most study patients were unemployed (118 [53.15%], however ~35% patients were clerks, shop-owner, farmer (n=76) or skilled workers (72 [32.43%]). About 56 patients (25.22%) were semi-professionals, while a small proportion of patients were professionals (28 [12.61%]), unskilled workers (22 [9.90%]) or semi-skilled workers (4[1.80]). Majority of the patients (75%) were graduate or postgraduates (n=166). Based on Kuppuswamy classification, socioeconomic status of most study patients was upper middle class (126 [56.76%]), followed by lower middle (50 [22.52%]), and upper lower class(28 [12.61%]).

**Other baseline characteristics :**

In this study, the mean ±SDweight and height of overall patients was 63.6±11.31 kg and 1.6±0.09 m respectively, while the mean ± SD waist circumferenceand BMI was 83.0 ± 10.41 cm and 24.6 ± 4.22Kg/m$^2$ respectively. Of 222 enrolled patients, 33 (14.86%) patients had a history of concomitant symptoms/conditions. Of these 33 (14.86%) patients, most presented with respiratory, thoracic and mediastinal disorders (13 [39.39%]), followed by gastrointestinal (8 [24.24%]), and infections and infestations (7 [21.21%]).

Results of blood parameters, radiological investigations, vital signs and physical examination performed at baseline were comparable with the EOT (Day 7 ± 1) observations.

In view of the study indication, all patients were administered with cough and cold preparations as a concomitant medication. Drugs for obstructive airway diseases (83 [37.4%]) and antihistamines for systemic use (63 [28.4%]) were the commonly used concomitant medications.

**Clinico-etiological profile :**

Clinical classification of most study patients was acute (199 [89.64%]), followed by sub-acute (12 [5.41%]) and chronic(11 [4.95%]). Approximately 43% patients reported the cough etiology to be allergy (n=95), followed by environmental factors(56 [25.23%]), respiratory tract infection (52 [23.42%]), post infectious cough (25 [11.26%]), and asthma (24 [10.81%]). Less than 10% patients presented gastroesophageal reflux disease (GERD), idiopathic, other risk factor and laryngopharyngeal reflux disease (Fig 1).

Concomitant symptoms are summarized in Fig 2. 'Tiredness' was the most prevalent symptom presentedby 136 (61.26%) patients, followed by sore throat (127 [57.21%]), and nasal discharge/ stuffiness (110 [49.55%]). Concomitant symptoms shown by ≥20% patients included hoarseness of voice (85 [38.29%]), frequent throat clearing (84 [37.84%]), wheezing and shortness of breath (73 [32.88%]), and fever (52 [23.42%]). Co-morbid conditions

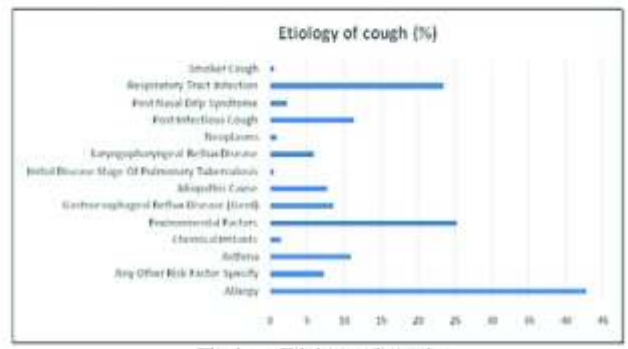


Fig 1 — Etiology of cough

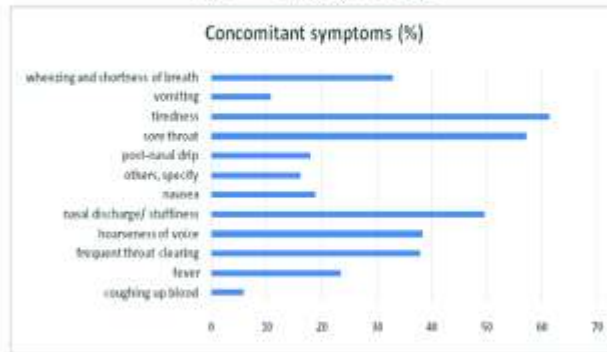


Fig 2 — Concomitant symptoms of cough

presented bye" 10% patients included acidity (32 [14.41%]) and bacterial infection (47 [21.17%]).

This study also recorded the rationale for prescribing the FDC of codeine phosphate and triprolidine hydrochloride. Most patients were recommended the study drug for its effectiveness in dry cough (205 [92.34%]) as a standard of care (80 [36.04%]) and due to its tolerability (73 [32.88%]).

**Effectiveness :**

The change in mean score of cough based on frequencyfor all enrolled patients at Day 7 compared to baseline are summarized in Fig 3. At Visit 1 (baseline), the mean ±SD score was 4.2±1.13 which significantly ($p<0.0001$) reduced to 0.7± 0.77by EOT (Day 7±1). Similarly, the change in mean score at EOT based on the severity of cough (100 mm VAS scale) indicated a significant ($p<0.0001$) reduction to 10.5 ± 10.68 from 68.0±19.16 (Fig 4). Furthermore, the change in mean score at EOT based on sleep disruption also demonstrated significant ($p<0.0001$) reduction to 0.8 ± 0.89 at EOT (Day 7 ± 1)from baseline score of 5.7 ± 2.41 (Fig 5).

Approximately 97% patients (n=215) achieved MID in a mean (± SD) duration of 5.0±0.27 days.

The mean change in LCQ score from baseline to Day 7 was significant for physical parameter (Mean ± SD: 16.5±7.60; 95% CI for mean: 15.48:17.49; $p<0.0001$), psychological parameter (Mean±SD: 14.7 ± 6.86; 95% CI

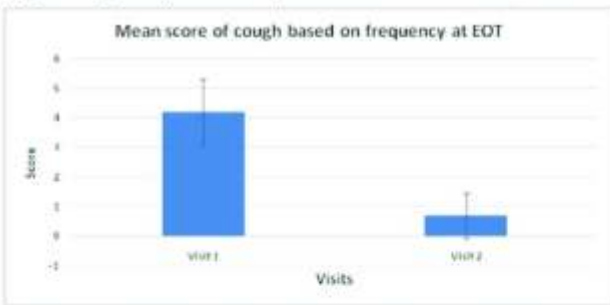


Fig 3 — Summary of Mean Score and Change in Mean Score at EOT from Baseline of Frequency of Cough-All Enrolled Analysis Set (N=222)

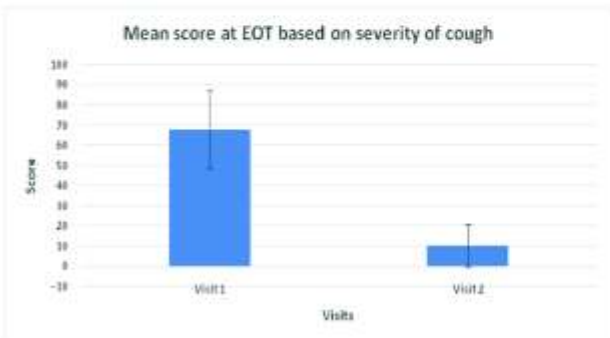


Fig 4 — Summary of Mean Score and Change in Mean Score at EOT from Baseline for Severity of Cough-All Enrolled Analysis Set (N=222)

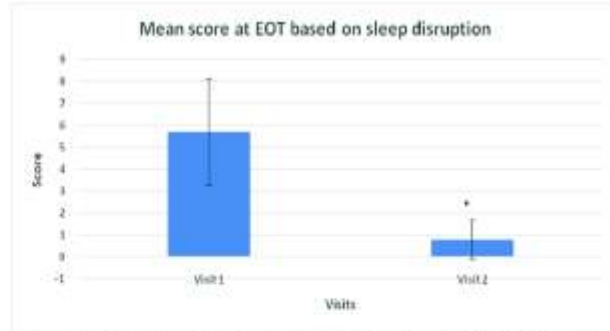


Fig 5 — Summary of Mean Score and Change in Mean Score at EOT from Baseline of Sleep Disruption-All Enrolled Analysis Set (N=222)

for mean: 13.80:15.61; $p<0.0001$) and social parameter (Mean±SD: 9.9±4.56; 95% CI for mean: 9.29:10.50; $p<0.0001$), indicating an overall improvement in the QoL of patients with dry cough treated with the FDC of codeine phosphate and triprolidine hydrochloride (Fig 6).

**Safety :**

No serious/non-serious ADRs were reported in the study.

## Discussion

Dry cough, which can be acute or chronic, is defined as absence of sputum/phlegm on coughing and is one of the most frequently reported problems among Indian population.[8] Combination therapy may result in greater effectiveness and reduced risk of adverse reactions compared with high-dose monotherapy, at a lower cost, with improved medication concordance.[14] A physician's survey in India found that codeine and/or its combination is preferred as an antitussive in patients with neoplasm postinfectious cough, unexplained cough, and in cough associated with allergy.[15] The codeine-triprolidine combination is available in the Indian market since decades.

In the present study, we assessed the demographic and clinico-etiological profile of patients who have been recommended with codeine phosphate and triprolidine hydrochloride combination for symptomatic cough relief. The effectiveness and safety profile of this combination in the study patients were also assessed.

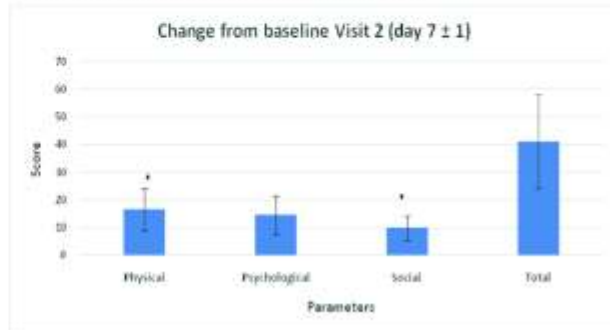


Fig 6 — Summary of Change in Mean Score of LCQ-Score from Baseline to Day 7-All Enrolled Analysis Set (N=222)

This multi-centric, observational study comprised of 222 patients across India who were prescribed with FDC of codeine phosphate and triprolidine hydrochloride for symptomatic relief of dry cough. The proportion of male (49.10%) *versus* female (50.9%) was comparable in this study. Most study patients aged either e"55 years (31.08%) or 18-35 years (30.18%) with a mean ± SD age of 45.76 ± 15.47 years for the study cohort. Occupation of the study cohort was recorded with an aim to establish the etiological association of dry cough among Indian population. More than 50% patients were unemployed which might be attributed to the age being above 55 years or between 18-35 years for most study patients. Occupation of ~35% patients were clerical, shop-owner, farmer or skilled workers which might expose to allergens triggering an incidence of dry cough in susceptible individuals.

Based on Kuppuswamy classification, most patients were classified in upper middle class (56.76%). Clinical classification of dry cough for most study patients was acute (89.64%), followed by sub-acute (5.41%) and chronic (4.95%). This study also recorded the etiology which was 'allergy' for approximately 43% patients, followed by environmental factors (25.23%), and respiratory tract infection (23.42%). Higher prevalence of acute form of cough due to reported etiological factors is in concordance to an Indian questionnaire-based survey conducted among 500 registered physicians.[15]

This study reported the concomitant symptoms of dry cough which was tiredness, sore throat, and nasal discharge/ stuffiness in more than 50% patients. In addition, co-morbid disorders were recorded as bacterial infection (21.17%) or acidity (14.41%).

Amongst the many antitussive agents available for the management of cough, codeine, is one of the most frequently used centrally acting cough suppressant and is considered as the 'gold standard' cough suppressant drug since a long time.[16,17] In this study, most patients were recommended FDC of codeine phosphate and triprolidine hydrochloride for variety reasons that included effectiveness in dry cough (92.34%), as a standard of care (36.04%) and safety profile (well tolerated) (32.88%). This observation is in concordance to an Indian survey that reported codeine as 'ranked 2' recommended antitussive by physicians.[15]

Furthermore, this is the also the first Indian study to evaluate the effectiveness of codeine phosphate and triprolidine hydrochloride combination by means of cough frequency using 7-point Likert scale, cough severity using VAS scale, sleep disruption by 10 cm VAS scale and LCQ score for QoL assessment. These constitute the validated instruments for analyzing the desired parameters. There was a significant reduction in cough frequency, severity, sleep disruption and improvement in QoL score shown by all study patientsat EOT (Day 7 ±1) compared to baseline. These observations corroborate the rationale of 'effectiveness' as reported by most physicians for prescribing the study drug in dry cough management. An Indian study comparing effect of pholcodiene plus promethazine with dextromethorphan plus chlorpheniramine and codeine plus chlorpheniramine also reported reduction in cough frequency and night awakenings after 7 days treatment of each FDC.[18] Moreover, minimally important difference (MID) was exhibited by 95% study patients at Day 5 of treatment as against Day 7 reported by an earlier study on pediatric patients treated with codeine plus chlorpheniramine combination.[18]

No serious/non-serious ADR were reported in this study at the given dose of 5 ml (codeine phosphate 10 mg plus triprolidine 1.25 mg), three times a day, till a maximum of 8 days treatment period. This could be the basis of prescription pattern for dry cough noted among Indian physicians in this study. A previous study reported erythema of the abdomen, epigastric pain and somnolence after 7 days monotherapy with dihydrocodeine but in lung cancer patients.[19]

## Limitations

Our study has several strengths. Firstly, this is the first of its kind pan India study which elucidated demographic and clinico-etiological profile of patients with dry cough. Secondly, patients of varying age, socioeconomic status were evaluated. This study has used standard and validated tools to assess effectiveness of study drug. However, as this was a single visit study, with single follow-up, the study could not provide insights on the long-term outcome. Further, being an observational study, no comparator analysis was performed.

## Conclusion

Cough is one of the health concerns among Indian population that seeks medical attention due to its manifestation as a secondary clinical condition, in turn impacting the QoL. In Indian set-up, dry cough was demonstrated equally by both the genders with primary presentation among elderly and young adults. Allergy was the most prevalent etiology of dry cough. Majority of the study cohort presented dry cough of acute severity. Most Indian physicians prescribed the study drug due to its effectivenessas a treatment measure. This rationale was supported by the EOTobservations that exhibited reduction in cough frequency, severity, sleep disruption and improved QoL. The FDC of codeine phosphate and triprolidine hydrochloride was found to be safe and well-tolerated by all study patients.

## Disclosure

This study was funded by Abbott Healthcare Pvt Ltd. Dr Thomas, Dr Balamurugan and Dr Shah were the

investigators in the study.

**Conflict of Interest :**

There are no other conflicts of interest to report.

**ACKNOWLEDGEMENT**

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Dr Vyavahare, Dr Sudhakar Vyavahare Clinic; Dr Ravi Dosi, Dosi chest care centre; Dr R S Vijayvargia, Dr R S Vijaywargiya Clinic; Dr N P Mishra, Dr N P Mishra Clinic; DrAnjani Kumar, Anjani Kumar ENT Clinic; Dr Ganesh Rajguru, Maxcare Hospital; DrVrusaliTelang, Vedaang ENT Clinic; Dr Vinit Niranjane, Breath Easy Advanced Chest care Centre; Dr Kapil Salgia, Kapil Polyclinic; Dr BVG Swamy, Yashoda Hospital; Dr Aparna Khulbey, Image Hospitals.

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## Lerning Points :

- **Codeine is an important natural opioid found in the poppy resin.**
- **Codeine is a selective cough suppressant at subanalgesic doses, which usually do not cause respiratory depression and constipation, which are common side effects of opioids.**
- **Codeine has good activity by the oral route and is commonly employed for the management of cough, sometimes in combination dose forms with antihistaminics.**
- **Triprolidine is a first generation antihistamine with anticholinergic properties. It is used to combat the symptoms associated with allergies and to provide general relief for cough.**
- **Codeine and tripolidine combination can be used as cough suppression.**
- **Use of combination of codeine and tripolidine should be used cautiously especially in children.**

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History of Medicine

# The Bhopal gas tragedy from a medical point of view : Taking a look back

On the fateful night of 2nd December, 1984, methyl IsoCyanate (MIC), a deadly toxic gas with the smell of boiled cabbage, escaped from tank no. 610 of the Union Carbide plant in Bhopal. Inadvertent entry of water in MIC tank caused the chemical to swiftly convert to gas and it spread like a yellowish-brown cloud in the direction of wind. The gas spread quickly to the nearby shanty town and railway station, killing thousands in its way. The exact number of dead will never be known because in many cases entire families were wiped out with no one to claim the deadbodies or claim compensation. But according to various observers, the number of dead varied between 16000 and 30000 with a further half a million suffering devastating health consequences. The health effects of this tragedy are very much present even today. This article will be a small attempt to analyse the Bhopal tragedy from a medical point of view. Since this was a socio-economic disaster of gigantic proportions, both the scientific as well as the popular account of the health effects will be described here. Thus, journalistic accounts will go side by side with discussion of scientific studies.

***Bhopal gas disaster at a glance :***

- **Date : Night of 2nd December, 1984**
- **Number of deaths : (official) 3787; (public claim) at least 20,000; Number affected : (official) 558, 125**
- **At sambhavna clinic**
  - **Over 2500 children with possible birth defects**
  - **Rates of malignancy 8 times higher compared to gas-unexposed population**
  - **Permanent disabilities: 4944**
- **High percentage of various psychiatric ailments : mostly untreated**
- **Ongoing silent disaster: contamination of groundwater from the plant**

## Immediate Effects :

**Popular account :**

According to eye witness accounts, both humans and animals suffered acutely as a result of the toxic fumes. MIC was the main gas released from the tanks but other deadly toxins in the mixture included phosgene, mono-methyl-amine and hydrocyanic acid. In most cases, the immediate effect of inhalation of this toxic mixture was respiratory arrest. Since the gaseous mixture was heavier than air, it travelled close to the ground and initially killed those who were sleeping on the ground or who were cripples. But all people did not have the merciful death of instantaneous respiratory and cardiac arrest. Many suffered a slow agonizing death, gasping for air with severe pulmonary haemorrhage and blood running from the corners of their mouths. Paradoxically, as people panicked and started running, they were forced to breathe heavily and this led to more inhalation of the toxic gas.

People started vomiting and as they fell, many drowned in their own vomitus. Later, the next morning, bodies were discovered with yellowish froth in the mouth and greenish or bluish hue of the skin. Many people had severe chemical burns of the cornea and became permanently blind (this last point is disputed).

However, only choking by the gas was not the sole cause of death. The effects of the gas caused people in the street to lose control of their cars, leading to many hapless mortals being run over. Some people jumped from bridges and roofs of houses in fear and confusion.

***Fun fact*** *— A Naga Sadhu was meditating in a park near the chemical plant. He was the only one who survived in that area. It was later surmised that his yogic habit of breathing once every three to four minutes may be the reason for his miraculous survival.*

People with pre-existing lung conditions like tuberculosis were quick to die in suffocation.

Animals like cattle did not fare any better. Thousands of cows, horses and buffaloes were found to have choked. The next day, the BBC reported that "Thousands of dead cats, dogs, cows and birds litter the streets…."

According to the doctors who attended emergency that night at Hamidia Hospital, Bhopal, people were gasping for breath like "fish out of water". Most of the doctors there had never even heard of MIC and there was no manual to guide initial treatment plans. The doctors also found many of the victims with amnesia and mania, apparently due to CNS effects of the gas. Many also suffered convulsions and myoclonus.

The toxic gas was absorbed in the garments and hair of the victims and the health professionals who were attending these victims also suffered from toxicity to a varying degree. There is an eye witness account of a junior doctor attempting mouth-to-mouth resuscitation of a child and dying in the process.

During post-mortem examination, the doctors found the lungs full of fluid and blood with the trachea full of blood clots. There was massive congestion of liver and spleen. The brains were reduced to gelatinous paste. Most of the bodies gave off smell of bitter almonds, due to the MIC breaking down into hydrocyanic acid inside the body.

**Scientific analysis :**

The toxicological analysis of MIC was in rudimentary stage at that time. Some animal studies had been done and the medical literature contained only a handful of reported cases. There was no manual or guideline for treatment. In fact, the Bhopal disaster caused the first real life experience with MIC toxicity.

MIC vapour was found to be intensely irritating to the cornea, leading to corneal ulcer, lid swelling and photophobia. In fact, at the Hamidia hospital, the first victim came with eye irritation. Many people also suffered from skin irritation. Autopsy on the lungs showed severe necrotising lesions all through the respiratory tract upto the alveoli. Patches of acute bronchiolitis were also seen. MIC

exposure in lethal doses caused complete destruction of respiratory epithelium in minutes, leading to massive alveolar edema. Chest X ray of the victims showed alveolar and interstitial edema. One term used to describe the effect of MIC on airways is "reactive airways dysfunction syndrome".

Dr DK Satpathy performed an incredible number of autopsies over the 24 hours following the disaster. He also found that the kidneys showed haemorrhage and tubular necrosis; GI tract showed submucosal haemorrhage and myocardium showed severe edema. He preserved the samples for further toxicological analysis. But no further analysis was performed and in 2006, the viscera in refrigerators were destroyed by a power cut.

## Intermediate Effects :

**Popular accounts :**

In July, 1985, the New York Times reported that deformed babies were being born in Bhopal as a result of the gas tragedy. Various citizens' right groups said that there were hundreds of abortions and still births in the immediate aftermath of the tragedy. Numerous babies with severe conditions like cerebral palsy and limb deformities were born. Also, a lot of adults reported persistent debilitating weakness and tingling of the limbs. The trail of the dead did not stop on 3rd December 1984; for the next 8-12 weeks, a number of the gas victims suffered slow painful death.

**Scientific outlook :**

A study among women who lived within 1 km of the plant and who were pregnant at the time of gas leak showed a 43% rate of abortion. There was 14% neonatal mortality. There was a significant rise in congenital deformities. Such deformities included spina bifida, congenital heart diseases and limb deformities.

## Delayed Effects :

**Popular account :**

By popular account, the aftermath of the Bhopal tragedy is still very much alive. According to activists and other ground level NGOs, delayed effects include persistent breathlessness, cough, dimness of vision, recurrent body ache, fatigue, depression and other psychiatric symptoms of post-traumatic stress disorder. Women suffer from menstrual irregularities, infertility and anemia. Children born to exposed parents suffer from growth retardation. Also, many activists claim that number of children born with deformity is rising in the gas-affected areas. There is an alarming rise in cancers among the survivors.

Recently there have also been claims of 3rd generation victims of the gas.

**Scientific account :**

The genotoxic effect of MIC has been proven in in vitro studies. However, inside the human cell, the MIC tends to react with the proteins first and its effect on the DNA is variable. The carcinogenic effect of MIC is even more debatable. An early study in 1999 did not find much increased risk of cancer among the survivors. However, a recent observation from the Sambhavna clinic of Bhopal, the main centre for treatment of gas victims, found very high risks of certain types of malignancy among the survivors.

However, one area where the long term effect of MIC has been documented unequivocally by follow up studies is neuro-behavioural and cognitive functions. Moderate and severely affected gas victims were found to have significant impairment in memory, learning, motor speed and precision, which persisted over the years.

There are also reports of continued respiratory effects of this gas exposure. Early on, restrictive lung involvement was documented. But later studies also documented significant irreversible obstructive pathology. Fibrotic changes of the lung were observed, especially among those who were infants at the time of the tragedy. Thus, MIC was able to cause severe lung fibrosis after a single exposure. These respiratory effects caused significantly high delayed mortality among the survivors at least for the next 5 years. Later studies showed that with time, type I pneumocytes in the lung decreased and infiltration with eosinophils increased.

Some recent reports claim that people who were exposed to the gas as children are more likely to give birth to babies with congenital malformations even today. However, there is no official data on this topic.

The Bhopal Gas disaster is perhaps the largest industrial disaster in history. We should never forget the lessons learnt from this tragedy so that future recurrences can be avoided. In a developing country like India, every doctor should have basic knowledge of the various industrial chemicals and their health effects.

***— RP***

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# Mediquiz

**Rudrajit Paul**[1]
*Quiz Master*

***Series - 2***

## Clinical signs in Neurology

***(1) We all know about dissociated sensory loss, ie, loss of pain and temperature sensations with preservation of light touch and vibration sense. But what may be the cause of dissociation between position and vibration senses (position sense severely impaired, vibratory sense preserved) ?***

(A) Peripheral neuropathy
(B) Spinal cord tumour
(C) Dorsal root ganglion lesion
(D) Thalamic lesion
(E) Parietal lobe lesion

***(2) A 23 year old woman came to the emergency with gradual onset loss of vision of left eye, impaired hearing in left ear, decreased olfaction and decreased sensation of left arm and legs. What may be the site of the lesion ?***

(A) Non-organic symptoms
(B) Base of skull
(C) Temporal lobe
(D) Lateral medulla
(E) Diffuse cortical disease

***(3) A 39 year old man came to the neurology clinic. His wife complained that he had recently developed deviation of face. However, on meticulous examination, the physician did not find any evidence of facial palsy. The wife was adamant in her description of the signs and said that when her husband was watching the TV and was laughing at a comedy show, she noticed this facial deviation. She also noticed this deviation during an argument. What may be the cause of this complaint?***

(A) Faulty observation by the wife
(B) Thalamic lesion
(C) Internal capsule lesion
(D) Pontine lesion
(E) Buccal cavity pathology

***(4) A 67 year old man presented with difficulty in vision. He could not describe the defect properly. On visual field test, it was found that he had loss of visual field for a large area around macula in one eye along with some loss in the upper outer field of the other eye. What is this condition called?***

(A) Junctional scotoma
(B) Tubular vision
(C) Hemianopia
(D) Cecocentral scotoma
(E) Heteronymous scotoma

***(5) Which of the following best describes the clinical sign of "pupillary escape"?***

(A) Light reflex absent; accommodation reflex present
(B) Constriction of Horner syndrome pupil with cocaine
(C) Dilatation of pupil after constriction on exposure to bright light
(D) Preservation of pupillary reflex in occipital lobe disorders
(E) Absence of pupil involvement in myasthenia gravis

***(6) An 8 year old boy was brought to the doctor due to problems at school. He complained that his friends would tease him whenever he started to eat. But he did not know the reason. The doctor at first did not find any facial abnormality. But then, as the boy opened his mouth to speak, the doctor noticed that the left eyelid was falling down synchronously, as if he was winking. What is this condition called?***

(A) Marcus –Gunn phenomenon
(B) Inverse Marcus Gunn phenomenon
(C) Hemfacial spasm
(D) Tics
(E) Bell's phenomenon

*(Answer : next page)*

## *Answer : Mediquiz*

**(1) (E)**

***Explanation :*** Generally, vibration and joint position senses are lost simultaneously due to lesions of dorsal column. Only rarely there is dissociation between the two. For example, demyelination of the lateral funiculus may cause loss of only vibration sense. The reverse, that is loss of position sense with preserved vibration, has been reported in lesions of the parietal lobe. It has also been reported in some lesions of the brainstem. This loss of position sense in parietal lobe lesions may cause athetosis like movements on eye closure.

**(2) (A)**

***Explanation :*** This constellation of symptoms is not possible from an anatomical point of view. Thus, this is classical of non-organic sensory symptoms or malingering. This combination of symptoms is called SHOT (sight, hearing, olfaction, touch) Syndrome

**(3) (B)**

***Explanation :*** The history of this patient is suggestive of emotional or mimetic facial palsy. The facial palsy is apparent only during emotional movements and not during volitional, wilful movements. This is a rare syndrome due to involvement of thalamus, usually infarction. This normal voluntary facial movement with palsy apparent only during emotions is called dissociated facial weakness. Of course, such weakness will always be of the UMN type.

**(4) (A)**

***Explanation :*** This pattern of visual field loss is called junctional scotoma. This is due to compression of one optic nerve near the chiasma, which also affects the inferior nasal fibres from the opposite eye. That is why there is superior temporal field defect in the opposite eye. Heteronymous scotoma is scotoma on opposite sides in the two visual fields, like scotoma of temporal fields of both eyes.

**(5) (C)**

***Explanation :*** On exposure to bright light, there is brisk constriction of pupil, followed by slight dilatation. This is said to be a normal phenomenon, but may be exaggerated in early optic nerve disorders.

**(6) (B)**

***Explanation :*** This phenomenon of increasing eyelid closure with jaw opening is called Inverse Marcus –Gunn phenomenon. This is a very rare phenomenon and some congenital cases have been reported. The exact neural mechanism of this phenomenon is unknown. Some authors say this is a synkinesis between 5$^{th}$ and 3$^{rd}$ nerve (LPS) and others opine that the synkinesis is between 5$^{th}$ and 7$^{th}$ nerve (orbicularis oculi).

Marcus gunn phenomenon: elevation of eyelid (usually one side) with jaw opening

Marcus Gunn pupil: relative afferent pupillary defect

Gunn's sign: hypertensive changes in retinal vessels seen on ophthalmoscopy

# Journey of Tuberculosis Control Programme : NTP to NTEP

*From Archive*

96 J. INDIAN M. A., VOL. 54, NO. 1, JANUARY 1, 1970

### Coagulation Studies in Women with Intra-Uterine Contraceptive Device (I.U.C.D.)

Singh, G., Kaur, S. and Sharma, S. D. (*J. Obstet. Gynaec. India*, **19**: 593, 1969) from Department of Pathology, Dayanand Medical College, Ludhiana and Family Planning Centre, Sector-22, Chandigarh, write:

One hundred and thirty-three cases who came for I.U.C.D. insertions were investigated for coagulation mechanism status prior to insertion.

The only abnormanity detected was the positive Hess test in 11 cases the results of the rest of the tests were all within normal range.

Out of 111 cases, who came for I.U.C.D. insertion, 19 showed markedly increased menstrual periods or menorrhagia. Out of these, 9 had positive Hess test even prior to loop insertion (47·4 per cent).

Use of Hess test as a screening procedure is suggested.

### Genetics and Laws Prohibiting Marriage in the United States

Farrow, M. G. and Juberg, R. C. (*J. Amer. Med. Ass.*, **209**: 534, 1969) from the Genetics Laboratory, Department of Paediatrics, West Virginia University, Morgantown, write:

Laws prohibiting marriage in the 50 states, the District of Columbia, and two territories have been classified as those inclusive for categories of lineal and collateral relatives, and those specific for lineal, collateral, and affinous relatives. A person may not marry a parent, grandparent, child, or grandchild except in Georgia, where a man is not prohibited from marrying his daughter or grandmother. While all political units prohibit marriage between a person and a sibling, an aunt, or an uncle, their prohibitions vary considerably for other degrees of collateral relationship. The uncle-niece marriage is not prohibited in Georgia and among Jews in Rhode Island. Generally, marriage between persons with a coefficient of relatedness equivalent to first cousins or closer has been prohibited. Fewer than one half of the political divisions have prohibitions regarding affinous relatives.

## CURRENT TOPIC

## Tuberculosis Programme as an Integral Component of the General Health Services

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#### Tuberculosis as a Problem of Suffering A Sociological Study

A sociological study (Banerji and Anderson, 1963) of the problem of tuberculosis in a rural community in South India revealed that, motivated by the suffering caused by the disease, more than half of all the infectious cases had sought treatment at different health institutions—primary health centres, dispensaries, clinics and hospitals; about a quarter of them was found to be 'worried' by the suffering and most of the remaining cases were 'conscious' of the symptoms of the disease.

A survey of the rural health institutions in this community revealed that most of the patients who visited them were not even diagnosed as cases of pulmonary tuberculosis, for the few who were diagnosed as a case, there were virtually no facilities to offer them the treatment.

#### A Felt Need Oriented Tuberculosis Programme as an Integral Part of the General Health Services

*Basic postulates*—The following findings led to the formulation of the two basic postulates of India's National Tuberculosis Programme: First, as already a very large number of patients are actively seeking treatment at various health institutions, top priority is to be given in the national programme to provide services to those who have a felt need, i.e., it should be a felt need oriented programme.

Secondly, as those who have felt need seek treatment at health institutions, tuberculosis services should be given as an integral part of the health services provided at different institutions. A series of operational research investigations were conducted to work out the details of such a felt need oriented programme as an integral part of the general health services (Banerji, 1965; Bordia, 1967; Baily *et al.*, 1967). Some of the major premises of the programme are: (a) Cases of tuberculosis can be diagnosed at rural health institutions by examining by microscopy sputum from those who come to health institutions with a complaint of chronic cough (Banerji, 1965). These findings, incidentally, confirmed the forecasts that were made on the basis of the sociological investigations: at least one out of every twenty-four persons reporting with chronic cough at health institutions in a sputum-positive case of pulmonary tuberculosis. (b) Domiciliary treatment of the diagnosed cases from near-by centres can give reasonably satisfactory results (Banerji, 1965). (c) Facilities for diagnosis and treatment of tuberculosis cases, including keeping of certain basic records, can be developed within rural health institutions by making marginal investment (Bordia, *loc. cit.*; Baily *et al.*, *loc. cit.*). (d) Services of specialised tuberculosis institutions at the higher levels (tuberculosis clinics, sanatoria, hospitals having chest surgery units, etc.) can be made available to the rural health institutions. This can enable them to refer the more complicated cases to them for getting additional facilities for diagnosis and treatment. (e) At the district level (covering a population of a million and a half), provision can be made to have a district tuberculosis centre. Besides providing referral facilities to the peripheral institutions within the district such a centre can be provided with trained staff (Bordia, *loc. cit.*) to carry out also the functions of planning, organisation, coordination, training and supervision of all tuberculosis work at various institutions within the district. The district tuberculosis centre can also maintain a tuberculosis case register for the entire population of the district. (f) As a step towards integration of the BCG campaign with the general health

# Journey of Tuberculosis Control Programme : NTP to NTEP

From Archive



services, BCG teams can be attached to district tuberculosis centres so that, apart from doing inoculation work, these teams can also participate in other activities of the tuberculosis programme, for instance, retreival of treatment defaulters. (g) There can also be a State tuberculosis centre, covering, on an average, population of about 30 million. Meeting the training requirements and evaluation of the tuberculosis programme in the State can be two of its special functions.

## Advantages of an Integrated Tuberculosis Programme

### Administrative advantages:

*Cost of the services*—In term of requirements of personnel, equipment and funds, cost of diagnosis and treatment of a case through an integrated programme is a small fraction of what it costs through specialised tuberculosis programmes in rural areas (Banerji, 1967).

*Balanced growth with the general health services*—One great advantage of an integrated tuberculosis programme is that even with very modestly developed health services, it is possible to build into it a tuberculosis programme. Later on, as more and more resources are funnelled in to strengthen the 'infrastructure' of the health services, it automatically strengthens the tuberculosis programme (Baily *et al*., *loc. cit.*). Growth of the tuberculosis programme thus becomes a function of the growth of the general health services.

On the other hand, a specialised tuberculosis programme grows by depriving the general health services of the resources that are badly needed for its growth. This is particularly so in developing countries where there is an acute scarcity of resources. Also, as mentioned earlier, in terms of cost of diagnosis and treatment per case, it gives very poor returns from the investment.

*Increased organisational effectiveness*—Integration of a tuberculosis programme also increases the effectiveness of the health organisation (Baily *et al*., *loc. cit.*) e.g., development of tuberculosis work leads to mobilisation of 'unutilised capacity' of the organisation. Use of the microscope for tuberculosis work may stimulate its use for diagnosis of other conditions, e.g., eosinophilia. Development of channels for referring of the causes who need specialised services at the district and State levels lead to more effective utilisation of these services.

### Sociological consequences:

*Providing a sociological basis for allocation of efforts*—Dealing with tuberculosis as a problem of suffering, side by side with the suffering caused by other health problems, ensures that investment of efforts for tuberculosis work broadly conforms to the importance attached to the disease by the community.

*Better acceptability*—Dealing with those who have felt need ensures better acceptance of the treatment.

*Effect of meeting the felt need*—Provision of reasonably efficacious services to those tuberculosis cases who have a felt need may, by itself, 'generate' felt need among those who are at present merely 'worried' or are 'conscious'. In this way a felt need oriented programme has a potential for including as many as 95 per cent of all infectious cases in the community (Banerji and Andersen, *loc. cit.*). Dealing with the felt need of millions of cases through a nation-wide network of thousands of health institutions can inspire confidence in the community and stimulate its active participation in other health and social development activities.

### Epidemiological implications:

In countries where the incidence of the disease has declined, factors other than a specific tuberculosis programme have played a dominant role (Dubos and Dubos, 1958; Grigg, 1938). Dubos and Dubos (*loc. cit.*) attributed it to a general rise in the standard of living in these countries; Grigg (*loc. cit.*) went a step further and claimed that mere exposure of a population to the tubercle bacillus over a period of time would lead to a decline in the incidence by a natural weeding out of the susceptible population. Some indirect evidence (Banerji, *loc. cit.*) of dealing incidence of the disease due to such nonspecific factors is also available with regard to the epidemiology of the disease in India, e.g., similar rates of prevalence in rural and urban population, higher prevalence rates among the upper age-groups, comparatively lower virulence of the Indian strains of *M. tuberculosis*, etc.

Therefore, launching of an extensive tuberculosis programme on the presumption that this alone can reduce the 'pool of infection' appears to be untenable even on epidemiological grounds; at best, it can only reinforce the nonspecific factors that are bringing about a decline in the incidence. On the other hand, when such a programme grows as a function of the overall growth of the general health services, this growth of the programme is justified primarily by the pressure of the felt need for such services in the community; the contribution of such a programme (which is capable of covering some 95 per cent of the infectious cases) to the decline of the incidence of the disease can be regarded as an additional and a valuable by-product.

## Summary

Sociological investigations have revealed that more than half of all infectious cases in rural areas seeks relief at various health institutions and that as many as 95 per cent of them are conscious of the symptoms of the disease. These findings lead to the formulation of a felt need oriented tuberculosis programme as an integral part of the services that are offered at the rural health institutions. Specialised tuberculosis institutions at the higher levels lend support to them by offering them referral facilities. For a population of a million and a half, there is a district tuberculosis centre to give them administrative support.

Such an integrated programme is not only very economical, but it also grows along with the general health services. Its orientation to felt need makes it more acceptable. It also has a potential for covering some 95 per cent of the infectious cases in the community. This indicates that, as it grows, it can have an impact on the incidence rates of the disease.

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## Comments :

**Dr Supriya Sarkar**

***MD (Resp Med), FICP, Professor & Head, Department of Chest Medicine, College of Medicine &Sagore Dutta Hospital, Kolkata 700058***

Sir, — Our fight against TB started with prayers and rituals, then isolation in sanatorium and then by surgery. Following the discovery of streptomycin (SM) by Wakesmann in 1944 the anti-TB chemotherapy started. Subsequently para-amino salysillic acid (PAS) followed by ethambutol (ETB) were added as companion drugs. Anti-TB chemotherapy was divided into intensive phase (for killing bacilli) and continuation phase (for prevention of relapse). With the discovery of rifampicin (RIF) and reintroduction of pyrazinamide (PZN) the *short course chemotherapy* (SCC) started. SCC is based on conceptual division of tubercular bacilli into i) rapidly multiplying bacilli (can be killed by all bactericidal drugs), ii) bacilli having intermittent spurts of growth (only RIF is effective), iii) intracellular bacilli in acid medium (PZN is effective) and iv) totally dormant bacilli (no drug is effective).

In India, *National Tuberculosis Control Program* (NTP) was started in 1962 aiming the control of TB with 5 drug regimes. In 1983, SCC was incorporated in NTP. In 1992 NTP was reviewed and was found to be a failure with only 30% case detection rate and out of them only 30% were treated successfully. Overall, with introduction of anti-TB chemotherapy the death rate was reduced and cure rate was improved substantially. But the *epidemiologically significant pool* that spread the disease remained unchanged to around 20%. More importantly, wild bacilli were replaced by drug resistant bacilli. Plethora of factors were thought to be responsible for NTP failure including more stress on radiology for diagnosis of TB, lower case holding rates, irregular drug supply, non-compliance etc.

Consequently, a change of NTP became inevitable and *Revised National Tuberculosis Program* (RNTCP) was conceptualized. In 1993 DOTS (directly observed treatment short course) pilot projects were undergone and gradually entire country was covered under RNTCP in March 2005. In RNTCP intermittent chemotherapy was prescribed based on the concept of "lag period", the time taken by the bacilli to recover and grow after cessation of exposure to a particular drug. Regimes prescribed are Cat I – for new seriously ill TB, Cat II – for older TB, Cat III – for new less serious TB and Cat IV – for drug resistant TB. Subsequently Cat III was withdrawn.

In 1993, world health organization (WHO) declared TB as *Global Emergency*. WHO guideline (2010) seriously questioned the usefulness of intermittent chemotherapy. WHO recommended daily regime and addition of ETB in continuation phase, particularly in countries with high initial INH resistance. After some initial delay and denies, RNTCP accepted WHO guideline and switched over to daily regime and added ETB as a third drug in continuation phase.

With the discovery of *molecular diagnostic tests*, WHO recommended cartridge based nucleic acid amplification test (CBNAAT) as point of care test (POCT) and line probe assay (LPA) for referral laboratory. Accordingly, RNTCP included molecular diagnostic tests. After initial CBNAAT testing of clinical material, TB cases are now classified into RIF-sensitive and RIF-resistant cases. RIF-sensitive cases are to be tested with 1st line LPA to detect INH and RIF resistance. RIF-resistant cases are to be tested with both 1st and 2nd line LPA to detect in addition the resistance to fluoroquinolone and injectable drugs. Two new drugs, Bedaquiline and Delaminidin, have been incorporated in RNTCP for use in drug resistant TB. Recently, 4 regimes are recommended in RNTCP i) regimen for drug sensitive TB, ii) regimen for isolated INH resistant TB, iii) longer all oral regime for drug resistant TB and iv) a shorter MDR-TB regimen.

We can analyse *the failure of NTP* in light of article published in JIMA 1970 January by Dr. D Banerji (Cornell). NTP was based on several assumptions.

*Passive case finding* based on the fact that large population of TB symptomatics seek treatment at various health institutes. We had limited resources available at that time. But TB still carries a social stigma and many TB symptomatics went to alternative treatment. Now, active case finding has been incorporated in RNTCP. The assumption that those who came by themselves would complete treatment was proved wrong. Patients came for symptoms and as expected they stopped treatment after relieve of symptoms (usually after 2-3 months). RNTCP is based on the concept of DOTS, treatment under supervision.

*Integration of TB program* with general health service made the importance of our fight against TB diluted as for example funds for NTP get diverted to other health services. As TB is a slow killer it draws less attention and more importance is given to rapidly killing diseases by health care system and media. Moreover, little stress has been given to TB in our MBBS curriculum. Recently government of India give more emphasis and separate budget for TB has been allotted.

*Domiciliary treatment* is based on the legendary Madras Chemotherapeutic Centre trial with small sample size, and it may not be accepted in current standard. As a result TB sanatoriums were closed. The lack of isolation might have enhanced the spread of TB in community, particularly in immuno-compromised persons. Nosocomial TB is now a recognized entity. Nowadays RNTCP proposed to open PMDT (Programmatic Management of Drug-resistant Tuberculosis) wards in medical colleges.

Diagnosis based on *sputum microscopy* has its problem particularly non-availability of samples in elderly, children, very ill patients and in extra-pulmonary TB. Even in pulmonary TB sputum positivity is found in less than half of the cases. RNTCP has incorporated molecular diagnostic tests for better diagnosis of TB and simultaneous detection of drug resistance.

In May 2012, Government of India has declared TB a *notifiable disease*. In 13th March 2018 our Prime Minister set a goal to *eliminate TB by 2025*, 5 years ahead of global target. In that direction RNTCP has been renamed as *National Tuberculosis Elimination Program* (NTEP) on 30th December 2019. The goal can only be achieved with active participation of all Indian citizens. We should actively participate in this sincere attempt by our Prime Minister, so that our next generation will not be subjected to the scourge of TB.

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# Letters to the Editor

*[The Editor is not responsible for the views expressed by the correspondents]*

## High Fibrinogen Level in Patients with Type 2 DM and Ischemic Cerebrovascular Accident — An Experience From A Tertiary Care Hospital of Eastern India

***JIMA, Vol 118, No 2, February, 2020***

Sir, — It has been correctly pointed out that plasma fibrinogen should be considered for screening program to identify people at high risk of vascular events.

The study has not elaborated the definition based on which, diabetic subjects were selected. Stress hyperglycaemia has not been ruled out also.

Glycated haemoglobin ($HbA_1C$) level estimation in these patients would have further helped to study the effect of chronic hyperglycaemia on fibrogen levels further.

The author has also rightly stated that the limitations of this study is the inability to rule out other causes of hyperfibrinogenemia.

MBBS, MD (Gen Med), MACP, **Dr Tanuka Mandal**
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## Outcomes of the tunnelled venous catheters for maintenance hemodialysis : an experience from Eastern India

***JIMA, Vol 117, No 12, December, 2019***

Sir, — I have reviewed the article. This is an interesting prospective observational study conducted at a tertiary care hospital, to evaluate outcome of right internal jugular vein (IJV) tunnelled venous catheter (TVC) in maintenance Hemodialysis (MHD) patients. Considering the fact that a good vascular access is life line of MHD patients and timely creation of arterio- venous fistula (AVF) is a major problem in country like India; Rt IJC TVCs should be more often utilized and explored. As an HD access, TVCs has several advantages over non tunnelled venous catheter (NTVC) and obviously better option in MHD patients with poor prospects for AVF. The article is generally well written and structured. However, I would like to put some questions to author like-

Whether C-Arm was used during the TVC placement.

Any special observation about TVCs in paediatric population; regarding complications and any difference from adult study population.

Is there any relation of TVCs related complications with no of HD sessions per week?

Whether prophylactic antibiotic lock was used in study population.

Though there are number of studies of TVCs, experience and report from eastern India is scarce and this study may add new information regarding is underutilised vascular access to treating physician. The study would have been more complete if bio film assessment and venography would have been done.

Consultent Nephrologist **Dr Koushik Bhattacharjee**
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## Prevalence of Autoantibodies in patient complaining of multiple joint pain in a tertiary care hospital

***JIMA, Vol 118, No 1, January, 2020***

Sir, — The authors showed the prevalence of auto-antibodies like ANA, RF and dsDNA in apparently healthy population with multiple joint pain. These patients are not categosized as active rheumatoid disease and non rheumatoid arthritis groups. No immaging studies as well as other tests like CBC, ESR, CRP, uric acid of the patients have been performed to classify the disease category and disease activity. There fore the corelation of these auto-antibodies with different arthritis /arthralgia are not well evident. They have observed that more females than males (22.42% versus 8%) had RF but in conclusion they mentioned "Further, RF was associated with gender as it was prevalent more in males compared to females." just opposite.

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Diamond Harbour 743331

## Relationship of neck circumference with metabolic syndrome

***JIMA, Vol 117, No 9, September, 2019***

Sir, — Salam Ranabir *et al*[1] have wonderfully pointed out the relationship between Neck circumference and Metabolic Syndrome. They have shown that "Measurement of NC is a simple, time saving and least invasive measurement tool to identifymetabolic syndrome risk factors in patients[1]." The landmark NIDDK Sleep Extension Study[2] has also shown that Greater NC is associated with Obstructive sleep apnea syndrome and metabolic syndrome in short-sleeping obese men and premenopausal obese women. It was noted that Addition of NC to the definition of metabolic syndrome should be considered and needs to be validated in future studies[2]. Girish Mathur *et al*[3] have also concluded that Neck Circumference can be used as a sensitive tool for metabolic syndrome and cardiovascular risk factors.

I would like to ask the authors regarding the large proportion of patients with cerebrovascular accident (CVA) (42.8% of the study population) included in the study. Was the study done in a neurology ward and won't the high proportion of CVA patient result in selection bias in the study ?

1 Lalrinfela H, Ravi Nishad, S Bhagyabati Devi, Robinson Ningshen, Ningthoukhongjam Reema, Salam Ranabir. Relationship of neck circumference with metabolic Syndrome. JIMA, Vol 117, NO 9, September 2019.

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**Press Release : 10.03.2020 : New Delhi**

## IMA appeals to halt the panic epidemic

INDIAN MEDICAL ASSOCIATION appeals to the nation to stop the panic reactions on corona epidemic. This epidemic by no means is a situation which has not been faced earlier. SARS 1, Swine flu, Nipah etc were on the same scale and considerable experience tells us that awareness, self precautions, contact tracing and self isolation are the Public Health measures required. Hand washing has emerged as the simple tool to fight the community spread. Easy and universal, the practice of thorough hand washing with soap and water is perhaps the only way to stop the corona epidemic. Masks for symptomless common people is not warranted. Healthcare workers and people with symptoms and possibility of droplet infection need to wear masks.

IMA appeals to the Government to classify the data of the epidemic and take appropriate action with clinical precision. Sharing of data on daily basis with the public who are clueless as to what is expected out of them, has created the panic across the country.

Doctors and Health care personnel have responded with diligence and responsibility. Hospitals are open and functioning. Doctors and hospitals remain a silver lining in otherwise clueless situation for the common man. IMA appeals to every doctor to function as a source of credible information in their locality and instill confidence and trust.

It cannot be denied that the high handed top down response in China is part of the reason for this global panic. The nuanced and balanced approach of the Indian Government is certainly better suited to handle the crisis in a country of 1.3 billion people. The Public Health systems in various states have withstood the pressure and have to remain alert. Contact tracing is the key public health function that will make a difference.

Indian Press and visual media have a big role in de escalating the panic. Their restraint and objectivity will save the day. Unbridled social media is both an asset and liability. However the Central Government has adequate powers to curtail disinformation and should use the same judiciously.

1. Self Hygiene: wash your hands with soap and water as often as deemed necessary.

2. Self restraint: Do not post unconfirmed negative messages and pseudoscientific dogmas.

3. Self isolation: Self isolation was our survival strategy in yesteryears against waves of smallpox. If you are symptomatic with fever and cough isolate yourself at home.

IMA works in consonance with the Health authorities in all states. IMA has updated the doctors in all its branches across the country. IMA is in advanced state of preparations for a 24X7 Helpline for the public in Hindi and English. The details will be in public domain shortly.

IMA is organising a National Workshop (both live and in web )on Saturday 14.03.2020 at IMA Hqs, New Delhi for its members. IMA also request the Government to utilise COVID-19 opportunity to track cases of Tuberculosis and also to include hand hygiene in Swachh Bharat programme.

Let us work together as a nation to redeem our people. Let each one of us contribute to de escalate the panic across the country.

| | | |
|---|---|---|
| **Dr Rajan Sharma** | **Dr K K Aggarwal** | **Dr R V Asokan** |
| National President IMA | IMA Resource Person | Hony Secretary General IMA |

**2nd State Presidents and State Secretaries Meet - Kanyakumari**





Thrissur - World Glaucoma Week


Coimbatore - Corona Virus Awareness programme

AKN Sinha Institute - BLS

Chikkamagaluru - CME

Ramgarh, Jharkhand.- Mission Pink Health Programme

Samastipur - Annual Conference

Begusarai - Bihar State Conference

Nagpur - OBs Meeting

Hyderabad Airport Branch -CME

Thalassery,- Corona Virus Awareness

Kottakkal - CME

North Parur- International Women's Day Celebration

Ramgarh, Jharkhand.- Mission Pink Health Programme

Courtesy Visit to Maharshtra Chief Minister


Behala - International Women's Day

Kerala State - On Corona Screening

Recognition for IMA Patient Care - Kerala

Pune - National Conclave on Healthcare & Quality

Pune - ITCON

Sulthan Bathery - Medical Camp


Calcutta Branch - Women's Day Celebration

Holi Utsav at IMA HQs.

**When to suspect? Febrile illness beyond 5 days, especially with multi-organ involvement**

Adult mite on a pinhead: CDC website

Vector borne disease

**Vector**

Trombiculid mite (adult does not bite)
Larva (chiggers): bites humans
Chiggers: In grasses and low lying vegetation
Attach to exposed skin for blood meal

Incubation period: 7—10 days

Bamboo bush: preferred site of chiggers in tropical areas

Field rodents: natural reservoirs

**Organism**

- **Orientia tsutsugamushi**
- **Gram negative intracellular organism**
- **Five major serotypes**

**Symptoms:**

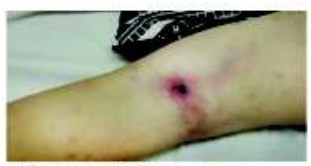
- Fever, rash
- Lymph-adenopathy
- Headache
- Myalgia
- Encephalitis
- Hepatitis
- AKI, ARDS

**Scrub Typhus: The new Epidemic**
Rudrajit Paul and Prof Jyotirmoy Pal
Issued in public interest by JIMA

**Diagnosis:**

- IgM antibody (IFA)
- Weil-Felix test (Titer >1:320)
- Cell culture (4 weeks)
- PCR

**No Vaccine**



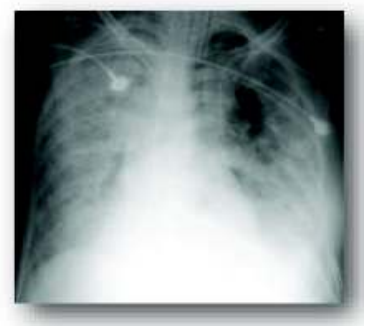
Eschar: The clue to diagnosis

More in rainy season but may occur throughout the year

**Treatment**:
Doxycycline: 100 mg BD (oral or iv) at least 7 days…may be used in all ages, avoid in pregnancy

Azithromycin: 500 mg OD for 5 days..avoid in CNS disease

Chloramphenicol, Rifampicin



CXR: ARDS in scrub typhus

**Control of vector: -**
Clearing of vegetation
Clothes smeared with insect repellant, especially in lower limbs
Spraying of residual insecticides

# Two Feathers in the Cap of Team JIMA in 2019

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