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Editorial

Novel Corona Virus : New Threat to Mankind

Prof. (Dr.) Jyotirmoy Pal
MD, FRCP, FRCP, FICP, FACP, WHO Fellow, Hony. Editor, JIMA

With the end of 2019 & dawn of 2020, a new threat in the form of novel Corona Virus has inflicted upon our World, which has been claiming lives incessantly.

History of viral diseases can be traced to twelve thousand years back. Research on Infectious Disease got momentum after the work of Louis Pasteur on Germ Theory in the 19th Century. After the discovery of Tobacco Mosaic Virus in 1892, at least three lakh viruses has been isolated as a causative agent of diseases in human beings. Lethal viruses are mostly zoonotic, against whom the human beings are least immune to. 20th Century Medical Fraternity concentrated mainly on Bacterial diseases and development of Antibacterial Agents. But from the end of 20th century, there have been a surge of viral diseases with high mortality and morbidity like - Dengue, Ebola, HIV, Zika, Avian Influenza, Corona, etc.

Rapid urbanisation, deforestation along with contact with animals which harbour the different viruses as a reservoir, have resulted in humans being the accidental host of these viruses. Even during evolution, human beings were not exposed to these viruses. So having less immunity and lack of research on antiviral agents have led to multiple viral epidemics all over the world.

Corona virus was first recognised in the mid sixties. Only four strains were identified which caused mild diseases like cough, sore throat, malaise and fever. In 2002, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), a new strain of Corona Virus was identified in China which spread to the East Asian countries claiming the lives of nearly 900 individuals. In 2012, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), another new strain of Corona Virus was identified in Saudi Arabia with a higher mortality rate than SARS taking a toll of 750 lives.

In 2019, December, another strain of Corona virus isolated from Wuhan, China. The never before identified strain of Corona virus in man, was named as novel Corona virus (2019-nCoV). The infection caused has now been named as Coronavirus Disease 2019 (COVID-19).

As on 11th February, as per WHO Bulletin, 43,103 confirmed cases (395 cases from outside China) with 1,018 deaths. 24 countries including India has reported confirmed cases of COVID-19. India, till now has reported 3 cases from Kerala, all of whom had travel history from China.

There is controversy regarding source of this new virus which may be animal, snake or bat. Mode of transmission initially thought to be animal to human, but possibly virus is spreading by large droplets, fomites or aerosols. Although the initial presentation is usually with Flu like symptoms, rapid deterioration occurs with development pneumonia and Acute Respiratory Distress Syndrome (ARDS), often resulting in death. Older people, and people with pre-existing medical conditions (such as asthma, diabetes, heart disease) appear to be more vulnerable to becoming severely ill with the virus but the virus has been reported in as early as 30 hour old baby. There is no scientifically proven antiviral drug available till date and only a few sporadic case reports on protease inhibitors has been described. There is urgent need a Randomised Controlled Trial (RCT) or meta analysis to prove the efficacy of these drugs.

Though India till now not affected much, but Indian Government and State and allied health authorities responded in robust manner to contain possible epidemic. Indian citizens in those affected provinces had been brought back to India and health check-up and quarantine done properly. India issued Health advisory on 17th January, 2020. Testing facility was put in NIV, Pune. High alert measures (health cheque up, thermal screening, quarantine etc) taken on all possible import sites . India is taking also leading role to help neighbour countries giving technical assistance to combat the crisis.

The impact of Coronavirus infection in world economy may be more than during SARS. During SARS, China only had share of 4% world economy which has increased to 16% - making it the 2nd largest economy of World .So if China sneezes, world will have cold. China's trading has almost extended all over world. World's leading companies are dependent on Chinese suppliers- whether it may be electronics, automobile, pharmaceuticals, mobile and so on. In 2018-19 India have 14% import from China & 5% export to China. In India one of the major effect may be on pharmaceutical industries. Raw material in this sector usually imported from China. So if this situation continues, there will be deficit in supply chain. So production of medicine in India and pricing may be negatively attached.

One question frequently asked is - whether virus can be transported with Chinese Goods? Although WHO has clearly denied the rumour, the concept may have adverse impact on trading in South East Asia particularly.

Emergence of COVID-19 has raised fear and concern across world. Whether it will emerge as Pandemic like Plague, Influenza or will be endemic like Dengue, Chikungunya is matter of concern. WHO shown knee jerk reaction to declare the epidemic as a Public Health emergency of international Concern on 30th Jan, 2020. This happened just before the Chinese New Year, the time when maximum tourists visit China to celebrate, festival- raising concerns regarding rapid spread the disease across the World.

In one hand discovery of effective drug/vaccine and other hand method to control spread need to be developed at the earliest. Cordon sanitaire in Hubei Province adopted by Chinese Govt may be controversial from Human Rights point of View.

Preventive measures in low income countries and in countries with huge population like India, Brazil is a challenge. So need to understand biology of the virus properly. Government and private agencies should work together and spend more money towards research and it should be transparent and with proper data sharing among all. Identification of the source, mode of transmission, incubation period, host factor, pathogenesis can only help in planning proper prevention and treatment. Otherwise unscientific steps will be taken by a panicked Government that will only create more catastrophe in terms of treatment and Human Rights.

Review Article

Lipid Management in Indian Scenario

Saumitra Ray[1]

Dyslipidemia has been established as the most important modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD). In the INTERHEART Study published in 2004, of the nine modifiable risk factors found to contribute to 90.4% of all heart attacks[1].

This is highly significant as this emphasized the role of HDL cholesterol as represented by Apo A1 besides more commonly established role of LDL cholesterol as represented by Apo B. This is particularly relevant for India as it has been found that in India dyslipidemia is more often characterized by high triglyceride (TG) and low HDL cholesterol than by high LDL cholesterol. In the India Heart Watch Study of 6123 people, it was found that among Indian men TG more than 150 mg/dl in 41.2%, HDL below 40 mg/dl in 34.1% and LDL above 130 mg/dl in 16.3% of population. The corresponding values for women were 31.5%, 53.1% (HDL below 50 mg/dl) and 15.1% respectively[2].

Overall, in urban India the prevalence of dyslipidemia is 25-30% whereas that in rural India is 15-20%[3]. In the Jaipur Heart Watch Study, it was found that over last two decades, the hypercholesterolemia prevalence remained relatively unchanged at 25% whereas that of hypertriglyceridemia increased from 25% to 33%.

In people with established ASCVD in India, the mortality varies directly in proportion to blood cholesterol level. With value below 200 mg/dl, the mortalities in terms of per 1000 person years in below 50 years age group is 5.4, in 50 to 59 years 23.8 and above 60 years 76.9. The respective values become 19.8, 38.5 and 12.6 when blood cholesterol level is 200 to 239 mg/dl and the corresponding values become 17.4, 39.8 and 108.2 for blood cholesterol level above 240 mg/dl.

A disturbing trend in India is the high prevalence of coronary heart disease (CHD) in younger population. In India it has been recommended to screen for ASCVD to all at age of 20 years or college entry[4]. As pharmacological intervention for elevating HDL to improve clinical outcome has so far been met with frustration and lowering of TG causes debatable clinical benefits, the focus remains to reduce LDL. In very high risk population with known ASCVD or with diabetic people with end organ damage or multiple additional risk factors and in familial homozygous hypercholesterolemia, the target for LDL is below 50 mg/dl. In high risk people as characterized by 3 or more ASCVD risk factors, diabetes, familial heterozygous hypercholesterolemia, advanced chronic kidney disease, LDL above 190 mg/dl, coronary artery calcium score (CAC) above 300 A, carotid plaque or Lp(a) above 50 mg/dl, the target LDL is 70 mg/dl. In moderate risk people with 2 ASCVD risk factors, CAC 100 to 299 A, increased carotid intima media thickness, Lp(a) 20 to 49 mg/dl or metabolic syndrome, the target is 100 mg/dl.

In Indian set up, particularly in the public health care system, it is prudent to screen for lipids in nonfasting state as most patients attend hospital clinics in fed state, especially with the fact that only TG varies with prandial condition in any significant way.

A moderate to high intensity statin is required to reduce LDL by a meaningful amount in majority of the patients. If the highest tolerable dose of statin does not reduce the LDL to the target level, ezetimibe should be added and tried for at least 6 weeks before deciding whether evolocumab is required to achieve the target LDL. As the benefits of evolocumab appear late, the patients must be primed to take the injections for long term before initiating. The cost burden must fully be explained to the patients. In younger people with recurrent acute coronary syndromes, LDL should be brought down more aggressively and more quickly.

Fenofibrate is the drug of choice if initial TG is above 500 mg/dl. Otherwise, TG should be reassessed after correction of LDL and excluding hyperglycemia, hypothyroidism, nephrotic syndrome and effects of drugs and alcohol. If TG is still above 150 mg/dl, then addition of fibrate to statin is considered. Saroglitazar significantly reduces TG levels, but lacks data from RCTs in industrialized countries[5].

In conclusion, as Indians are prone to premature ASCVD, early aggressive detection and treatment of risk factors, with special focus on dyslipidemia, is urgently needed.

Conflict of Interest : None

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Review Article

Familial Hypercholesterolemia (FH) — Importance of General Awareness and Early Diagnosis

Raman Puri[1], A Muruganathan[2], Rashmi Nanda[3], Rashida Patanwala Melinkeri[4]

Familial Hypercholesterolemia (FH) is an autosomal dominant disease characterized by severely elevated serum low-density lipoprotein cholesterol (LDL-C) leading to premature atherosclerotic cardiovascular disease (CVD). The homozygotes develop CVD in their teens. The contribution of FH to premature cardiovascular disease in India is unknown. The heterozygous (HeFH) phenotype is encountered most often (1 in 250-500) whilst the rarely encountered homozygous (HoFH) pheno-type has a worse prognosis (1 in million). Considering the Indian population of 1.32billion, approx-imately 2.6 million cases of HeFH and 2500 cases of HoFH are estimated to be present.

The diagnosis of FH is based on biochemical values of total cholesterol & LDL-C, clinical findings of lipid stigmata, family history, and genetic testing. Early diagnosis is important for the prognosis of the patient and it also has implications for the family members who may have inherited the same disorder. A child or adult with FH requires life long medications under medical supervision. Keeping in mind the lack of awareness of FH amongst the medical fraternity and the general population, creating a registry may be an eye-opener to the incidence and prevalence of this entity in the Indian Society. LAI has taken an initiative to offer genetic studies to cases registered with LAI FH Registry at concessional rates.

[*J Indian Med Assoc* 2020; **118(2):** 12-5]

Key words **: Familial, Homozygous, Hypercholesterolemia, Registry, LAI awareness.**

One baby is born with familial hypercholesterolemia every minute. FH is underdiagnosed and undertreated globally. Over 90% of FH patients were characterized by the presence of cardiovascular disease at the time of death. Three out of four FH patients had experienced one or more myocardial infarctions prior to death. Classical risk factors were more prevalent in FH patients who died at a younger age.

Editor's Comment :

- **FH is a highly atherogenic disorder increases risk of CHD by 10-20-fold.**
- **LAI recommendations will help in early diagnosis of FH.**
- **Early diagnosis and aggressive LDL-lowering treatment will prevent premature CHD and patients with FH can potentially live a full life.**
- **There is a need to increase awareness among doctors and public.**

What is FH ?

Familial hypercholesterolemia (FH) is an inherited condition leading to severely elevated serum low density lipoprotein cholesterol (LDL-C) that leads to premature atherosclerotic cardiovascular disease (ASCVD) and accounts for 2–3% of the cases of myocardial infarction in patients aged <60 years[1].

What is the Cause of FH ?

It is caused by mutations in the genes of the LDL-R (LDL receptor), Apo B (Apolipoprotein B) or PCSK-9 (Proprotein convertase subtilisin/kexin type 9) that interfere with clearance of LDL-C by the liver[2]. Elevated circulating markers of vascular inflammation and endothelial dysfunction are present in children with FH, reflecting early atherogenesis.

What are the Types of FH and How Common are they ?

Clinically, the heterozygous (HeFH) phenotype is encountered most often (1 in 250-500) whilst the rarely encountered homozygous (HoFH) phenotype has much worse sequelae (1 in million)[3].

Considering the Indian population of 1.32 billion and the ratio of HeFH of 1 in 500 there will be approximately 2.6 million population of HeFH and 2500 cases of HoFh if the prevalence of 1 in one million is considered. Most of these patients are undiagnosed and are responsible for premature coronary artery disease in India.

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What are the Characteristics of Heterozygotes (HeFH) and Homozygotes (HoFH) ?

HeFH is seen when an individual inherits one mutant gene and is characterized by a 3–4-fold higher LDL-C concentration. Lipid stigmata including corneal arcus and tendon xanthomata can be seen and patients develop premature cardiovascular disease in their 4th decade, although women may develop these later. Untreated HeFH cases experience fatal or nonfatal coronary events in their 40s and 50s but can be readily treated with cholesterol-lowering medication in addition to lifestyle modifications[6]. In addition to statins, agents like bile acid sequestrants and cholesterol absorption inhibitors (eg, ezetimibe) may be required. In contrast, patients with HoFH inherit the defective genes from both the parents, have 4–8-fold higher LDL-C concentration as compared to the general population and they develop cutaneous stigmata and atherosclerotic cardiovascular disease in their teens[4]. LDL values in HeFH cases are generally between 350–550 mg/dl, whereas in HoFH, this value is between 650–1000 mg/dl. Ten-don Xanthomas are pathognomonic of FH, especially HoFH[5]. Accelerated atherosclerosis of the coronary, carotid, and lower limb arteries leading to cardiovascular diseases, recurrent transient ischemic attacks, strokes, intermittent claudication or gangrene is commonly seen at a younger age. Severe coronary artery disease requiring percutaneous interventions or coronary bypass sur-gery is common and the disease has high mortality in the second decade of life.

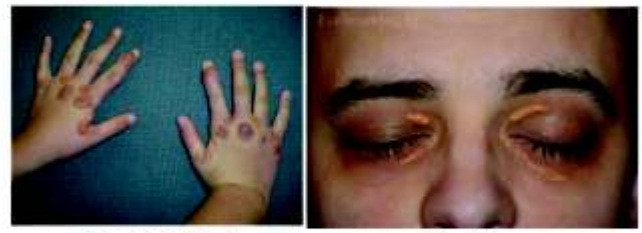
How do you Diagnose FH ?

Lipid Association of India (LAI) recommends the Simon Broome criteria for the diagnosis of FH be-cause of ease of applying and diagnosing cases based on the criteria. The Simon Broome Criteria takes into consideration total cholesterol and LDL-C concentrations, presence of tendon xantho-mata, presence of the family history of premature vascular disease and the total cholesterol & LDL-cholesterol concentration in the family members[7].

Typical Physical Findings (Stigmata) of FH :

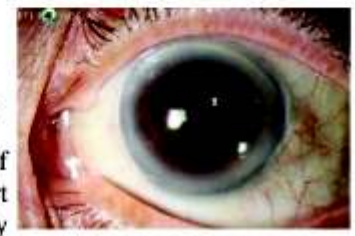
The clinical diagnosis of homozygous familial hypercholesterolemia is typically based on the pres-ence of cutaneous xanthomas before 10 years of age and an untreated low-density lipoprotein cholesterol >500 mg/dL. Interdigital xanthomas, particularly between the thumb and index finger, are pathognomonic for homozygous familial hypercholesterolemia.

Tendon xanthoma over ankle and elbows



Interdigital Xanthoma. Xanthelasmas

What is the Significance of Family History ?



Corneal Arcus

The family history of premature ischemic heart disease helps to identify an autosomal dominant mode of inheritance. If both parents have very high LDL-C (>190 mg/dL) and/or history of heart disease before age 55-65, this may suggest that they both have FH and can each pass a mutated gene to their children. When each parent has HeFH, by chance, 1 of 4 children will have a normal cholesterol level, 2 of 4 children will have HeFH and 1 of 4 children will have HoFH. LAI recom-mends Simon Broome criteria for the diagnosis of FH.

Simon Broome diagnostic criteria for Familial Hypercholesterolemia[8] :

Definite FH if the following are present —

• Total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL in a child less than 16 years or total choles-terol > 300 mg/dL and LDL-C > 190 mg/dL in an adult with tendon xanthomas or evidence of these signs in a first- or second-degree relative

OR

• DNA-based evidence of an LDLR mutation, familial defective Apo B-100 or a PCSK9 mutation.

Possible FH if the following are present —

• Cholesterol concentrations defined as above and at least one of the following-

• Family history of MI in a first-degree relative younger than 60 years or a second-degree relative younger than 50 years, or

• Family history of raised total cholesterol >300 mg/dL in an adult first- or second-degree relative or >260 mg/dL in a child, brother or sister aged younger than 16 years.

The Dutch criteria use a point system for LDL-C concentration, presence of xanthomata and pres-ence of CVD and a total score of over 8 is considered as definite FH and 6–8 as probable FH[9]. The US Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria uses age and relative-specific LDL-C concentration for diagnosing FH[10].

What is Cascade Testing ?

It involves performing the lipid profiles on the relatives of the "Index" patient. It helps in the identification of new cases and also in the institution of early therapy[11]. The index patient is diagnosed either clinically through history, physical examination, and a lipid profile or by molecular diagnosis. Subsequently, the cascade testing of the family can be carried out similarly using lipid profiles followed by molecular testing in those meeting the criteria for FH. Training health professionals in the construction of the genetic tree is an important aspect of cascade testing[11].

What is the Significance of Molecular Diagnosis ?

A diagnosis of FH can be confirmed by genetic testing. However, it should be understood by health care providers that failure to detect a mutation does not exclude a diagnosis of FH and interven-tion with lipid-lowering therapy is required even if the diagnosis is clinical. Remember to "Treat the Phenotype and Counsel the Genotype"[12]. Financial restrictions due to the additional expense of genetic testing to family's needs to be kept in mind.

What is the Management of FH ?

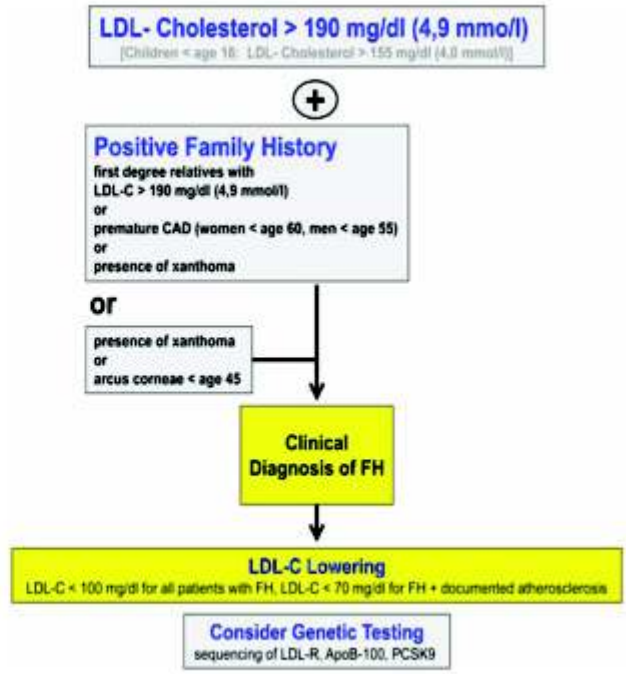
Lifestyle issues such as physical activities, dietary modifications, smoking cessation, alcohol restriction and stress management should be addressed and other ASCVD risk factors should be meticulously looked for and treated.

Statins at high doses is the mainstay of therapy. Other drugs like Ezetimibe may need to be added[4]. Bile acid resins are now available in India. Both mipomersen and lomitapide have the potential for use in HoFH[13]. Apheresis, a standard therapy in other countries is not easily available in India. PCSK-9 inhibitors lower LDL-C levels by up to 60% in patients already on statins and have been recommended in heterozygotes. Evolocumab (Repatha) is presently available in India though cost remains a constraint[14].

What are the Implications of Early Diagnosis ?

The diagnosis of FH is important not only for the prognosis of the patient but also has implications for the

Simplified Algorithm to Detect and Treat Individuals with high LDL-associated Genetic Risk



Ulrich Laufs, and Klaus G — Parhofer Eur Heart J 2015; 36: 3004-3006

family members who may have inherited the same disorder. The contribution of FH to premature CVD in Indians is unknown, mainly due to the lack of awareness of this condition among both health care providers and the general population.

Homozygous FH is a serious medical condition and is life-threatening if not treated at a young age, preferably beginning in early childhood. A child or adult with HoFH needs life-long medications and other specialized treatments to lower the LDL-C and prevent heart attacks. This requires the expertise of a lipid specialist.

What is the need for the Maintenance of a Registry ?

Keeping in mind the lack of awareness of the seriousness of FH amongst the medical fraternity and the general population, creating a registry may be an eye-opener to the incidence and prevalence of this entity in the Indian Society. We need to remember that FH contributes to premature coronary events. Timely intervention may help to reduce the existing and ever-expanding trend of cardiovascular disease amongst Indians.

LAI has taken the initiative to offer genetic studies to cases registered with LAI FH Registry at INR 5200 (Courier

charges extra).

The year 2020 will be dedicated to the FH awareness India campaign by the Lipid Association of India.

For further information or to join FH registry log on to lipid .net. in / call on 9871071919 or email at lipidaoi@gmail.com

LAI Recommendations :

- Lipid profile estimation of children to be done at 2 years of age in those with a family history of FH and premature ASCVD.
- Universal screening of lipids to be carried out at age 20 years or at the time of college ad-mission.
- LAI recommends the Simon Broome criteria for the diagnosis of FH.
- In an established case of FH, LAI recommends the estimation of Lp(a) levels.
- Genetic testing and cascade screening should be performed wherever feasible.
- Look for other ASCVD risk factors and manage them appropriately.
- Strict dietary recommendations and lifestyle modifications as advised.
- Drug therapy to be started at age 8 years or earlier in individualized cases.
- LDL-C targets to be achieved :<70 mg/dL for HoFH and <100 mg/dL for HeFH in children and in adults <50 mg/dL in HoFH and 70 mg/dL in HeFH or at least 50% reduction in LDL-C from the baseline.

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Original Article

A Study of Adverse Drug Reaction to First Line Antitubercular Drugs in DOTS

Palak Prajapati[1], Savita Jindal[2], Trupti Gadhavi[3], Vishakha Kapadia[4], Sanjay Tripathi[5]

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium Tuberculosis*. India has adopted and enforced Directly Observed Treatment Short Course (DOTS) strategy to combat TB. The first line medicines in DOTS are more effective and less toxic but still it cause adverse effects like gastritis, hepatotoxicity and skin allergies. This study is proposed to determine the occurrence of such adverse effects in patients under DOTS therapy and to assess their impact if any on patient compliance.

Objectives : (1) To study the demographic and clinical profile of patients diagnosed with TB. (2) To study the Type & Severity of Adverse Drug Reaction (ADR).

It was Prospective observational study done in duration of March 2018 to December 2018, in Patients who had tuberculosis on 1st line Anti Tubercular Treatment on the directly observed treatment short course (DOTS) enrolled and monitored for Adverse Drug Reactions (ADRs). All the ADRs spontaneously reported or identified (by observation and record of patients) by the researcher were recorded and analyzed.

Out of Total 796 patients were enrolled, 102 patients had ADR. There were 61(59.8%) male and 41(40.19%) female. In my study prevalence rate of ADR was 14.96%. Most common manifestation was gastro-intestinal upset (42.15%), followed by hepatitis (28.43%), joint pain (15.68%), itching and rashes (5.88%), Giddiness and tinnitus (4.9%), visual blurring (0.98%), and Thrombocytopenia (0.98%).

[*J Indian Med Assoc* 2020; **118(2):** 16-9]

Key words **: Tuberculosis, Anti Tuberculosis Drug, Adverse Drug Reaction.**

Tuberculosis is the primary worldwide cause of death due to infectious disease. The WHO TB statistics for India for 2016 give an estimated incidence figure of 2.79 million case of tuberculosis for India[1].

Directly observed treatment, short course (DOTS) chemotherapy is a part of Revised National Tuberculosis Control Programme (RNTCP)[2] which cause Adverse Drug Reactions (ADR) that result in diminished quality of life, increased physician visits, hospitalizations, and even death[3]. Various factors such as the dose and time of day at which the medication is administered, patient age, nutritional status, the presence of preexisting diseases or dysfunctions like impaired liver function, impaired kidney function, HIV co-infection, and alcoholism may be related to adverse reactions to Anti-tuberculosis drugs. The aim of this study is to know the prevalence of ADRs in patients receiving first line Anti-Tuberculosis Treatment (ATT) and to determine the pattern of various ADRs associated with use of anti-tubercular drugs.

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Editor's Comment :

- **It must be kept in mind that severe side effects with anti-TB drugs are common among patients of pulmonary tuberculosis.**
- **They should be followed up by closer monitoring for the side effects related to anti-TB drugs for better management.**

Materials and Methods

This is a prospective observational study conducted at the Department of Respiratory Medicine in LG Hospital, Ahmedabad, Gujarat, from March 2018 to December 2018. All patients those who have TB (PTB+EPTB) and put on treatment under RNTCP (category 1 or category 2) and met inclusion and exclusion criteria were identified. The study was approved by the IRB committee and written informed consent from study group was taken before enrollment.

Inclusion Criteria :

(1) Patients > 15 years.

(2) Having Pulmonary Tuberculosis (PTB) and Extra Pulmonary Tuberculosis (EPTB).

(3) Taking treatment under DOTS in category 1 or 2 of RNTCP regimens in our hospital.

(4) Who gave consent.

Exclusion Criteria :

(1) MDR case and XDR cases.

(2) Previously existing severe cardiac, renal, hepatic disease.

(3) History of recurrent psychotic disorders, alcohol or drug abuse within the previous year.

(4) Pregnant and lactating women.

All registered patients who were taking treatment of tuberculosis according to category 1 or category 2 under RNTCP were observed. Patient who were having ADRs, their relevant findings were recorded during each clinical visit and their responses were documented. Patients were asked to come for follow up every fortnight & in between whenever needed.

Baseline investigations like Complete Blood Count, Liver Function Tests, Renal Function Tests, Serum Uric Acid were done for each patient before starting anti-tuberculous treatment. Relevant investigations according to patients sign and symptoms were repeated if patients developed ADRs.

Severity of the ADRs were classified according to Hartwig *et al*[4] as:

(1) Mild ADR which were self-limiting and able to resolve over time without treatment and did not contribute to prolongation of length of stay.

(2) Moderate ADRs were defined as those that required therapeutic intervention and hospitalization prolonged by 1 day but resolved in <24 hour or change in drug therapy or specific treatment to prevent further outcome.

(3) Severe ADRs were those that were life threatening, producing disability and those that prolonged hospital stay or led to hospitalization, required intensive medical care, or led to the death of the patient.

All the data of patient having ADRs were recorded according to case record form and analyzed. All adverse events, even if it feels minor for the patients were also recorded. Episodes of hepatitis were considered drug induced if transaminases were normal before therapy, increased during therapy, and returned to normal after discontinuation of the responsible drug. Patients with Moderate degree ADR in whom we had to stop anti-tubercular drug, rechallenge was done after patients improved by starting that drug in regimen. Patients were told to return at any time if new or same symptoms or complaints arise during therapy.

Statistical Methods :

Proportions were expressed as percentages and for continuous variables ranges were used with mean and standard deviations. Accordingly Chi-square test was used to compare data.

Result

Adverse drug reactions due to ATT are expected to be present in majority of patient as part of adverse drug reaction. Total 796 patients were enrolled in my study, out of them 102 patient had ADR. There were 61 male and 41 female, % of ADR in Male & Female is 59.8% and 40.19% respectively. In my study prevalence rate of ADR was 14.96%.The age of the patients screened in the study ranges from more than 15 to 75 years. Maximum number of patients were in their 2nd and 3rd decade of life. Statistically significant higher occurrence of ADRs was found in age group of 21-30 years with mean age 23.03±6.7 year ($p<0.001$). In Present study patient with Low BMI were more prone to develop ADR, statistically higher significant ratio in patient having BMI <18.5(36.27%). Out of 102 patients 65(63.72%) having PTB and rest 37(36.27%) were EPTB. Statistically higher significant ratio for developing ADR in patient of sputum positive PTB (58.2%) (Table 1).

Table 1 — *Demographic and baseline parameters of patients having TB and its association with occurrence of ADRs (n=102)*

Parameter	No of patient with ADR (%)	No of patients without ADR (%)	P value
Age (years)			<0.01
≤20	22 (21.56%)	88 (12.68%)	
21-30	28 (27.45%)	97 (13.97%)	
31-40	21 (20.58%)	242 (34.87%)	
41-50	12 (11.76%)	135 (19.45%)	
51-60	11 (10.78%)	102 (14.69%)	
≥61	8 (7.84%)	30 (4.32%)	
BMI (kg/m²)			<0.01
<18.5	37 (36.27%)	236 (34%)	
18.5-24.9	34 (33.33%)	278 (40.05%)	
25.-29.9	26 (25.49%)	135 (15.12%)	
>30	5 (4.9%)	45 (44.11%)	
Gender			>0.05
Female	41 (40.19%)	274 (39.48%)	
Male	61 (59.08%)	420 (60.51%)	
Site of TB			>0.05
Pulmonary	65 (63.72%)	432 (62.24%)	
Extrapulmonary	37 (36.27%)	262 (37.75%)	
Category			>0.05
Cat – 1	63 (61.76%)	364 (52.44%)	
Cat – 2	39 (38.23%)	330 (47.55%)	
Sputum Status			<0.01
Positive	60 (58.82%)	256 (36.88%)	
Negative	5 (4.9%)	176 (25.36%)	

Different manifestations of ADRs are shown in Table 2. Out of 102 patients, gastro-intestinal upset was the main complaint in majority (n=43) patients due to Rifampicin in mean of 10.34±7.4 days, followed by hepatitis (n=29) due to Rifampicin, Pyrazinamide and Isoniazid in a mean of 28.13±6.01days, followed by joint pain (n=16) due to Pyrazinamide in a mean of 15.2±6.24 days (Table 3).

Table 2 — *Distribution of adverse drug reactions due to directly observed treatment strategy therapy in tuberculosis patients*

System	Manifestations	Patients	Action for ADRs
Gastrobilliary	Nausea, vomiting, epigastric pain	43(42.15%)	Symptomatic treatment
Hepatobilliary	Jaundice	29(28.43)	Rifampicin, Pyrazinamide, Isoniazid stopped temporarily
skeletal	Joint pain	16(15.68%)	Symptomatic treatment, Pyrazinamide stopped temporarily
Otovestibular	Giddiness, tinnitus	5(4.9%)	Streptomycin stopped
Ophthalmologic	Visual blurring	1(0.98%)	Ethambutol stopped
Dermatologic	Itching, rashes	6(5.88%)	Symptomatic treatment
Blood	Thrombocytopenia	1(0.98%)	Rifampicin stopped
Dress syndrome	Fever, cutaneous eruption, thrombocytopenia	1(0.98%)	Rifampicin, Pyrazinamide, Isoniazid, Ethambutol stopped temporarily

Severity assessment :
- 49(48.03%) of the cases were mild (level-1)
- 34(33.33%) were moderate (level 2)
- 19(18.62%) were severe (level 3)
- 0% was lethal (level 4)

Out of the n=102 patients who developed adverse drug reactions, only n= 7(6.86%) patients required complete stoppage of that offending drug, while n=38(37.25%) patients require interruption of treatment and most of the patients n=64(62.74%) were managed with supportive medication without removing anti tubercular drug from their treatment regimen.

Outcome of patients having adverse drug effects are shown in Table 3. Out of these 102 patients, majority n=78(76.87%) declared cured at the end of treatment, while only n=05(4.90%) patients were declared as failure on treatment. In this study n=03(2.94%) patients defaulted during treatment because of adverse drug reaction or because of poor compliance towards anti-tubercular treatment, while n=0 patients had died during the treatment.

Table 3 — *Outcome of anti-tubercular treatment*

Outcome	No of ADR (n=102)	%
Cured	78	76.40
Relapsed	15	14.70
Failure	5	4.90
Default	3	2.94
Alteration in Therapy	1	0.98

Discussion

After implementation of Revised National Tuberculosis Control Programme (RNTCP)[4] the cure of tuberculosis has been possible. One of the common reasons responsible for noncompliance to RNTCP guidelines are development of ADRs.

Among 102 reported adverse drug reactions, the highest numbers of ADRs were observed in males (60.51%) and (39.48%) was observed in female in the ratio of 6:4. A study conducted by Sainul Abideen P et al reveals[5] that the presence of ADR due to TB is more in males than in the females in the ratio of 7:3. Also the National Tuberculosis Program (NTP) and other study summarized as the ratio of occurrence of ADR of TB between male & female were 5:2[6-8].

ADR due to TB was more prevalent in the age group 21-30 years (13.97%) in current study, Edoh and Adjei *et al*[9] found higher incidence of ADR in the age group of 21-40 years. This may be because the people in this age group are usually involved in activities like smoking, large alcohol intake, etc., which results in the weakening of immunity.

In our study, common ADRs were related to GIT system that is gastritis. This can be attributed to multi drug therapy by oral route. The drugs responsible for these side effects were Pyrazinamide and Rifampicin. 29 (28.43%) patients developed hepatic dysfunction as ADRs. The drugs responsible for this side effect were Pyrazinamide, Rifampicin, and Isoniazid. Six patients (5.88%) experienced allergic skin manifestations as ADRs. The drugs responsible for this side effect were Pyrazinamide, Rifampicin, and Isoniazid. 16 (15.68%) patients experienced joint pain, drug responsible for that was Pyrazinamide, 1 patient experienced visual blurring due to Ethambutol, 1 patient had thrombocytopenia due to Rifampicin. Study done by Yee D *et al*[8] showed that rash present in 12 patients, hepatitis in 12 patients, gastric upset in 11 patients and arthralgia in 1 patients. Other study done by Scharberg T *et al*[10] showed hepatotoxicity (11%), exanthema (6%) and arthralgia (2%), study done by Amit Dedun *et al*[11] showed

16 patients had gastritis, 14 patients had skin rash, 7 patients had giddiness, and 1 patient had thrombocytopenia. Most of the ADRs (48.05%) were mild, only 18.62% were severe reaction (hepatic dysfunction). Study done by Yee D *et al*[8] showed 37 patients had severe reaction. Study by Amit Dedun *et al*[11] showed that 30 patients had severe reaction.

According to my study Indian patients experienced Gastrointestinal symptoms more than other symptoms compared to western study, patients who had Rash and Hepatitis due to ATT[8]. Major limitation of the study is that it was a single centre study on few patients. Larger studies directed towards specific population are required before generalizing findings of this study to whole community.

Conclusion

Management of active tuberculosis includes the initiation and the completion of anti-TB therapy, but there may be interruption of treatment due to side effects related to anti-TB drugs. So due vigilance is needed while patient is on ATT so that patient can complete the treatment and get cured which can be beneficial for the society too. Limitation of the study is that it is a single centre study on few patients. Larger studies directed towards specific population are required before generalizing findings of this study to whole community.

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Original Article

Prescription Patterns in Valve-replaced Rheumatic Heart Disease Patients in a Tertiary-care Hospital in South India

Indranil Ray[1], Eippa Matthan Kovoor[2], Ananya Chakraborty[3], Durga Prasad Reddy[4]

The worldwide prevalence of rheumatic valvular heart disease is 15.7 million persons. It was 13.17 million in 2015 in India which is considered the highest among all countries. These patients require valve replacement cardiac surgery. Postoperatively multiple drugs are usually required. The objective of this study was to analyse prescription patterns in such patients: (1) to identify the drugs most commonly prescribed after operation and (2) to ascertain the adherence to World Health Organization prescribing indicators and the recent List of Essential Medicines. A prospective, analysis of prescriptions of patients who underwent valve replacement surgery at the Cardio-Thoraco-Vascular-Surgery Department was undertaken, from January to December, 2017. Demographic data and clinical profile of patients were recorded. Various classes of drugs prescribed and percentage of individual drugs in each class were collected. The drugswere analysed based on WHO prescribing indicators. The most commonly prescribed, antibiotic was combination of intravenous cefuroxime and sulbactam (80%); analgesic &/or antipyretic was oral paracetamol (100%); anticoagulant was either acenocoumarol or warfarin; anti-ulcer agent was oral pantoprazole and antiemetic was intravenous ondansetron. They were used for diseases or surgeries. Polypharmacy, like more than 3 antibiotics per patient and 14 drugs per prescription was universal (100%) as was the use of brand names and the absence of generic names.

Such prescriptions and non-adherence to WHO prescribing indicators leads to increased cost, adverse effects, drug interactions, antibiotic resistance, increased morbidity, increased mortality and prescribing & dispensing errors. Changes in knowledge, attitudes and practice, and intermittent prescription audits are essential to improve prescription habits.

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Key words **: Rheumatic heart disease; surgery; prescriptions; prescribing indicators; polypharmacy.**

Rheumatic Heart Disease (RHD) of the valves primarily involves 2/3rd mitral valve and 1/3rd aortic valve.The disease has a prevalence worldwide of 15.7 million[1] and in India 13.17 million[2]. It is caused by group A Streptococcus (GAS). It begins with sore throat, causing Acute Rheumatic Fever (ARF) and finally it may affect the heart[3]. RHD is putatively due to immune destruction of heart valves[4] and manifests as breathlessness, pedal oedema, fatigue and tachycardia on account of heart failure[3]. Management of ARF includes penicillin prophylaxis, Non-steroidal anti-Inflammatory drugs (NSAID)s, bed rest, fluid restriction, cardiac medications, with prior and intervallic cardiologic assessment including echocardiography, timely surgical referral and replacement of valves[5]. In case of prosthetic valves anticoagulants are frequently used[6]. Till date, our literature search did not find any published articles on the prescription patterns in valve-replaced rheumatic heart disease patients.

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Editor's Comment :

- **Prescribers should avoid polypharmacy and irrational use of medicines.**
- **Always prescribe according to WHO prescribing indicators like 1.4 to 1.8 medicines per prescription, 13.4% to 24.1% injectable, 20% to 27% antibiotics, 100% drugs by generic names and from List of Essential Medicines.**
- **Non-adherence to WHO prescribing indicators can cause adverse effects, anti-microbial resistance, high cost, morbidity and mortality.**
- **Analysis of prescribing pattern or prescription audit should be done periodically to create awareness.**

To make medical care cost-effective and rational, the study of prescribing patterns is essential to monitor, evaluate and suggest modifications, if necessary[7]. Microbial resistance, adverse effects, economic loss, increased morbidity and mortality are related to the irrational use of medications[8]. Prescribing, dispensing, administering and facilitating rational use medicines are

the main focus of prescription pattern monitoring studies[9]. As per World Health Organization (WHO) prescribing indicators the number of drugs per prescription should rang from 1.4 to 1.8 of which antibiotics make up 20% to 27%, injectable medicines constitute 13.4% to 24.1% and all prescription should quote generic names which should also be derived from the Essential Drug List (EDL), currently termed as list of essential medicines (LEM)[10]. The present study was designed to: (1) analyse prescription patterns, identify the most commonly prescribed drugs and (2) ascertain whether the prescriptions for post-operative RHD patients in a tertiary care hospital ward in south India after valve-replacement adhered to WHO prescribing indicators and complied with the 19th WHO List of Essential Medicines (LEM).

Materials and Methods

The study was conducted among Cardio-Thoraco-Vascular Surgery (CTVS) inpatients department (IPD) of Vydehi Hospital affiliated to Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, after taking approval from the Institutional Ethics Committee. This was a prospective study of one year duration, from January 2017 to December 2017. Prescriptions included for analysis were those issued post-operatively after aortic, mitral or double, valve replacement surgery using mechanical prosthetic valves, for RHD. Prescriptions were excluded for any combined surgery like two different categories of CTVS operations or history of known drug hypersensitivity or history of embolism or hemorrhagic diathesis. Demographic data (age and sex) and clinical profile of patients (diagnosis and operation or surgery) were recorded. Various classes of drugs prescribed and percentage of individual drugs in each class were collected. The drugs utilized were assembled into groups and analysed based on WHO prescribing indicators. Collected data were entered on Microsoft Office Word and Excel spreadsheet formats. The baseline data like demography (age, sex), diagnosis, treatment or operation were subjected to descriptive statistical analysis and expressed as mean + SD, frequencies and percentages. The drug utilization results were expressed as percentages.

Observations

A total of 60 prescriptions were analysed. The results are as follows :

(1) Demographic details :

Age and sex : The mean age ± SD was 41.07 ± 11.808. 20 (33.33%) patients were belonged to age group of 41 to 50 years, 16 (26.66%) patients were belonged to 51 to 60 years, 14 (23.33%)patients were belonged to 21 to 30 years, 8 (13.33%) patients were belonged to 31 to 40 years and 2 (3.33%) patients were belonged to 18 to 20 years. There was male preponderance; 39 (65%) were male and 21 (35%) were female.

(2) Clinical profile :

The clinical profile of patients were noted as shown in Table 1.

(3) Prescription analysis :

(I) Prescribed drugs — The drugs utilized post-operatively were assembled into groups of various classes and percentage of individual drugs, as shown in Table 2, Fig 1, Table 3, Fig 2 and Table 4. Drugs were prescribed for

Table 1 — *Clinical profile*

Diagnosis	Operation or surgery	Distribution (n=60)
Mitral stenosis (MS), Mitral regurgitation (MR)	Mitral valve replacement (MVR)	29 (48.33%)
Aortic stenosis (AS) and Aortic regurgitation (AR)	Aortic valve replacement (AVR)	14 (23.33%)
MS, MR, AS and AR	Double valve replacement (DVR)	17 (28.33%)

Table 2 — *Antimicrobial, Analgesics and/or Antipyretics*

Antimicrobial agents

Drug	Dose	Route	Frequency	Overall %
Cefuroxime & sulbactam	1gm & 500 mg	Intravenous	BID	80%
Meropenem	500 mg	Intravenous	TID	52.72%
Imipenem	500 mg	Intravenous	QID	52.72%
Gentamicin	80 mg	Intravenous	BID	47.27%
Colistin	5mg/kg/day	Intravenous	BID	7.27%
Vancomycin	500 mg	Intravenous	BID	7.27%
Teicoplanin	200 mg	Intravenous	BID	5.45%
Benzathine Penicillin	2.4 Million Unit	Intramuscular	4 weekly	52.72%
Amoxicillin & potassium clavulanate	500 mg &125 mg	Oral	TID	67.27%
Cefixime	200 mg	Oral	BID	65.45%
Cefuroxime	500 mg	Oral	BID	52.72%
Linezolid	600 mg	Oral	BID	50.9%
Ciprofloxacin	500 mg	Oral	BID	20%
Faropenem	200 mg	Oral	TID	14.54%
Moxifloxacin	400 mg	Oral	OD	12.72%
Nitrofurantoin	100 mg	Oral	BID	10.9%
Rifaximin	200 mg	Oral	BID	7.27%

Analgesics &/or Antipyretics

Drug	Dose	Route	Frequency	Regularity
Diclofenac	75 mg	Intramuscular	BID/SOS	58.18%
Tramadol	100 mg	Intramuscular	TID/SOS	29.09%
Paracetamol	650 mg	Oral	TID/SOS	100%
Indomethacin	75 mg	Oral	BID	16.36%
Pregabalin	75 mg	Oral	OD	12.72%
Diclofenac, Menthol,Methyl salicylate & Oleum Lini	1.16%, 5%, 10% & 3%	Topical	BID	32.72%
Choline Salicylate, Magnesium Salicylate & Benzalkonium Chloride	9%, 9% & 0.02%	Topical	BID	29.09%

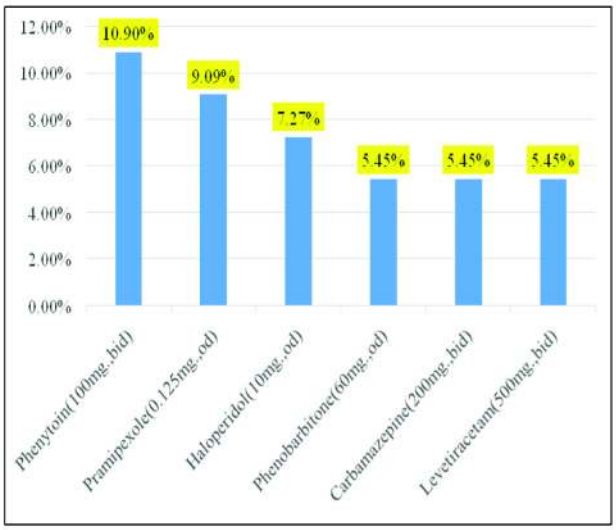

Fig 1 — Drugs (oral) affecting Central Nervous System

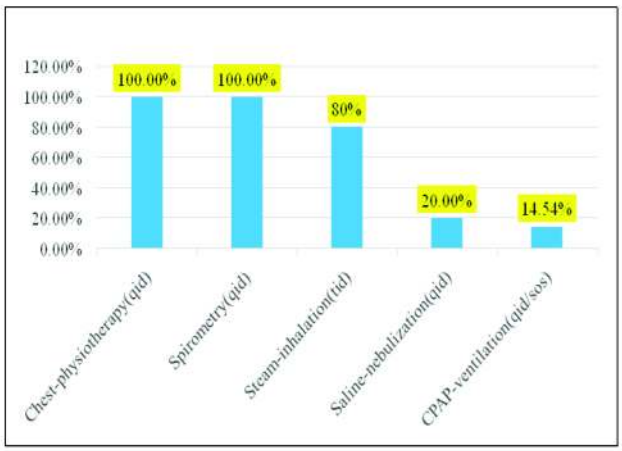

Fig 2 — Miscellaneous or Supportive therapy

7 days after operation, in different doses like in gram (gm.), milli-gram (mg), micro-gram (µg) and in different frequencies daily like once (OD), twice (BID), thrice (TID), four times (QID) daily, SOS (as and when required).

As dietary supplement egg white (TID, 52.72%) and protein powder (TID, 38.18%) was given to the patients.

(II) Analysis of prescribed drugs based on WHO prescribing indicators and the 19th WHO List of Essential Medicines — A total of 60 prescriptions were analysed for (60 participants. A total of 840 drugs (92 types) were prescribed, and an average of 14 drugs were prescribed per patient.Out of 17 antibiotics prescribed none was given as monotherapy. All 92 types (100%) of 840 drugs (100%) were prescribed as per 19th WHO List of Essential Medicines. No drug was prescribed by generic name. Out of the 92 types of drugs prescribed, 17 (15.64%) were prescribed as injections. Every prescription had more than 3 antibiotics. Brand names were used in all prescriptions.

Table 3 — *Drugs affecting Cardiovascular &/or Renal and Respiratory system*

Drugs affecting Cardiovascular &/or Renal system

Drug	Dose	Route	Frequency	Regularity
Furosemide	20 mg	Intravenous	BID	56.36%
Spironolactone	25 mg	Intravenous	BID	25.45%
Furosemide	20-40 mg	Oral	OD	90.9%
Digoxin	0.125-0.25 mg	Oral	OD	74.54%
Sildenafil	20 mg	Oral	BID/TID	67.27%
Spironolactone & Furosemide	25 mg & 20/40mg	Oral	BID	60%
Verapamil	20-40 mg	Oral	OD/BID/ TID	52.72%
Atorvastatin	10 mg	Oral	OD	50.9%
Metoprolol	25 mg	Oral	OD/BID	49.09%
Aspirin & Atorvastatin	150 mg & 20mg	Oral	OD	40%
Spironolactone	25 mg	Oral	BID/TID	40%
Potassium chloride	0.5 gm	Oral	TID	40%
Nifedipine	10-20 mg	Oral	BID/TID	38.18%
Amiodarone	200 mg	Oral	TID	38.18%
Ramipril	1.25-5 mg	Oral	OD	34.54%
Bisoprolol	1.25 mg	Oral	OD	29.09%
Nitroglycerin	6.5 mg	Oral	OD	25.45%
Mannitol	20%	Oral	SOS	20%
Diltiazem	60 mg	Oral	OD	9.09%

Drugs related to Respiratory system, like, Expectorants, Bronchodilators, Mucolytics and Mucokinetics

Drug	Dose	Route	Frequency	Regularity
Hydrocortisone	100 mg	Intravenous	TID	30.9%
Guaifenesin & Terbutaline	50 mg & 2.5 mg	Oral	TID	52.72%
Ambroxol	15 mg	Oral	TID	52.72%
Terbutaline & Bromhexine	2.5 mg & 8 mg	Oral	TID	49.09%
N - Acetyl cysteine	600 mg	Oral	BID	43.63%
Dexamethasone	8 mg	Oral	BID	40%
Bromhexine	8 mg	Oral	TID	38.18%
Deriphyllin	150 mg	Oral	TID	34.54%
Orciprenaline	10 mg	Oral	TID	12.72%
Acetyl cysteine	20%	Inhalational (Nebulization)	TID	56.36%
Normal Saline, Salbutamol & N - Acetyl cysteine	0.09 %, 200 µg & 20 %	Inhalational (Nebulization)	TID	43.63%
Levosalbutamol & Budesonide	200 µg & 200 µg	Inhalational (Nebulization)	BID	38.18%
Budesonide	200 µg	Inhalational (Nebulization)	TID	25.45%
Formoterol & Budesonide	12 µg & 200 µg	Inhalational (Nebulization)	BID	25.45%

It was noticed that directions for drug, dose, route, time, duration, doctor'ssignature, doctor's medical registration number and signature of the dispensing person was not completely written everywhere. In all prescriptions

Table 4 — *Drugs affecting blood coagulation, Gastro-intestinal system, Haematinics and/or Multivitamins and/or Multiminerals supplements and Endocrine system or Hormones*

Drugs affecting blood coagulation, bleeding thrombosis, like, Anticoagulants, Antiplatelets				
Drug	**Dose**	**Route**	**Frequency**	**Regularity**
Heparin	5000 Unit	Subcutaneous	QID	25.45%
Acenocoumarol	2-4 mg	Oral	OD	50%
Warfarin	2-5 mg	Oral	OD	50%
Aspirin	75 mg	Oral	OD/BID	40%
Clopidogrel & Aspirin	10vmg & 75 mg.	Oral	OD	16.36%
Drugs affecting Gastro-intestinal system				
Drug	**Dose**	**Route**	**Frequency**	**Regularity**
Ondansetron	4 mg	Intravenous	OD	43.63%
Ramosetron	0.3 mg	Intravenous	OD	7.27%
Pantoprazole	40 mg	Oral	OD	74.54%
Pantoprazole & Domperidone	40 mg & 30 mg	Oral	OD	25.45%
Ursodeoxycholic acid	150-300 mg	Oral	BID	10.9%
Haematinics and/or Multivitamins and/or Multiminerals supplements				
Drug	**Dose**	**Route**	**Frequency**	**Regularity**
Multiple Vitamins	-	Intravenous	OD	34.54%
Iron,Cyanocobalamin & Folic acid	40mg, 7.5mg and 0.5mg	Oral	OD	71 %
Vitamin-C	500 mg	Oral	OD	67.27%
Vitamin B complexes	-	Oral	OD	61.81%
Zinc, Vitamin B1, B2, B6 & Folic acid	41.4 mg, 10 mg, 10 mg, 3mg & 1.5mg	Oral	OD	43.63%
Calcium, Magnesium, Zinc, Vitamin B, D, E, H	-	Oral	OD	30.90%
Drug affecting Endocrine system or Hormones				
Drug	**Dose**	**Route**	**Frequency**	**Regularity**
Levothyroxine sodium or Tetraiodothyronine	100 µg	Oral	OD	5.45%

abbreviations were used. Capital letters were not used in writing the majority of prescriptions.

Discussion

Duration is comparable to studies like Kolasani *et al*[8] and Gambre *et al*[11]. Mean age ±SD is similar to study done by Kolasani *et al*[8]. Sex ratio is comparable to study like Vakade *et al*[7]. Carapetis *et al*, mentioned similar findings of valve replacement cardiac surgery being done in MS, MR, AS and AR cases of RHD patients[5]. Drugs affecting cardiovascular and/or renal system are similar to other studies like Vakade *et al*[7], Rajathilagam *et al*[12] and Teng *et al*[13]. Laudari *et al*, mentioned that RHD patients require surgical treatment[14]. Here various classes of drugs and their percentages were evaluated. Similar analysis was done by Vakade *et al*[7], Teng *et al*[13], Kolasani *et al*[8], Begum *et al*[15] and Shah *et al*[16]. Same analysis procedures based on WHO prescribing indicators were used in other studies like Pallavi *et al*[9], Sidamo *et al*[10], Gambre *et al*[11] and Rajathilagam *et al*[12]. Commonly (80%) prescribed injectable antibiotic class (Cephalosporins) is comparable to other studies like Pallavi *et al*[9], Begum *et al*[15] and Shah *et al*[16]. Commonly (67.27%) prescribed oral antibiotic was Amoxicillin & potassium clavulanate. Here, most commonly used analgesic was injectable Diclofenac (58.18%), which is similar with other studies like Kolasani *et al*[8] and Qoul *et al*[17]. Paracetamol was most commonly (100%) used oral analgesic, which is comparable to other studies like Begum *et al*[15] and Sandvik *et al*[18]. Intravenous Furosemide (56.36%), intravenous Spironolactone (25.45%), oral Furosemide (90.9%), Oral Digoxin (74.54%), oral Sildenafil (67.27%), oral Spironolactone and Furosemide combination (60%), oral Verapamil (52.72%) and oral Atorvastatin (50.9%) were the mostly prescribed drugs affecting cardiovascular and/or renal system. Chest physiotherapy (QID, 100%), Spirometry (QID, 100%) and steam inhalation (tid, 80%) were the mostly prescribed miscellaneous or supportive therapy. Vitamin K antagonists like acenocoumarol (50%) or warfarin (50%) were used in all participants, which is comparable to other studies like Saksena *et al*[6] and Harter *et al*[19]. Subcutaneous Heparin (5000 unit, QID) was used in 25.45% patients. Here, oral Pantoprazole was used most commonly (74.54%). In another study Gamelas *et al*, mentioned that the main appropriate indication for prescribing proton pump inhibitor was anticoagulation alone, mostly to prevent gastrointestinal bleeding[20]. The most commonly used injectable antiemetic was Ondansetron, similar to another study done by Kolasani *et al*[8]. Levothyroxine sodium or Tetraiodothyronine was prescribed for hypothyroidism in 5.45% patients. No patients were detected as diabetes mellitus.

Limitations :

Less numbers of prescriptions (only 60) of valve-replaced rheumatic heart disease patients were analysed and the duration of the study was less (only 1 year).

Conclusion:

Polypharmacy, use of trade names, no generic name and non-adherence to WHO prescribing indicators were observed in this study. All these lead to increased cost,

adverse effects, drug interactions, antibiotics resistance, increased morbidity and mortality. All the afore mentioned may cause prescribing and dispensing errors. Awareness, education on drug prescription methodology, standard treatment guidelines, hospital formulary and periodic prescription audits are essential to improve prescription habits. To ensure safe medication preparation and administration "7 rights" like right patient, right drug, right dose, right time, right route, right reason and right documentation"should be followed.

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Original Article

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

Md Hamid Ali[1], Krishna Sen[2], Kaushik Ghosh[3], Udas Chandra Ghosh[4], Sharmila Mallick[5]

Diabetes Mellitus (DM) is a known predisposing factor for development of cerebrovascular accident. Fibrinogen plays a vital role in inflammation, atherogenesis and thrombogenesis which leads to stroke by promoting platelet adhesion and aggregation. A descriptive observational study was done at Murshidabad Medical College and Hospital, Berhampore, Murshidabad, which included 186 patients in 3 groups ie, DM with CVA-62 patients, CVA without DM-54 patients and DM without CVA- 70 patients. Fibrinogen, FBG (Fasting Blood Glucose) and PPBG (Post Prandial Blood Glucose) were tested. The result shows that the mean Fibrinogen level is high in all the group's but highest in DM with CVA group which was statistically significant. High Fibrinogen level is a good prognostic factor. [*J Indian Med Assoc* 2020; **118(2):** 25-7]

Key words **: Fibrinogen, Diabetes mellitus, Cerebrovascular accident.**

Fibrinogen is a soluble glycoprotein found in the plasma with a molecular weight of 340 K Dalton. As a clotting factor, fibrinogen is an essential component of the blood coagulation system. However, at the "usual" plasma levels of 1.5 to 4.5 gm/l, its concen-tration far exceeds the minimum concentration of 0.5 -1 gm/l necessary for homeostasis[1].

Fibrinogen plays a vital role in different pathological processes in the body including inflammation, atherogenesis and thrombogenesis. It increases with age, Body Mass Index, smoking, diabetes and post menopause and is related to fasting serum insulin, low density lipoprotein, cholesterol lipoprotein (a) and leukocyte count. Conversely, it decreases with moderate alcohol intake, physical activity,increased HDL cholesterol and hormone replacement therapy[2].

India, the diabetes capital of the world, has 41 million diabetic. Every fifth diabetic in the world is an Indian. Type 2 Diabetes Mellitus (DM) is the commonest for constituting 90% of diabetic population in our country[3]. In around 80-90% of subjects with type 2 DM and in approximately 25% of the general population, insulin resistance is found. Levels of fibrinogen is elevated in insulin resistant subjects, an association that suggests a possible role for acute phase cytokines in the abnormalities of coagulation and endothelial function[4].

Atherosclerosis is the basic pathogenic process in the development of stroke. By using immunoflurocent technique one study has shown the deposition of fibrinogen in the intima of cerebral arteries and has indicated its role in atherosclerotic process[5]. So in this background we conducted the present study to measure the fibrinogen level in DM patients with or without stroke, to establish the relationship between the level of fibrinogen and stroke.

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Editor's Comment :

- **Plasma Fibrinogen may be considered as an important risk factor for Ischemic. Vascular events specially in young and middle aged person.**
- **Hence, Fibrinogen Level Should be considered during screening programme of risk factor assesment.**

Material and Methods

This study was a descriptive observational study conducted at the medical inpatient department, outpatient department of Murshidabad Medical College and Hospital during the period from August 2013 to August 2015. Total 186 cases included in this study, out of which 70 were only Diabetes Mellitus (DM), 62 were DM with cerebrovascular accident (CVA), and 54 were CVA without DM. The patients were selected by purposive sampling technique from inpatient department and outpatient department.

All the cases of CVA are confirmed by obvious clinical signs and Non Contract CT scan. Level of fibrinogen in blood was tested by electrochemical clot detection method from a National Accreditation Board for Testing & Calibration Laboratories (NABL) accredited laboratory in Berhampore. FBG and PPBG were tested from Biochemistry department of Murshidabad Medical College.

Exclusion Criteria :

(1) All hemorrhagic strokes.
(2) Liver diseases.
(3) Renal diseases.
(4) Coagulopathy and sickle cell diseases, thalassemia,

polycythemia Vera.

(5) Systemic malignancy.

(6) Systemic vasculities.

(7) History of myocardial infarction or majorsurgery within preceding 3 months.

(8) Patients taking drugs like Bezafibrate, B-blockers, Pentoxyfyline and Ticlopidine.

(9) DKD (Diabetic Kidney Disease)

(10) NAFLD in DM

(11) Ischemic cardiomyopathy in DM

Observations

In the present study, out of total 186 patients , 90 (48.4%) were of age group of 61-70 years, 68(36.6%) were of 71-80 years and 28(15%) patients were in the age group of 51-60 years. None of the patients were included in the age group >80 years and <50 years.

In Table 1, p>0.05; signifying that there are no significance in distribution of male and female among different study groups. However, in each group male are more affected than their female counterparts.

In Table 2 result signifies that there are obvious differences in respect to fasting blood glucose among the different study group as p value <0.05.

In diabetes with CVA group, the number of patients with FBG>200mg% are more than the patients with FBG within 126-200 mg%, and the number of patients whose FBG is within 126-200 mg% are more than the patients with FBG>200 mg% in the DM without CVA. This is seen that the number of patients with PPBG within the range of 200-300mg% are more in each study group but the number of patients with PPBG>300mg% are more in the diabetes with CVA group than in Diabetes without CVA group. So, there is no statistically significant difference in the distribution of PPBG level in two diabetes groups.

The unpaired t test performed between fibrinogen level in DM with CVA group and that of CVA group without DM. The p value is <0.0001. The results of unpaired t test between fibrinogen level DM with CVA group and that of DM without CVA group shows the p value =0.0001. These signifies that difference in the mean blood fibrinogen level between the groups is statistically significant. But the p value is 0.46 when the 2 groups of CVA without DM and DM without CVA are compared, which signifies that difference in the mean blood fibrinogen level between two groups is statistically not significant (Table 3).

The result of an unpaired t-test shows the p value is 0.91 assuming the null hypothesis, signifying that there is no statistical significant difference in the mean of blood fibrinogen level in the male and the female population, though the mean blood fibrinogen level is slightly higher in the female than their male counterpart (Table 4).

Here Pearson correlation co efficient r=0.241 and p value=0.01. So the rise of mean fibrinogen level with rise of fasting blood glucose is statistically significant (Table 5).

Pearson correlation co efficient r=0.240 and p value=0.01. So the change of mean fibrinogen level with post prandial blood glucose is statistically significant (Table 6).

Discussion

As per objective of this study, the mean fibrinogen level was compared among the entire study group. It is found that the mean fibrinogen level is high in all the groups but highest value is seen in Diabetes with CVA group. Similar results observed in one study group of south Asian patients in 2002 as increased fibrinogen and tissue plasminogen activators level in insulin resistant South Asian patients with ischemic stroke[6]. Insulin resistance was significantly higher in stroke patients. Stroke patients showed elevated level of fibrinogen. Higher levels of fibrinogen, von Willebrand factor and tPA in South Asian stroke patients disappeared after adjustments for features of insulin resistance syndrome but persisted after adjustment for presence of diabetes, confirming that these changes are essentially dependent on features of insulin resistance syndrome. In many studies this has been already published that in both the diabetes and the CVA group the mean fibrinogen level is increased. In one study of the department of Medicine, Seth G S Medical College, Parel, Bombay, Maharastra it is shown that the plasma fibrinogen level is markedly high in the patients of stroke with DM[7].

As per sex distribution in this study no statistical significance was observed, though in the table no-1, it is shown that in all 3 groups males are more affected.

Table 1 — *Distribution of sex in the study group*

Study subjects	Male	Percentage	Female	Percentage	Total
CVA with DM	44	70.97	18	29.03	62
CVA without DM	42	80.65	12	19.35	54
DM without CVA	48	64.52	22	35.48	70

Chi square test was done to find the statistical significance between different groups. x^2=2.03, df = 2, p = 0.363

Table 2 — *Distribution of glycemic status in two diabetes group with respect to fasting blood sugar and post prandial blood sugar*

Group	Fasting blood glucose			Postprandial blood glucose		
	126-200 mg%	>200 mg%	Total	200-300 mg%	>300 mg%	Total
DM with CVA	26	36	62	44	18	62
DM without CVA	52	18	70	56	14	70

Table 3 — *Distribution of blood fibrinogen level in the different study group*

Group (Mg/dl)	Mean fibrinogen level	SD
DM with CVA	651.064	123.908
CVA withourt DM	499.555	67.335
DM without CVA	484.741	87.275

Table 4 — *Distribution of mean fibrinogen level in relation to sex*

Sex (n=186)(mg/dl)	Number	Mean fibrinogen level	SD
Male	134	544.30	120.39
Female	52	547.46	125.93

Table 5 — *Distribution of mean fibrinogen level with rise of fasting glucose*

Fasting glucose (mg%)	No of patients (n=186)	Mean fibrinogen level (mg/dl)	SD
<126	54(29.0%)	499.55	67.33
126-176	74(39.8%)	579.95	132.55
177-227	42(22.6%)	566.85	138.75
>227	16(8.6%)	554.56	145.54

Table 6 — *Distribution of mean fibrinogen level with rise of post prandial glucose*

PPBG (mg/dl)	No of patients N=186	Mean fibrinogen level (mg/dl)	SD
<200	54(29.0%)	499.55	67.33
200-250	32(17.2%)	551.26	119.60
251-300	66(35.5%)	558.47	143.78
301- 350	28(15.1%)	578.15	141.11
351-400	06(3.2%)	572.00	59.39

In the present study, the mean fibrinogen level was higher in the females. Though most of the similar studies showed higher fibrinogen level in female but few studies also failed to demonstrate a significant gender difference in plasma fibrinogen level. The second WHO monitoring trends and determinants in cardiovascular disease Augsburg (MONICA) study found the crude fibrinogen values to be consistently higher in women than men of all ages.

From Table 2, it is clearly observed that in DM with CVA group the number of patients with fasting blood glucose >200 mg% is more than the number of patients with FBG within 126-200 mg% and the number of patients with FBG within 126-200 mg% is more than FBG >200mg% group in DM with CVA. Though the number of patients with PPBG within 200- 300% is more in each group but PPBG >300mg% is more in number in DM with CVA group than DM without CVA group. Seven years follow up study based on reprehensive cohorts of non-diabetic and diabetic subjects from Finland demonstrated that the risk of stroke for Noninsulin Dependent Diabetes Mellitus (NIDDM) women were five times more than non-diabetic women, and two to three times in case of man.

The present study showed that the mean fibrinogen level is high with increasing fasting blood glucose and also postprandial blood glucose (Table 5 & Table 6). To evaluate the determinants of elevated fibrinogen levels and the impact of hyperfibrinogenemia on vascular complications in diabetes one study of Joslin Diabetes center, Boston showed the overall fibrinogen levels in diabetic patients were elevated compared with control subjects[8].

In another study, it has been showed that patients with type 2 DM were having elevated levels of plasma fibrinogen levels (450mg/dl to 980mg/dl) when compared to the normal values (286±67mg/dl) obtained in controls. Plasma fibrinogen levels were higher in hypertensive (831±107mg/dl, 41 pts.) than in normotensives (599±113 mg/dl, 49 pts.)[9].

It can be concluded that blood fibrinogen level is higher in patients with CVA and co- existent diabetes. However in many studies it is proved that elevated fibrinogen predicts future ischemic strokes particularly in men and in the young and middle aged and is associated with advanced atherosclerosis[10]. Thus, fibrinogen may contribute to better risk assessment in younger and middle aged men, in contribution with established methods.

Plasma fibrinogen levels could be considered for screening program to identify people at high risk of vascular events and attempts should be made to strengthen the treatment of other risk factor in these patients groups[11]. Future directions require determination of the "critically elevated" fibrinogen level threshold value, development of drugs that would specifically and safely decrease plasma fibrinogen level and conduction of interventional trials to study the influence of lowering fibrinogen levels on overall cardiovascular risk profile.

Limitations

Hyperfibrinogemia leads to atherosclerosis and thrombogenesis resulting in ischemic stroke.But comparison between the other factors of atherosclerosis and thrombogenesis ie, Hypertension, Obesity, Smoking, Cholesterol and Hypercoaguble condition is not done in this study. Beside this there is no determined cut off value of hyperfibrinogenemia, so all the cases of high Fibrinogen is taken in this study.

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Case Report

Tricuspid Valve Libman Sack Endocarditis with Pericardial Effusion in an Antiphospholipid Syndrome Negative, Systemic Lupus Erythematosus Patient : An Interesting Case Report

Niladri Bhowmick[1], Jotideb Mukhopadhyay[2], Manjari Saha[3], Soumyadip Kar[4], Abhinav Das[5]

Non bacterial thromboembolism (NBTE) and pericardial effusion represent some of the unusual manifestation of systemic lupus erythematosus. Right sided endocarditis in SLE is uncommon and can lead to pulmonary embolism. Pericardial effusion in SLE patient can be due to disease activity as well as infection like tuberculosis. Routine screening can reduce morbidity from these conditions. NBTE can develop in anti Phospholipid syndrome serologically negative patients.

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Key words **: Libman-Sacks endocarditis, SLE, Antiphospholipid syndrome, tricuspid valve, pericardial effusion.**

Libman-Sacks endocarditis is a non infective verrucous thrombotic endocarditis and cardiac manifestation of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS)[1]. Libman-Sacks lesions are associated with lupus duration, disease activity, anticardiolipin antibodies, and antiphospholipid syndrome manifestations[2].

Case Report

Our patient is a 28 year old, non diabetic, non hypertensive, non hypothyroid female patient who presented to us with fever, joint pain and pedal swelling for five months duration. The joint pain was inflammatory in nature involving large and small joints. The fever was high grade in nature with no typical localizing symptoms. The patient had a gradually progressive shortness of breath which was predominantly exertional but there were two bouts of shortness of breath for which she required admission to local hospital prior to presenting to us. She also complained of mild vague chest pain in the left axillary region on deep expiration or occasional coughing for the last 1 month. But there is no history of cough or expectoration. Patient had normal urine output. She had no significant weakness associated with joint pain. On asking, she gave history of 3 abortions, all were spontaneous and in first trimester. She has two living children currently. Her menstrual and obstetric history is otherwise non significant. After admission on examination she was found to have moderate pallor and pedal swelling. Her JVP was not engorged. She had tachypnea and tachycardia; Respiratory rate was 28/min,pulse rate was 110/min. She had multiple firm, non matted palpable cervical lymph nodes of size around 2.5cm which were non tender.Her cardiovascular and chest examination revealed muffled heart sounds and bilateral vesicular breath sound respectively. She had palpable hepatomegaly and traube's space percussion was dull. Immediate echocardiography was done which revealed a pericardial effusion measuring 20mm anteriorly with normal ejection fraction. Pericardiocentesis was done and the fluid was sent for investigation. Her routine blood report showed a normocytic normochrmic anemia with normal WBC count and deranged urea creatinine. Her serum LDH was raised and serum potassium was on the higher side of normal. A blood for Direct Coomb's test was sent which came back positive. Serum Anti nuclear antibody was positive with low complement and high dsDNAlevels.Her APS profile including anti Cardiolipin, anti beta2 GPI and Lupus anticoagulant were negative. Urine routine examination showed active sediments with hematuria and proteinuria which was quantified and came back to 1.46gm/24 hours. Her kidney size was normal. During hospital stay, her blood creatinine values normalized gradually without any intervention. Kidney biopsy was done which revealed Class III C proliferative lupus nephritis. Her APS profile was negative (Repeated). Pericardial effusion study had increase fluid protein 6.1gm and raised ADA level 48.8U/L but fluid CBNAAT was

Editor's Comment :

- In SLE, dyspnoea may be due to valvular involvement, pericardial effusion or pulmonary involvement.
- In diffuse alveolar disease of SLE, alveolar hemorrhage must be ruled out as it is rapidly life-threatening.
- The possibility of seronegative APLA must be thought of in SLE with suitable clinical features like recurrent foetal loss.

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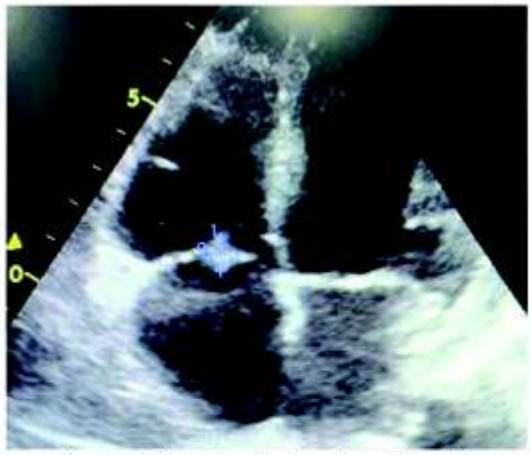

Fig 1 — Figure showing the echocardiographic imaging of the vegetation on tricuspid valve

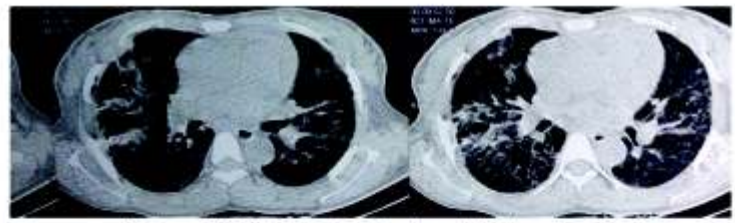

Fig 2 — HRCT thorax showing interstitial lung disease

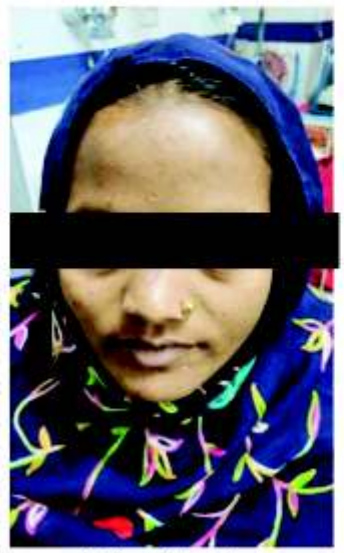

Fig 3 — The patient

negative. The patient was started on 0.5mg/kg steroid and Hydroxychloroquine and was planned for NIH regimen Cyclophosphamide. But the patient then developed sudden onset shortness of breath with severe tachypnea. Repeat echocardiography (Fig 1) revealed vegetation on tricuspid valve of size 7*4 sqmm which was further confirmed by transesophageal echocardiography. But the pericardial effusion was reduced, She had right ventricular strain pattern on ECG during the episode. Blood culture sent by infective endocarditis protocol came back negative. HRCT thorax and CT pulmonary angiography was done. It showed diffuse parenchymal lung disease with alveolar hemorrhage and there were no signs of chronic or acute thromboembolism (Fig 2&3). This presented a therapeutic dilemma about the need for anticoagulation, and considering the alveolar hemorrhage, it was not given. BAL study was done which revealed no bacterial, mycobacterial or fungal growth and RBC were seen in the BAL fluid, thus confirming alveolar hemorrhage. On steroids and supportive management, the patient stabilized and was discharged for follow up of vegetation size, renal parameters and lung manifestation (Table 1).

Table 1 — *Table showing the various blood parameters during hospital stay*

	D1	D3	D5	D10	D14
			(steroid from D4)		
Hb(gm/dl)	7.0	6.0	6.8	8.1	9.1
PCV(%)	23.6	20.4	23.1	26.4	31.4
TLC (per µL)	10,000	9000	8900	13400	11000
Ur/Cr(mg/dl)	92/5.1	110/2.8	64/1.8	47/1.1	55/1.1
Na/K (mEq/l)	134/5.5	137/5.0	134/4.2	140/3.4	138/4.4
ESR (mm)	130				
CPK(U/L)	62				
ALP/ALT/AST IU/L	74/14/18		74/18/10		60/12/16
pH	7.315		7.335		
pCO2/HCO3	24.7/12.4		25.9/13.5		
LDH (U/L)	920				
C3/C4 (mg/dl)		18.5/5.15			
dsDNA (IU/ml)		810			
Ferritin(mcg/L)		47			
PT(control)/	16.4(14.2)/				
APTT(control)/	32.9(33)/				
INR	1.15				

Discussion

The most frequently involved valve in SLE with endocarditis is the mitral valve followed by the aortic valve. Tricuspid valve isolated involvement is rare3. Libman-Sacks endocarditis has been assumed to involve the formation of fibrin-platelet thrombi on the altered valve, the organization of which leads to valve fibrosis, distortion, and subsequent dysfunction[4]. They could be the main source of complications, including ischemic strokes, peripheral embolization, severe valvular regurgitation, and need for surgery.Libman sacks endocarditis is usually more commonly present in APS positive individuals, but can be present even in isolated SLE patients. APS profile can be negative in so called seronegative APS patients owing to IgA antibodies, or undetectable antibodies 4.Differentiating pericardial effusion of tuberculosis from SLE disease activity remains a clinical challenge.

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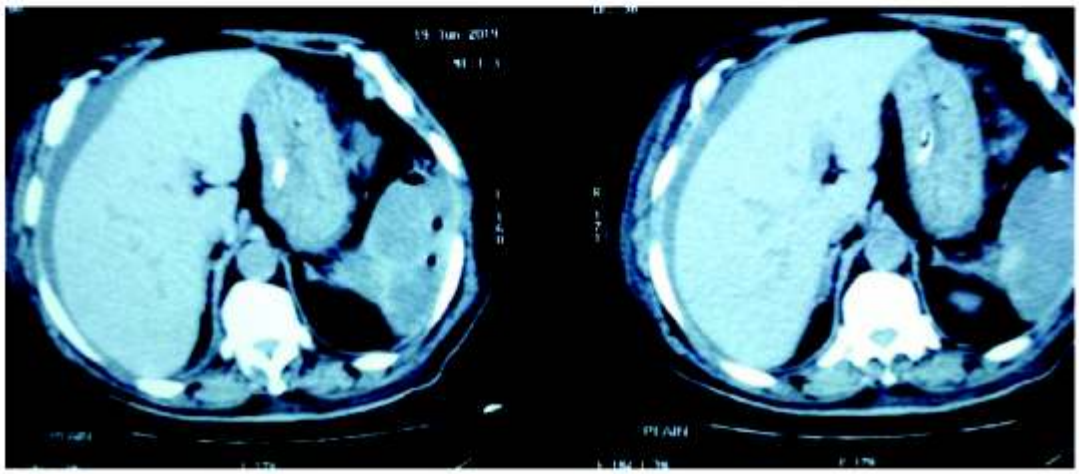
Pictorial CME

A Case of PUO

Rudrajit Paul[1], Sankha Sen[2]

A 72 year old man, a known diabetic with poor metabolic control, presented with continuous fever for 3 weeks. The fever was low grade intermittent to start with, but at the time of presentation, it was high grade (102-103°F) and nearly continuous. The hemoglobin was 6.6 g/dl, total leukocyte count 25600/cmm, neutrophil 90% and platelet count 3.5 L/cmm. There was no lymphadenopathy or organomegaly, no rash and no arthritis. The patient was given i.v. antibiotics but the fever persisted for one more week. Viral serology was negative. Then, a CECT abdomen was done (Figure below)



1. **What is the diagnosis?**
2. **What are the common aetiologies for this condition?**
3. **What is the treatment?**

Answers

1. The diagnosis is splenic abscess. As seen in this abdominal scan, there are areas of hypo-density in the spleen with two or three gas pockets. This is suggestive of splenic abscess. Early splenic abscess is sometimes difficult to discern even in contrast enhanced CT scan.
2. The etiology of splenic abscess can be monomicrobial or polymicrobial. Gram-negative organisms usually predominate. Other rare causes include Burkholderia pseudomallei, mycobacterium, candida, Brucella and sometimes, plasmodium.
3. The treatment for splenic abscess was only splenectomy earlier. But now, conservative management with i.v. antibiotics and percutaneous drainage has been found to be successful. In some reported case series, splenectomy was completely avoided with this approach. In rare cases like Melioidosis of spleen, antibiotics (i.v followed by oral) may be needed up to 3 months.

Editor's Comment :

- **In poorly controlled diabetes, PUO can be due to obscure infections like splenic abscess.**

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Newer Advances

Molecular Assays as Initial Tests for the Diagnosis of Tuberculosis

D P Singh[1], S K Ghosh[2]

Tuberculosis (TB) is caused by Mycobacterium Tuberculosis which chiefly affects lungs (PTB) but it can involve other parts of the body (EPTB). TB spreads through droplet infections and is highly contagious. One sputum positive TB patient can infect 10-15 normal contacts during a period of one year. TB still remains one of the world's deadliest communicable diseases because of delay in initial diagnosis and poor control. With timely diagnosis and effective treatment by category 1 first line drugs onward journey of TB transmission can be stopped. According to global tuberculosis report 2019[1], 10 million people developed tuberculosis and 1.5 million died from this disease. One million children contracted this disease and more than 2 Lakhs succumbed to TB. Recent data show that more than 5 Lakhs new cases of multi drugs resistant (MDR) patients are reported annually.

India alone accounts for ¼th of all TB cases. Each day more than 1,000 peoples are estimated to die of TB. Most of these TB deaths could be prevented with early diagnosis and appropriate treatment. Every effort should be made to achieve the END TB GOAL by 2025.

Paradigm Shift in Diagnosis[2] :

In order to curtail the global TB epidemic there should be paradigm shift from the conventional approach to diagnose tuberculosis to more accurate and early diagnosis of all forms of TB pulmonary as well as extra-pulmonary including rapid detection of drug resistance.

The most widely used test to diagnose TB is sputum microscopy for Acid-Fast-Bacilli (AFB). It lacks sensitivity and specificity. Culture is the gold standard in diagnosis of tuberculosis but it is time consuming (4-8 weeks). There has been rapid evolution of molecular techniques in diagnosis of TB. Molecular assays involve polymerase chain reaction (PCR) or real time PCR which are much more sensitive than sputum microscopy and culture. Several test systems based on mycobacterial nucleic acid amplification are available during recent years[3]. These Nuclei Acid Amplification tests (NAATs) will usher a new era of easy, speedy and accurate diagnosis of tuberculosis. Three tests using molecular techniques have been approved by WHO for tuberculosis control program.

(1) Xpert MTB/RIF (Cepheid Sunnyvale, USA) in 2010

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Editor's Comment :

- **Xpert MTB/RIF and Trunat test utilise molecular techniques based on amplification of mycobacterial nucleic acid in test samples.**
- **They are most useful in the rapid diagnosis of pulmonary as well as extra pulmonary tuberculosis patients of all ages.**
- **They are also very useful in TB HIV coinfection.**
- **The use of these sensitive and specific tests is the right step as initial tests for early diagnosis of TB and rifampicin resistance.**

(2) Xpert MTB/RIF-Ultra (Cepheid Sunnyvale, USA)

(3) Truenat MTB, MTB Plus (Molbio diagnostic Goa)

Other tests which are also used are LPA (Line Probe Assay), Urine lipoarabinomannan lateral flow assay and Molecular loop-mediated isothermal amplification assay (LAMP).

(1) Xpert MTB/RIF[4-6] — Gene Xpert TB assay is an automated PCR test and it detects MTB and Rifampicin Resistance (RR) within two hours. Several studies approved by WHO reported that xpert MTB/RIF is a sensitive method for rapid diagnosis of TB as compared to conservative one.

(2) Xpert MTB/RIF-Ultra[7] — Assay was designed by adding two amplification targets. In 2015, alland et al found that xpert MTB/RIF-Ultra is much more sensitive than xpert MTB/RIF. It is likely to be as sensitive as TB culture.

(3) Truenat-TB Test — Truenat TB test is a new molecular TB test which detects TB bacteria and RR TB by using PCR techniques. In other words it is a real time micro PCR system which enables near patient diagnosis of MTB and it issimple, robust and user friendly. It is a chip based PCR and it involves extraction of DNA, amplification and reading the presence of specific genomic sequence (by PCR Analyzer).

The Truenat has been developed by the Indian Firm Molbio diagnostic Private Limited, Goa.

It takes about 25 minutes to do the DNA extraction, another 35 minutes to diagnose TB and additional 1 hour for testing Rifampicin Resistance.

Truenat Machine is a point of care (POC) tool which is not fully automated. It is designed for situations where there is no electricity and where the need is for one test to be done at a time. In contrast the Gene Xpert is designed for larger volumes and needs reliable electrical supply. Truenat MTB is fully fit to be a POC test for diagnosis of TB and Rifampicin Resistance in primary health

centers(PHC) of India and other middle and low income group countries.

Rapid Communication of WHO, January 2020 :

There is a rapid communication from WHO which aims to provide latest evidences on the use of molecular assays as initial diagnostic test for PTB, EPTB and RR-TB in adults and children.

Key Findings of Latest Evidences by Using Molecular Assays in Initial Diagnosis of Tuberculosis and Resistant TB:

(1) Results of expert MTB/RIF as initial tests to diagnose pulmonary TB have diagnostic accuracy and improved patient outcomes replacing sputum smear microscopy.

(2) Xpert-Ultra has got high diagnostic accuracy replacing smear microscopy. It shows additional advantage of simultaneous detection of Rifampicin Resistance.

(3) Xpert MTB/RIF and xpert-Ultra both are better tools to diagnose TB and Rifampicin Resistance in respiratory and non-respiratory specimens in children.

(4) Xpert MTB/RIF and Xpert Ultra offer better results in diagnosis of TB and detection of Rifampicin Resistance.

(5) Truenat MTB and MTB plus also show high diagnostic accuracy and specificity in diagnosis of tuberculosis replacing sputum smear microscopy and sequentially detect Rifampicin Resistance comparable to Xpert MTB/RIF and Xpert MTB/RIF-Ultra.

Studies and Trials :

Xpert MTB/RIF — 70 studies involving 30 Thousand patients from 37 Countries show that xpert MTB/RIF offer high diagnostic accuracy of pulmonary TB in adults with 85% sensitivity (smear positive and smear negative both) and 98% specificity. In diagnosis of TB with HIV co-infection sensitivity is 81% and specificity 98%. Data suggest that xpert MTB/RIF may be replaced for sputum smear microscopy as initial test.

48 studies involving 8 Thousand patients from 33 Countries confirm simultaneous detection of Rifampicin Resistance with overall sensitivity (96%) and specificity 98% when compared to phenotypic drug sensitivity testing.

Xpert MTB/RIF-Ultra — 6 studies involving 2 Thousand patients from 14 Countries exhibit high diagnostic accuracy of xpert MTB/RIF-ultra with 90% sensitivity with 98% specificity. In HIV co-infection results are similar to xpert MTB/RIF.

5 studies involving 1 Thousand patients from 12 Countries showed similar results of xpert ultra for simultaneous detection of Rifampicin Resistance as compared to xpert MTB/RIF.

Xpert MTB/RIF and Xpert Ultra in Children — Results of 43 studies involving 6 Thousand patients from 21 Countries showed variable results in sensitivity in different specimens (Nasopharyngeal-46%, Stool-61%, Sputum-65% and Gastric Specimen-73%) but specificity was 98-100%. Similar results were obtained in xpert ultra. Results of Rifampicin Resistance showed 90% sensitivity and 98% specificity.

Xpert MTB/Rif and Xpert Ultra in EPTB — EPTB always poses diagnostic difficulties in obtaining extra pulmonary specimens and confirmation of diagnosis. Molecular assays have proved a pillar in diagnosis of extra pulmonary tuberculosis.

Results from 59 studies from 26 Countries showed variable sensitivity from 50% from pleural fluid to 97% from synovial fluid. The specificity also varies from 79% for Lymph node Biopsy to 99% for pleural fluid. Both xpert molecular assays showed overall high performance for simultaneous detection in Rifampicin Resistance.

Truenat — FIND (The Foundation for Innovative New Diagnostics) coordinated multi-central field evaluation study from 4 countries involving 744 participants showed overall sensitivity of the truenat MTB assay (83%) and MTB Plus assay (89%) and specificity of both assays was 98-99%. Truenat MTB/RIF Dx showed comparable diagnostic accuracy for sequential detection of Rifampicin Resistance.

Data Collected from National Tuberculosis Elimination Program (NTEP) Jawaharlal Nehru Medical College, Bhagalpur (Bihar).

Using the conventional approach of LED sputum microscopy in more than 6,000 patients only 10.13% positivity could be detected during 2018 & 2019 (Table 1).

Using Xpert MTB/RIF (CBNAAT) involving more than 6,000 patients more than 22% patients detected to be MTB Positive while there was simultaneous detection MTB Resistance in more than 3% cases. Data proves that use of CBNAAT gives clear advantage for early initial diagnosis of tuberculosis over conventional sputum microscopy. Limitation of this data is non-confirmation of this data with reference to culture and DST (Table 2).

Table 3 shows data involving more than 900 patients when subjected to CBNAAT testing showed more than 19% positivity in smear negative cases.

In more than 700 extra-pulmonary specimens 11% of these showed Rifampicin Sensitivity and about 2% showed Rifampicin Resistance (Table 4).

In cases of TB and HIV co-infection MTB detection was found to be around 10% and Rifampicin Resistance was detected in more than 2% (Table 5).

Table 1 — *Details of specimen tested by smear microscopy*

Year	Total specimen tested by smear microscopy (LED)	Total AFB positive detected	No of M TB detected	Rifampicin resistance detected
2018	3066	282 (9.19 %)	NA	NA
2019	3695	403 (10.90 %)	NA	NA
Total	6761	685 (10.13%)		

LED - Light Emitting Diode

Table 2 — *Details of specimen tested by CBNAAT (Xpert MTB/RIF)*

Year	Total specimen tested by CBNAAT	No of M TB detected	Rifampicin resistance detected
2018	3169	604 (19.05 %)	113 (3.56 %)
2019	2926	745 (25.46 %)	88 (3.00 %)
Total	6095	1349 (22.13%)	201 (3.29%)

Table 3 — *Details of smear negative cases further tested by CBNAAT (Xpert MTB/RIF)*

Year	Number of smear negative cases further tested by CBNAAT	No of M TB detected	Rifampicin resistance detected
2018	246	39 (15.85 %)	3 (1.21 %)
2019	667	136(20.38 %)	15 (2.24 %)
Total	913	175 (19.16%)	18 (1.97%)

M TB - Mycobacterium Tuberculosis,
CBNAAT - Cartridge Based Nucleic Acid Amplification Test

Table 4 — *Details of extra-pulmonary specimen tested by CBNAAT (Xpert M TB/RIF)*

Year	Number of extra-pulmonary specimen tested by CBNAAT	No of M TB detected	Rifampicin resistance detected
2018	312	38 (12.17 %)	8 (2.56 %)
2019	443	50 (11.28 %)	7 (1.58 %)
Total	755	88 (11.65%)	15 (1.98%)

In pediatrics cases MTB detection was more than 10% and Rifampicin Resistance was detection in more than 1%.

Data from NTEP Jawaharlal Nehru Medical College, Bhagalpur also shows that if Xpert MTB/RIF (CBNAAT) is used as initial test for diagnosis of tuberculosis in adults with pulmonary and extra pulmonary TB, HIV co-infection and pediatric tuberculosis it will lead to early diagnosis and hence early initiation of treatment of tuberculosis.

Conclusions :

(1) All the latest evidences reviewed by WHO recommend the continued use of Xpert MTB/RIF and Xpert MTB/RIF-Ultra as initial diagnostic test of PTB of all ages.

(2) These data support the use of both these molecular assays in the diagnosis work-up of EPTB and Childhood tuberculosis.

(3) Both assays also exhibit high diagnostic accuracy in diagnosing Rifampicin Resistance simultaneously.

(4) Performance of Truenat MTB, MTB Plus and MTB/RIF Dx assays show comparable accuracy with xpert MTB/RIF and xpert Ultra for TB detection and for sequential Rifampicin Resistance (Truenat MTB/RIF Dx)

(5) Truenat MTB and MTB Plus assays are comparable to TB-LAMP assay as replacement test for sputum smear microscopy.

(6) Truenat MTB/RIF Dx is comparable to Line Probe Assays in diagnostic accuracy.

Table 5 — *Details of specimen of PL-HIV cases tested by CBNAAT (Xpert MTB/RIF)*

Year	Specimen of PL-HIV cases tested by CBNAAT	No of M TB detected	Rifampicin resistance detected
2018	379	28 (7.38 %)	7 (1.84 %)
2019	200	28 (14.00 %)	7 (3.50 %)
Total	579	56 (9.67%)	14 (2.41%)

Table 6 — *Details of specimen of pediatric cases tested by CBNAAT (Xpert MTB/RIF)*

Year	Specimen of pediatric cases tested by CBNAAT	No of M TB detected	Rifampicin resistance detected
2018	159	18 (11.32 %)	2 (1.25 %)
2019	208	21 (10.09 %)	2 (0.96 %)
Total	367	39 (10.62%)	4 (1.08%)

The updated Guidelines on Molecular Assays as initial tests for the diagnosis of TB are to be released in April 2020. Meantime "National TB Programmers and other stakeholders are encouraged to conduct high-quality implementation/operational research to collect more evidence on the accuracy,effectiveness, feasibility,acceptability,cost,and impact of WHO-recommended diagnostic tools for TB".

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Case Discussion in Medicine

A 19 year-old-primigravida with new onset headache and seizure at the third trimester

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Section 1 :

19 year-old-primigravida, 38 weeks gestation presented with acute onset of headache of 2 days duration followed by four episodes of generalised tonic-clonic seizures of 1 day duration . On examination patient had elevated blood pressure 164/96 mmHg, pedal oedema, drowsy state and withdrawal movements of limbs to painful stimuli and no neck stiffness. She was immunized and had regular antenatal visit with no comorbidities.

Question for consideration :

(1) What are the differentials based on the history and examination ?

Section 2 :

The patient was previously healthy and presented with new onset headache and seizure in third trimester of pregnancy and examination showed elevated blood pressure and altered sensorium. (a)Eclampsia would be the first differential (b) subarachnoid haemorrhage (c) cerebral venous sinus thrombosis. d) Ischemic stroke and haemorrhage . CVA was less likely as there was no focal deficit but cannot be ruled out without imaging. e) Central nervous system infection was least likely as there was no fever and neck stiffness.

Question for consideration :

(1) What is the next step?

(2) What is the Antiepileptic drug choice and imaging choice in this patient?

Section 3 :

Magnesium sulphate is the recommended drug for eclampsia. If seizure is not controlled by magnesium sulphate, antiepileptic drugs like fosphenytoin, levetiracetam and lacosamide can be added but other management of eclampsia should be addressed immediately which includes immediate termination of pregnancy by emergency C-section and blood pressure reduction. our patient received intravenous magnesium sulphate loading dose followed by maintenance dose for seizure and inj. labetalol for hypertension. Investigations revealed proteinuria further supporting eclampsia with normal blood parameters and electrolytes except low hemoglobulin (10.5 gm/dl).

Editor's Comment :

- **Acute encephalopathy associated with hypertension, PRES should be one of the differentials.**
- **Accelerated hypertension, eclampsia, autoimmune diseases, renal failures and drugs are the known risk factors.**
- **CT Brain is the immediate investigation and MRI Brain with MRA and MRV is the ideal investigation for PRES.**
- **Parieto-occipital pattern (most common), holo-hemispheric watershed pattern, superior frontal sulcal pattern and central pattern are different radiological presentations of PRES.**
- **PRES carries good prognosis and management involves treatment of risk factors, blood pressure and antiepileptic drugs.**

Though CT brain has radiation exposure to foetus, it is the first investigation done in neurological emergency. To minimize radiation exposure to foetus, it can be done with lead shield covering abdomen. Our patient didn't have infarct or haemorrhage in CT brain. She underwent emergency C-section in view of eclampsia. Post C-section patient didn't have any seizure and magnesium sulphate was continued along with antihypertensive.

Question for consideration :

(1) Is MRI brain necessary in this patient?

Section 4 :

Though CT brain is the first investigation, it is not ideal investigation for neurological emergency. MRI brain with MRA and

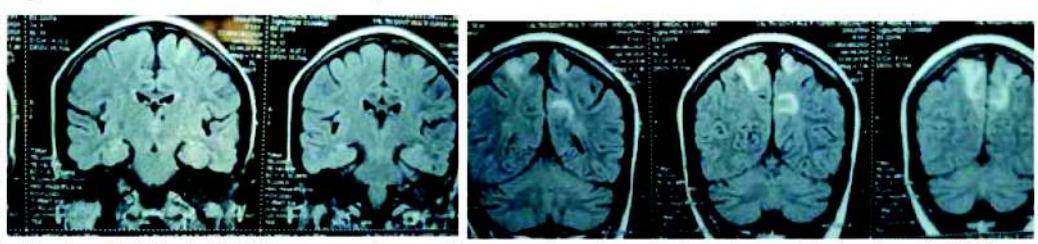

Fig 1 — MRI brain FLAIR sequence shows white matter hyperintensity in parieto-occipital region s/o PRES

MRV should be done to rule out cerebral venous sinus thrombosis in this case which can be easily missed in plain CT brain. Our patient underwent MRI brain on day 2 post C-section which revealed bilateral T2/FLAIR hyperintensity in white matter of parieto-occipital region suggestive of Posterior Reversible Encephalopathy Syndrome (PRES) (Fig 1). Patient sensorium improved with supportive treatment and oral labetalol was continued with blood pressure monitoring. She was discharged in full conscious state with no focal deficit on day 12 post LSCS and labetalol was stopped during follow up.

Question for consideration :

(1) What is posterior reversible encephalopathy syndrome (PRES)?

(2) What is the association between PRES and Eclampsia?

(3) What are the radiological features of PRES?

(4) How do you treat it?

(5) What is the prognosis and complications of PRES?

Section 5 :

Posterior reversible encephalopathy syndrome (PRES) is a clinical-radiological syndrome characterised by reversible acute neurological symptoms like headache, blurred vision, seizure and altered sensorium associated with an imaging evidence of vasogenic oedema in the white matter of brain predominantly in parieto-occipital region[1]. It occurs as a result of failure of cerebral blood pressure autoregulation when blood pressure is elevated suddenly leading to hyperperfusion and vasogenic oedema and other mechanisms include toxic or immune mediated damages to endothelial cells of brain capillaries leading to white matter oedema. Accelerated hypertension, eclampsia, renal failure, autoimmune diseases (Systemic lupus erythematosus, polyarteritis nodosa) and drugs (cyclosporin A, bevacizumab, cisplatin, methotrexate, biological agents) are the known risk factors associated with PRES which mediate above pathogenesis[2]. Though it is a neurological condition, it is often encountered in other specialities like obstetrician, nephrologist, rheumatologist and medical oncologist due to these associated risk factors.

In pregnant woman, PRES is commonly seen in association with preeclampsia/eclampsia.Among 104 eclampsia patients, 74(71%) eclampsia patients had radiology features of Posterior reversible encephalopathy syndrome in a large prospective Indian cohort study[3]. It usually occurs at the third semester and puerperium. Headache and seizure in peripartum period should include PRES as one of the differential diagnosis apart from eclampsia, cerebral venous thrombosis, vascular insult and meningoencephalitis.

Four patterns have been described in MRI based on the region involved (1) Parieto-occipital (most common), (2) Holo-hemispheric watershed pattern, (3) Superior frontal sulcus pattern and (4) Central pattern involving deep white matter, basal ganglia and brainstem[4]. Our patient had most common parieto-occipital pattern.Normally anterior circulation is adequately supplied by adrenergic sympathetic fibres compared to posterior circulation which has inherent deficiency of adrenergic control making it more susceptible for hyperperfusion injury and vasogenic oedema in posterior region of brain.Top of basilar stroke causing bilateral posterior cerebral infarction should be differentiated from PRES as both causes bilateral posterior lesion but latter usually spares calcarine and paramedian parts of occipital lobe.

Management of PRES involves treatment of risk factors, antihypertensives, stopping offending drugs and antiepileptics. Our patient received magnesium sulphate for seizure and pregnancy was terminated immediately with C-section as a management of eclampsia and blood pressure was controlled with inj. labetalol.Blood pressure control is very important in PRES management as inadequate control and delay are associated with an increased morbidity and mortality. Blood pressure needs to be gradually reduced except in malignant hypertension as more aggressive reduction leads to cerebral ischemia and clinical worsening. The general recommendation is to reduce 10-25% of mean arterial blood pressure over a 24-hour period except in malignant hypertension where 25% of blood pressure reduction is recommended in first 6 hours. Nicardipine, labetalol, clevidipine are short acting, rapidly reversible, the titratable safe intravenous antihypertensive drugs for hypertensive emergencies.

PRES is a reversible condition and 75 to 90% recover fully. Irreversible neurological injury and permanent deficits are seen in around 10-20% cases where MRI brain reveals associated complications like infarction or haemorrhage. Our patient recovered fully with out neurological deficit and MRI brain also didn't reveal any infarction or haemorrhage.

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History of Medicine

Women in Medicine : The path was never easy

For a long time, women were denied entry into medical schools all over the world. While this was true for all branches of education, for medical science, the professional environment was particularly hostile towards women. The pioneering psychiatrist of England in the nineteenth century, Henry Maudsley, even commented that too much education, especially in medical science, may cause menstrual irregularity and sterility in girls!! This short article will narrate the resistance faced by some of the early female doctors in the nineteenth and twentieth centuries.

In Britain, Elizabeth Garrett Anderson was the first woman qualified to add her name to the medical register in 1866. She obtained her Society of Apothecaries licence in 1865 and joined the medical register a year later. She had to take this circuitous route as no medical school at that time allowed female students. Elizabeth had at first enrolled as a nurse in Middlesex hospital and started attending classes for male doctors. But when those students complained, she was barred from attending the classes. So, she applied to the society of Apothecaries and was able to study there. But after her graduation, even the Society of Apothecaries changed its rules to prevent future female students. She was able to join the British Medical Association in 1873 and for 19 years, remained the sole female member.

In 1875, Mrs Anderson was scheduled to read a paper on Obstetrics at the annual conference of the BMA in Edinburgh. At the last moment, the organizers became aware that the speaker was a woman and they tried to protest and block her from the presentation. However, she was able to speak nonetheless. However, after this event, the other members of the BMA added a clause to the articles so that no other woman would be able to get membership of the association. This prohibition was lifted only in 1892.

In 1866, Garrett also opened the St. Mary's Dispensary for Women in London. For a long time, she was the only physician there as male physicians of the time did not want to work with a woman. So she remained the physician, surgeon, pharmacist, midwife and clerk of that hospital and also did home visits. In 1970, she passed her MD from the University of Paris (as British schools did not have provisions to admit female students). She travelled from London to Paris repeatedly and successfully passed all parts of the examination. Her thesis was on migraine. But the British Medical register did not recognise her degree at that time.

In 1878, Dr Anderson performed the first ovariotomy as a woman surgeon. But the operation could not be performed in a hospital as it was considered a risky procedure and death of the patient would risk the reputation of the hospital. So she had to rent a private house, get the rooms cleaned and bring in the nurses.

Dr Anderson also helped found the London School of Medicine for Women in 1874. She taught there for 23 years and later became the dean. However, the founding of this medical school required the determination of another woman, Sophia Jex-Blake, whom we will describe next.

Kadambini Ganguly
— the first female in India to get a degree in Western Medicine in India

For Sophia Jex-Blake, the path was even more difficult. She was born in a conservative family in Sussex. However, it was her trip to America that influenced her profoundly and inspired her to take up medicine as a career. She was admitted to Women's Medical College of the New York Infirmary in 1868. But the next year, her father died and she had to return to England.

In 1869, Jex-Blake was admitted to the Edinburgh University medical school but the university later overturned the decision and decided not to allow females to study. But Jex-Blake was not someone to give up easily. She campaigned hard and in 1870, she and four other female students were readmitted. But they had to attend separate classrooms and pay higher tuition fees. But pressure was mounted by the opponents of female education and the University soon stopped the separate classes and ordered the female students to seek tuition at the nearby Royal Infirmary. Some faculty member at Edinburgh commented that ".....women didn't understand their position, that they did their own work in the world badly, that they had not sufficient strength for medical practice." The hospital refused to teach female students.

On 18th November 1870, a memorable incident took place, known as "Surgeon's Hall Riot". The female medical students at the University of Edinburgh were to attend an anatomy examination at the Surgeon's Hall. As they were about to enter, they were blocked by a large group of male students and other hoodlums. They were verbally abused, refuse and mud was pelted on them and the gate was closed. They were finally able to enter but the problems were far from over. During the examination, a live sheep was released into

the examination hall to disrupt the process. By the time the examination ended, the female students were all covered in mud. This was not an isolated incident but the culmination of months of bullying, threatening mails and negative social environment. Even when the sheep was pushed inside the examination hall, one of the professors is said to have remarked "The sheep can stay, it is clearly more intelligent than those out there."

However, media coverage of this riot helped create groundswell support for the women. A General Committee for Securing a Complete Medical Education for Women was formed, Charles Darwin being one of the members. This group tried to garner support in favour of female medical education.

Finally these medical students were refused graduation by the university in 1873. They appealed in court, but failed. In desperation, Jex-Blake opened the London school of medicine for Women.

Bu the battle was not over. This new London school could teach female students but they were not authorized to give degrees. For that they needed approval of a university. But all the British universities declined to allow female medical students to sit for final exams. Finally, in 1876, the UK Medical Act was passed which allowed female students to be licenced as doctors. The College of physicians of Ireland was the first to implement this new rule and Jex-Blake was finally able to sit her final exam in Dublin to get the degree. She also obtained an MD from Berne. But it was still difficult for her to get accepted in the medical world. For example, when she wrote an article for the Lancet, she received the reply that the journal "...could not stoop to record medical experiences, however interesting, if they occurred in the practice of the inferior sex."

Just to mention here, Jex-Blake was a trailblazer in more ways than one. She had to struggle for her degree and also struggle for her personal life. In a time when homosexuality was seen as unnatural in the UK, she maintained a lifelong romantic relation with Dr Margaret Todd. This must have also created hardships for her.

There were altogether seven women in this saga, known as "Edinburgh seven". One of them, Dr Edith Pechey, moved to the then British colony of India. In Mumbai she became medical officer of the Cama Women and Children's hospital. Among other pioneering works she did, was sponsoring one of the first female doctors of India, Rukmabai.

We will end this article with the story of two Indian female doctors. In 1889, Rukmabai went to England, helped by Dr Pechey and Eva McLaren, to study medicine at London school of medicine for Women. But before going to England, she was already famous for a different reason. Rukmabai was married off at the age of eleven, as was the norm then in India. She lived with her parents for education. Later, when her husband asked her to go and live with him, she declined. She said that she had been married in her childhood without consent and she did not want to continue the marriage. There was a memorable court case. Rukmabai lost the case and was ordered to live with her husband or face imprisonment. She refused to go to her husband. Finally, she appealed to Queen Victoria, who overruled the court verdict and annulled the marriage. This case paved the way for age of consent in marriage in British India.

Rukmabai went to England. She successfully completed her degree and came back to practice in India. She mainly worked in Surat. She was the second woman after Bengal's KadambiniGanguly, to practice medicine in India.

Kadambini Ganguly (1861-1923) was the first female in India to get a degree in Western Medicine in India. She did not stop there and travelled to Europe to get additional qualifications from Edinburgh, Dublin and Glasgow. She came back to India and started her private practice. There were many men who opposed her work and in one prominent Bengali magazine, her moral character was also questioned. Also one prominent Bengali magazine (so called symbol of Bengali enlightenment) tried to start a campaign against her that she was unqualified. But facing male opposition was nothing new to her. Many male teachers at the Calcutta Medical College were against her education and it is said that one teacher deliberately failed her by one mark in one subject in the final examination. But these incidents did not stop her. She managed a household of eight children, did a successful private practice and also was active in contemporary politics.

These anecdotes make it clear that the first women in medicine, the trailblazers, had to endure a lot of obstacles to get their foothold in the medical world. Their struggles made it easier for later women to excel in medicine and overcome gender inequality. Occurring in nineteenth century England, these anecdotes are all the more surprising as a woman, Queen Victoria, was at the helm of power in that country. This article is not exhaustive. There are many other stories to be told. But the author wishes to reserve them for a future publication if he gets the opportunity.

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Mediquiz

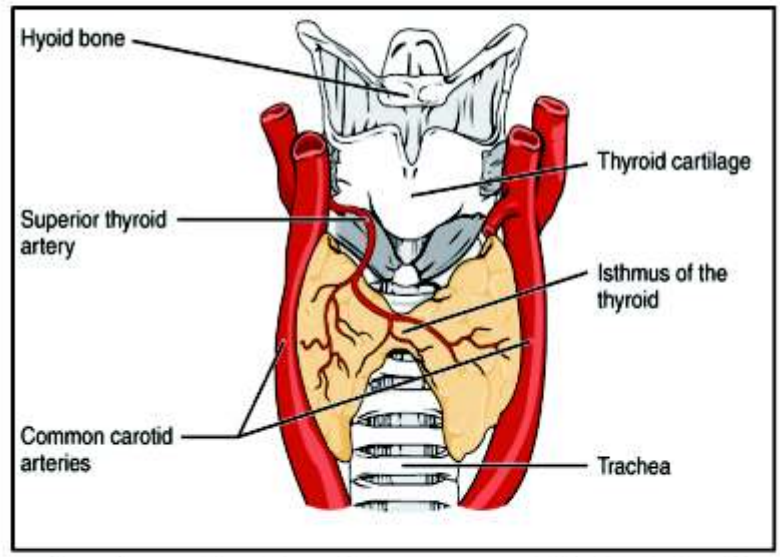
Rudrajit Paul[1]
Quiz Master

Series - 1

Thyroid disorders

(1) A 38 year old woman came to the emergency with palpitation, tremor and restlessness. On examination, she had pulse: 130/min, BP : 150/70 mm of Hg and fine tremor in hands. There was no goiter, exophthalmos or thyroid bruit. She was sweating profusely. Emergency ECG showed only sinus tachycardia. Her brother said that she had had similar episodes twice in the past, which were diagnosed as anxiety disorder. She denied any addiction. The next day, her TSH value came as 0.03 µIU/L. Serum T4 was elevated. What is the next best test for diagnosis of the condition ?

(a) Serum T3
(b) Thyroid scan
(c) Serum thyroglobulin
(d) Serum anti-TPO antibody level



(2) A 29 year old woman, a primigravida, presented in the 11th week of gestation with severe vomiting. She also complained of headache, weakness and palpitations. Her pulse was 110/min, regular and blood pressure was normal. Rest of the clinical examination was normal. Laboratory reports showed TSH 0.1 µIU/L and fT4 38 pmol/L (N; 10—20). What is the next best course of action?

(a) Wait and watch
(b) Start anti-thyroid drugs (PTU)
(c) Terminate the pregnancy
(d) Do a thyroid scan to determine the cause

(3) Plummer's nails are a typical feature of hyperthyroidism. Which is the commonest anatomical location for this nail change?

(a) Great toe
(b) Thumbs
(c) Little finger
(d) Ring finger

(4) A 49 year old woman presented with abdominal swelling, weight loss and profuse sweating. She had tachycardia, tachypnea and pedal edema. Her TSH level was 0.03 µIU/L. There was no goitre, eye signs or skin changes. Serum thyroglobulin was high. What is the next best test to be done for diagnosis?

(a) Thyroglobulin level
(b) CECT abdomen
(c) TrAb level
(d) Thyroid gland colour Doppler study

(5) A 23 year old man is admitted with recurrent palpitations. He had been diagnosed with atrial fibrillation 1 year ago and started on amiodarone. This time, on examination, he is found to have nogoiter. TSH level was 0.07 µIU/L and fT4 level was 50 pmol/L. Anti-TrAb was negative. A thyroid scan showed markedly reduced uptake. What is the next best line of management ?

a. Oral steroids
b. Stop the Amiodarone
c. Wait and watch
d. Start anti-thyroid drugs

(Answer : next page)

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Answer : Mediquiz

1. C

Explanation : This patient has presented with features of hyperthyroidism, which is also supported by the preliminary biochemical tests. From history, this seems to be a case of recurrent hyperthyroidism episodes. Grave's disease can rarely cause such episodes. But in complete absence of any other clinical feature, this is unlikely. Recurrent thyroiditis is a possibility, as is factitious thyrotoxicosis. In thyroid scan, both will show decreased uptake. But serum thyroglobulin will be high in endogenous thyrotoxicosis like thyroiditis or drug induced thyroid hyper-function while it will be low in exogenous thyrotoxicosis. So, if serum thyroglobulin level is low in this scenario of biochemical hyperthyroidism, then exogenous thyroxin intake is the only possibility and this will clinch the diagnosis easily. Serum anti-TPO level is a non-specific marker. It can be positive in Grave's disease or thyroiditis.

(2) A

Explanation : The presentation of this woman is likely to be transient gestational thyrotoxicosis. This is a common occurrence, especially in women with hyperemesis gravidarum. This apparent thyrotoxicosis is caused by high levels of HCG, which have a common subunit with TSH. This can, thus, stimulate the TSH receptor and lead to high T3 and T4 levels. There is no need of anti-thyroid drugs as the condition resolves spontaneously by 14-15th gestational week. So, symptomatic management with replacement of fluid and electrolytes is mostly enough. If the biochemical hyperthyroidism persists after 20th week of gestation, then search for other pathologies may be needed. Of course, if there are florid clinical signs of Grave's disease in first trimester, like exophthalmos or goiter, then the management will be different. Thyroid scan is contraindicated in pregnancy.

(3) D

Explanation : Plummer's nails are a rare manifestation of thyrotoxicosis. But if present, they are highly suggestive of the diagnosis. Historically, it has been seen that this clinical finding is commonest in the fourth digits of hands. Differential rates of growth of the nails and underlying nail beds lead to onycholysis. In advanced stages, other fingers may also be involved.

(4) B

Explanation : This patient has features of thyrotoxicosis with abdominal swelling, pedal edema and weight loss. So, the possibility of an abdominal tumour causing ectopic thyroid hormone secretion must be thought of. If this is an ovarian tumour, the condition is called struma ovarii. This is a rare tumour and in 10% of cases, it may be malignant. So, a CECT abdomen would be the best next step for diagnosis. Serum thyroglobulin level will be high in Struma ovarii and thus, it will not help in diagnosis.

(5) A

Explanation : This patient has amiodarone induced thyroiditis (AIT) type 2. This is diagnosed by reduced radiotracer uptake, absence of goitre and absence of antibodies. For this condition, oral steroids are the first choice of therapy. Amiodarone can only be stopped in consultation with the cardiologist, provided alternative drugs are available. But this decision will take time. But AIT is a medical emergency and the steroid has to be started early.

Drug Corner

Nitrofurantoin : Old Molecule Revisited

Prem Kumar[1]

Urinary tract infections (UTIs) are one of the most common bacterial infections affecting nearly 150 million people each year worldwide. The main goal of the UTIs therapy is to provide symptomatic relief for the patients. Several antibiotics are available for the management of UTIs. Nitrofurantoin is unique and first-line antibiotic approved for the treatment of UTI. It a broad-spectrum bactericidal antibiotic that, through a complex mode of action which is not completely understood, affects both Gram-negative and Gram-positive bacteria. Nitrofurantoin macro-crystalline formulations has several advantages over initially developed microcrystalline form with less side effects. The macro-crystalline formulations of nitrofurantoin has replaced the initially developed micro-crystalline because of its advantages like low interaction with food, better tolerance and lesser side effects. Many clinical studies have proven that nitrofurantoin is an effective antibiotic and compares well with the other antibiotics for the long-term prophylaxis. It is indicated for the treatment of lower UTI, recurrent UTI, uncomplicated UTI or acute uncomplicated cystitis in women, etc. Nitrofurantoin was safe and effective for the treatment of UTIs in children, diabetes and in pregnant women. Several guidelines such as IDSA, NICE and SIGN have recommended nitrofurantoin for the treatment of UTI. The present review discusses the mechanism of action, antimicrobial spectrum, pharmacology, safety profile and therapeutic use of nitrofurantoin, including recent data which highlight its role in the management of urinary tract infection.

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Key words **: Urinary tract infection, Nitrofurantoin, Macro-crystalline Nitrofurantoin, Recurrent UTIs, Cystitis.**

Urinary tract infections (UTIs) are one of the most common bacterial infections affecting nearly 150 million people each year worldwide.[1] UTI occurs due to the presence of microbial pathogens within the urinary tract. Depending on the site of infection it is classified as cystitis (bladder), pyelonephritis (kidney) or bacteriuria (urine).[2]While, clinically UTI is categorized as complicated or uncomplicated UTI.[1]

UTI is more prevalent in women as compared to menand is the most common concern for women.[3]Approximately, 60% of the adult women and 10% of the post-menopausal women would be presented with at least one symptomatic UTI in their life.[4] Also, the UTIs prevalence increases with age such that it increases 10 to 20% in women age more than 65 years. All these makes UTI an important concern in the increasingly aging population. UTI leads to 8.6 million health care visits and around 1.6 billion dollars of an estimated costs.[3]The key clinical classification of UTI according to the most recent guidelines is depicted below[4] (Table 1).

PREDISPOSING FACTORS :

The most common diagnostic symptomsof UTIs are change in urination frequency, dysuria, urgency, and presence or absence of vaginal discharge, these symptoms present differently in older women (Table 2).[3]

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Editor's Comment :

- **Nitrofurantoin is a broad spectrum antibiotic with complex mode of action.**
- **It is recommended as a first-line antibiotic for the treatment of UTI.**
- **Macro-crystalline formulations of nitrofurantoin has several advantages with fewer side effects.**
- **It is indicated for LUTI, recurrent UTI, catheter associated UTI, multi drug-resistant strains UTI and acute uncomplicated cystitis in women.**
- **Nitrofurantoin is also indicated for treatment of UTI in special population such as pregnant women, diabetes and children.**

PATHOGENESIS :

Urinary tract infection is a complex event. The infection arises when the bacterial virulence mechanisms overcome the host defense mechanisms. In the pathogenesis of UTI, bacterial adhesion to the uro-epithelium is an important step.[5]Gram-positive and Gram-negative bacteria, as well as certain fungi are the causative agents for UTIs. Out of which the most common causative agents for both the complicated as well as for uncomplicated UTIs is *Escherichia coli*.[1]

MANAGEMENT :

There are several antibiotics available for management of UTIs. The main goal of the UTIs therapy involves symptomatic relief for the patients. For the appropriate clinical response antibiotic therapy which achieves higher concentration in urinary tractis recommended. For cystitis,

Table 1 — *Key classification of UTIs*[4]

Classification	Definition
Uncomplicated UTI	A UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk or developing serious complications
Acute uncomplicated cystitis	A lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis
Acute uncomplicated pyelonephritis	An upper UTI with persistent symptoms including flank pain, flank tenderness, or fever (>38°C)
Asymptomatic bacteriuria	A positive urine culture (>10^5 colony-forming units/mL) in the absence of urinary
Recurrent uncomplicated UTIs	A recurrent UTI refers to the occurrence of ≥2 symptomatic episodes within 6 months or ≥3 symptomatic episodes within 12 months

UTI, urinary tract infection

Table 2 — *Predisposing risk factors for UTI*[5]

Patient population	Risk factors
Premenopausal women of any age	• Diabetes • Diaphragm use, especially those with spermicide • History of UTI or UTI during childhood • Mother or female relatives with history of UTIs
Postmenopausal and older adult women	• Estrogen deficiency • Functional or mental impairment • History of UTI before menopause
Men and women with structural abnormalities	Extrarenal obstruction associated with congenital anomalies of the ureter or urethra, calculi, extrinsic ureteral compression, or benign prostate hypertrophy Intrarenal obstruction associated with nephrocalcinosis, uric acid nephropathy, polycystic kidney disease, hypokalemic or analgesic nephropathy, renal lesions from sickle cell disease

response occurs within 24 hours and in 48-72 hours for pyelonephritis. The selected antibiotic should have lesser impact on normal bacterial flora of vagina. Antibiotic which has less adverse events should be used for the treatment.

Hydration is often done which removes the infected urine by frequent bladder emptying during the UTI management. Depending on the susceptibility of *E coli* and other uropathogens, therapy was initiated. The recommended first-line antibiotics for the treatment of UTI includes nitrofurantoin, trimethoprim/sulfamethoxazole, fluoroquinolones, and fosfomycin.[5]

Nitrofurantoin has good efficacy, used as first-line agents for UTI in pregnancy, etc. and susceptible towards most of the uropathogens compared with other antibiotics.[3]

NITROFURANTOIN

Nitrofurantoin is a unique antibiotic approved by FDA in 1953 for the treatment of uncomplicated lower UTI.[6] It belongs to the nitrofuran family, characterized by a hydantoin ring with a nitro-substituted furanyl side chain (Fig 1).[7]It is effective against both gram-positive and gram-negative organisms.[6]

Mechanism of action :

The exact mechanism of nitrofurantoin is not fully understood and presumably multifactorial.[8] It uses various mechanisms to achieve an antimicrobial effect.[6] The nitrogroup coupled onto the heterocyclic furan ring is the specific active site of the drug.[7] It gets activated inside the bacteria by rapidly reducing to 'highly reactive electrophilic' reactive metabolites by flavoproteins (Nitrofuranreductase).[8,9]

These reactive intermediates inhibit ribosomal proteins, DNA, RNA, metabolic enzymes, and other intracellular components that involve in bacterial carbohydrate metabolism at three points in the Krebs cycle as well as interfering with cell wall synthesis.[7] The multiple mechanism for nitrofurantoin responsible for the low resistance against it.[9]

Antimicrobial spectrum :

Nitrofurantoin is a broad spectrum antibiotic. It is effective against most of the gram-negative, gram-positive, and anaerobic bacteria. It hasbactericidal activity against most of the common uropathogens, including *Escherichia coli, Enterococci, Klebsiella, Staphylococcus saprophyticus, and Enterobacter*. Shigella, *Salmonella, Citrobacter, Neisseria, Bacteroides,* group B *streptococcus, Staphylococcus aureus, and Staphylococcus epidermidis* are also included in its spectrum of susceptibility.[6]

Pharmacology :

Nitrofurantoin has 80% bioavailability in the healthy adults and is well absorbed in gastrointestinal tract.[6] It is mainly excreted in the urine and bile with urinary excretion rate of 40%.[7] It achieves its therapeutically active concentrations in the lower urinary tract and does not reach to its therapeutic concentrations in the other sites of the body.[10]

As compared to other drugs nitrofurantoin is relatively safer. Nausea, vomiting, loss of appetite and diarrhea were few commonly reported side effects. While, the newer macro-crystalline formulations has less side effects than the older microcrystalline one.[7]

Nitrofurantoin macro-crystalline vs. microcrystalline formulations:

Initially, nitrofurantoin was developed in microcrystalline form as nitrofurantoin monohydrate. But, recently macro-crystalline formulations has replaced

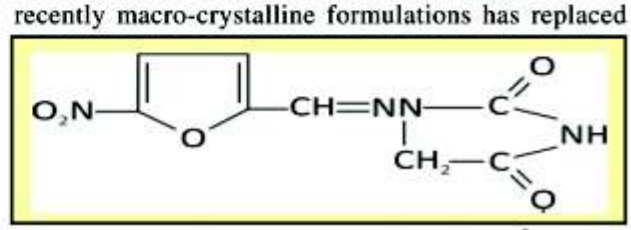

Fig 1 — Chemical structure of Nitrofurantoin[7]

Macro-crystalline formulations advantages: [11]

- **Less side effects.**
- **Slower absorption rate improved gastrointestinal tolerance.**
- **Slower excretion rate. [microcrystalline formulation has 50% higher excretion rate]**
- **Administration with food:**
  - ✓ **Increase exposure to uropathogens**
  - ✓ **Minimizes side effects**
  - ✓ **Increases absorption rate**
- **Higher plasma concentrations (1.8 mg/L) [while microcrystalline formulation has 0.99 mg/L] which increases up to 4.6 mg/L with food.**

microcrystalline formulations due to the unwanted gastrointestinal side effects seen withmicrocrystalline formulation because of its rapid absorption.[10]

Indications :

The recommended doseof nitrofurantoin for UTI is 50 mg or 100 mg four times a day.[7] Till 1970swhen trimethoprim-sulfamethoxazole and newer beta-lactam antibiotics became available,nitrofurantoin was widely used for the treatment of LUTIs. But recently, several major guidelines have recommended nitrofurantoin as the first-line therapy for the treatment of uncomplicated LUTIs.

Use of nitrofurantoin was re-started with increasing resistance to newer antibiotics corresponding with increasing prevalence of extended-spectrum beta-lactamase (ESBL) producing bacteria.The treatment and prophylaxis of UTI was the primary use of nitrofurantoin.It shows equivalent results as that of comparators in themeta-analysis for clinical cure of uncomplicated UTI. Clinical studies demonstrated that nitrofurantoin is an effective antibiotic and compares well with the other antibiotics for the long-term prophylaxis.[6] Nitrofurantoin is used for:

- LUTI
- Recurrent UTI
- Uncomplicated UTI in women
- Acute uncomplicated cystitis in women
- Multi-resistant strains UTI
- Nosocomial vancomycin-resistant *enterococci* (VRE) or VRE catheter-associated bacteriura
- Catheter-associated bacteriuria
- *E.coli* against Non-ESBL
- Alternative for ESBL-producing *E.coli*-related LUTI

In special population :

- Bacteriuria in pregnancy
- UTI in pediatrics
- Bacteriuria in neurogenic bladder patients
- First line management of UTI in diabetes patients-100 mg three times daily for 5 days[12]

CLINICAL EVIDENCES:

- **Assessing safety and efficacy of nitrofurantoin for lower urinary tract infection (LUTI)[13]**

One of the most common life threatening infection is the urinary tract infection (UTI). For the treatment of UTI, various antibiotics are used but, increase in the resistance among pathogenic organisms is the major concern in choosing effective treatment. Bansal N, et al., conducted the study to investigate the efficacy and safety of nitrofurantoin in the treatment of LUTI.

The open-label, single-arm study enrolled 70 patients diagnosed with LUTI. Enrolled subjects received 100 mg nitrofurantoin two times a day for five days after which the efficacy was evaluated by the loss of symptoms and eradication of organism on culture.

The sensitivity of the nitrofurantoin was reported to be 84.3%. While, the highest sensitivity was observed with Proteus (87.5%), followed by *E. coli* (84.7%), *Staphylococcus aureus* (83.3%), *Klebsiella* (70%), amongst all the pathogenic organisms. On the repeat culture, 91.5% was the bacterial eradication rate (Fig 2). While, nausea was the common reported adverse effect.

The study concluded that nitrofurantoin was safe and effective in the treatment of LUTI with lowest reported resistance.

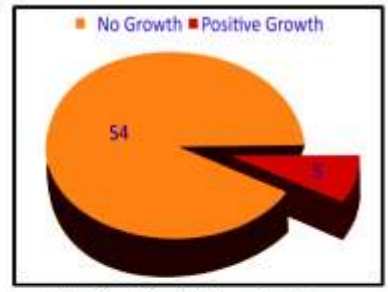

Fig 2 — Bacterial eradication on repeat urine culture

- **Evaluating the safety and efficacy of nitrofurantoin in comparison with the ciprofloxacin in the UTI patients[9]**

The prospective study was conducted by Kaur R *et al.*, with an aim to evaluate the efficacy and tolerability of nitrofurantoin and ciprofloxacin in the UTI patients.

The prospective, open, randomized, parallel-group, comparative study enrolled 60 patients diagnosed with acute/uncomplicated or recurrent UTI. The subjects were randomized (1:1) to receive nitrofurantoin 100mg BD or ciprofloxacin 500mg BD for 5 days for uncomplicated UTI and for 15 days in case of recurrent UTI. Bacteriological response was recorded by evaluating urine culture at the end of the study.

The study reported that *E. coli* (80%) was the most common uropathogen related with uncomplicated UTI, while, *Klebsiella, Staphylococcus aureus, Providencia* were the other organisms detected (3.33%). Post treatment urine culture, significant difference was observed between the two groups in the growth of micro-organisms (P= 0.017) (Fig 3).

The results suggests that nitrofurantoin is more effective than ciprofloxacin as it leads to statistically significant bacteriological improvement on urine culture. Increased antibiotic resistance of ciprofloxacin amongst the uropathogens is responsible for less bacteriological improvement on the urine culture.

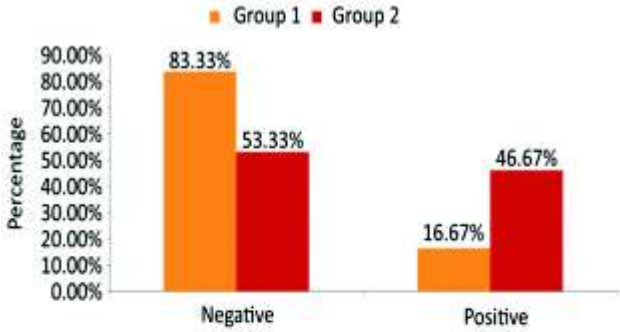

Fig 3 — Posttreatment culture results[9]

- **Investigating the first-line and second-line therapies for the treatment of uncomplicated UTI[14]**

The retrospective study was conducted to evaluate the most effective and relevant method for the treatment of uncomplicated UTIs.

A retrospective, clinical study analyzed antimicrobial susceptibility patterns from the 10417 collected urinary isolates.

The study results indicate that nitrofurantoin has significantly greater susceptibility to *E. coli* urine isolates with an average resistance rate of 2.3% than ciprofloxacin, levofloxacin and co-trimoxazole ($P<0.05$). *E. coli* resistance to nitrofurantoin ranged from 0.8% in 2003 to 3.3% in 2007 as compared to ciprofloxacin and levofloxacin which ranged from 20% to 25% (Fig 4).

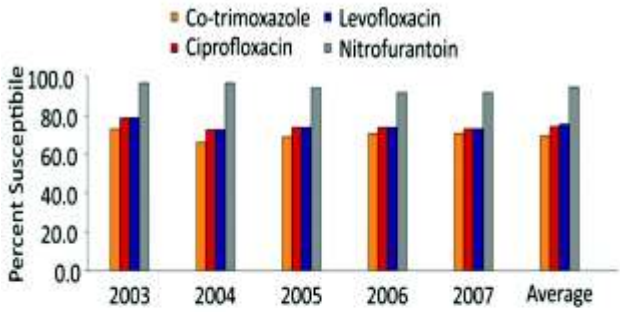

Fig 4 — Susceptibility patterns of E. coli from 2003 to 2007[14]

In conclusion, study demonstrates that nitrofurantoin is an acceptable treatment for uncomplicated UTIs, and should be considered for the first-line therapy.

- **Comparing one-day and seven-day nitrofurantoin regimen for the treatment of asymptomatic bacteriuria in pregnancy[15]**

Asymptomatic bacteriuria prevalence in pregnancy ranges from 2-11%. Most of the antibiotics prescribed for the treatment of asymptomatic bacteriuria in pregnancy are resistant to uropathogens. But, little or no modifications in the bacterial resistance was observed with nitrofurantoin. Thus, the study was conducted to evaluate the efficacy of 1-day and 7-day nitrofurantoin regimen in eliminating asymptomatic bacteriuria during pregnancy.

A multicenter, double-blind, randomized, placebo controlled, noninferiority trial included 778 pregnant women with asymptomatic bacteriuria. The enrolled subjects were randomized to receive either a 1-day or a 7-day course of 100 mg nitrofurantoin twice daily.

Primary outcome : bacteriologic cure after the treatment.

Secondary outcome: incidences of symptomatic UTI, preterm delivery, and adverse effects.

The study observed that *Escherichia coli* was the most commonly detected pathogenic bacteria with 50%prevalence. The bacteriologic cure rates after the treatment was lower in one-day as compared to the seven-day regimen group with–10.5% as the cure rate difference (Fig 5 and 6). Significantly lower birth weight and

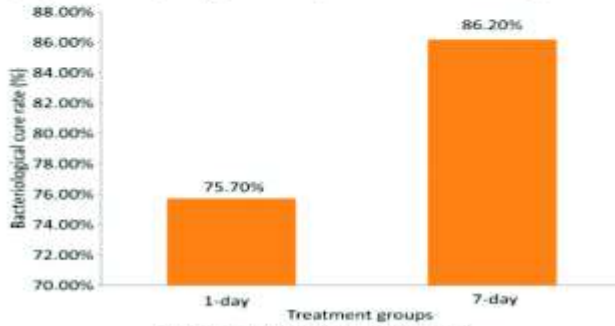

Fig 5 — Bacteriological cure rate[15]

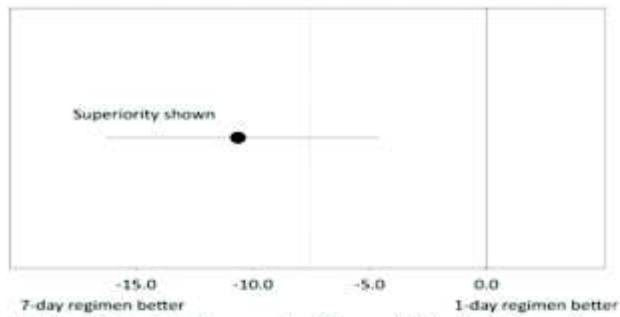

Fig 6 — Bacteriologic cure rate difference (%) with 1-day regimen compared with 7-day regimen[15]

gestational age was reported at delivery in the one-day regimen group. Fewer adverse effects were observed in the one-day regimen group.

The study results demonstrates that nitrofurantoin one-day regimen is significantly less effective as compared to the seven-day regimen. Thus, pregnant women with asymptomatic bacteriuria should receive the standard seven-day regimen.

- **Investigating the efficacy of low-dose nitrofurantoin for the management of urinary tract infections in the patients with spinal cord injury[16]**

A prospective study was conducted to evaluate the low-dose nitrofurantoin efficacy for the prevention of urinary tract infections (UTI) in the patients with spinal cord-injury.

The study enrolled 60 patients with spinal cord injury and were randomized to (Group I) receive 50 mg nitrofurantoin (in the form of encapsulate macro-crystals)

every 12 hours and Group II with no antibacterial treatment. Additionally all the patients received same level of catheter care. The urinalysis, sediment examination and culture test were performed urines in all the patients.

The study reported that all the patients presented with bacteriuria at least one time during the study period. But, significantly increase bacteriuria with a pathogenic organism followed by an increase in pyuria was observed in Group II as compared to group I.

Fourteen patients in Group 1 and 29 patients in Group 2 experienced a total of 35 weeks and 11 weeks of sterile urines, without pathogens or colonizers. Whereas, pseudomonas was isolated in 23 and 17patients from urines in the group I and II respectively.

From the results it is evident that, low dose nitrofurantoin therapy even with a history of previous urinary infections is effective in preventing repeated pathogenic organisms invasion of the bladder urine in spinal cord injured patients. Additionally, low dose-nitrofurantoin prove to be non-toxic and free from side effects with no reported emergence of bacterial resistant.

- **Evaluating the safety and efficacy of nitrofurantoin and fosfomycin long-term use in the treatment of recurrent urinary tract infections in type-2 diabetes women[17]**

Management of recurrent urinary tract infections in the type-2 diabetes patients is still an unsettled issue. Thus, the study was done with an aim to compare the safety and efficacy of nitrofurantoin and fosfomycin for the long-term treatment of recurrent uncomplicated lower urinary tract infections (uUTIs).

The study enrolled 50 type 2 diabetic women suffering from uUTIs with at least three recurrent episodes. The subjects were randomized to receive 3.0 g fosfomycin (FT) and 100 mg nitrofurantoin (NF) with a 6-months of follow-up. During the follow-up, urine bacteriology and complete blood cell count were performed, aminotransferase levels and renal function parameters were assessed.

At 3months, 96% in NF group and 92% in FT group patients were without the signs of UTI but the difference was not statistically significant (Fig 7). No significant differences was observed in the percentage of patients with UTIs at 3 and 6 months of long-term treatment between the study groups (Fig 7 and 8).

From the study results, it is evident that nitrofurantoin and fosfomycin are effective for the treatment and prevention of recurrent uUTIs in type 2 diabetes women and can be continued for several months.

- **Assessing the nitrofurantoinefficacy for the treatment of lower urinary tract infection (UTI) caused by extended-spectrumb-lactamase (ESBL)- producing *E.coli* in children[18]**

One of the commonest infections in children is urinary tract infections (UTI). The prevalence of acute cystitis due to ESBL- producing *Escherichia coli (E.coli)* is increasing

Table 3 — *Incidence of urinary infections*[16]

Incidents of UTI	Group 1 NF* (31 Patients)	Group 2 no NF (29 Patients)
0	24 (74%)	4 (14%)
1	7	6
2	1	9
3	0	4
4	0	6
Total UTIs	9 (8 patients)	60 (25 Patients)

*NF – nitrofurantoin 50 mg q. 12 h.

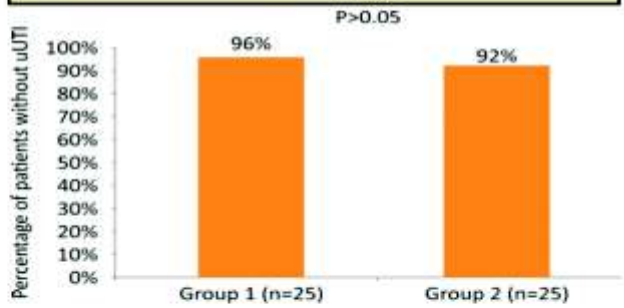

Fig 7 — Percentage of patients per study group without the signs of urinary tract infection at 3 months of long-term antibacterial treatment[17]

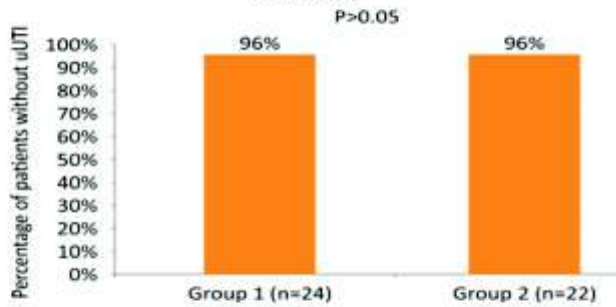

Fig 8 — Percentage of patients per study group without the signs of urinary tract infection at 6 months of long-term antibacterial treatment[17]

Table 4 — *Response rates and laboratory parameters after nitrofurantoin therapy*

Parameters	Observation
Clinical response (loss of symptoms) (%)	100%
Inflammatory response (loss of pyuria) (%)	98%
Bacteriological response (sterilization of urine cultures after treatment) (%)	98%
Non-scarring on renal Tc-99 m DMSA (%)	96%
Serum creatinine levels (mg/dL)	0.42 ± 0.19

in the children. The prospective study was conducted to assess the clinical and microbiological efficacy of nitrofurantoin for the lower UTI treatment caused by ESBL-producing *E.coli.*

Fifty children with lower UTI due to ESBL-producing *E.coli* were enrolled for the study. Patients who are susceptible to nitrofurantoin were given oral nitrofurantoin treatment for 10 days. Patients were assessed for

symptoms, clinical and laboratory parameters at 3-4 days after the end of treatment. 1-3 months after the end of treatment, renal scintigraphy was performed.

The study observed that 49 of 50 patients shows bacteriological response (98%). Normal serum creatinine levels was reported for all the patients. No symptoms and significant side effects were reported in any of the patients after the treatment. Renal scintigraphy, 1-3 months after completion of treatment, reported non-scarring in 48 of 50 of the patients (96%).

The study demonstrates that UTIs due to ESBL-producing *E. coli* are a serious problem which is due to the bacteria's multi-drug antibiotic resistant pattern. The results suggest that nitrofurantoin would be better alternative in the pediatric patients with UTIs caused by ESBL-producing *E. coli*.

RECOMMENDATIONS:

Recommendations	
IDSA (Infectious Diseases Society of America)[19]	Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage and efficacy comparable to 3 days of trimethoprim-sulfamethoxazole.
SIGN[20]	• Treat non-pregnant women of any age with symptoms or signs of acute LUTI with a three day course of nitrofurantoin. • Treat non-pregnant women of any age with symptoms or signs of acute LUTI with a three day course of nitrofurantoin.
NICE[21]	• As a first-line therapy in recurrent UTI: # for ≥16 years- 100 mg single dose when exposed to a trigger or 50 to 100 mg at night of nitrofurantoin (if eGFR e"45 ml/minute) # for <16 years- 3 months to 11 years, 1 mg/kg at night; 12 to 15 years, 50 to 100 mg at night (if eGFR ≥45 ml/minute)

Summary:

Nitrofurantoin is a unique antibiotic which is effective against both gram-positive and gram-negative organisms associated with UTIs. As compared to other drugs nitrofurantoin is relatively safer. The macro-crystalline formulations of nitrofurantoin has several advantages over micro-crystalline one with fewer side effects. It is commonly used for LUTI, used for recurrent UTI, catheter associated UTI, acute uncomplicated cystitis in women, multi drug-resistant strains UTI and in the UTI with special population including in pregnancy and diabetes.Nitrofurantoin was safe and effective in the treatment of LUTI with lower risk of developing resistance.

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Letters to the Editor

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

Prevalence of Periodontal diseases in Type 2 Diabetes
JIMA, Vol 117, No 11, November, 2019

Sir, — The authors have pointed comprehensively, the Periodontal disease is a less recognised, but well documented complication of diabetes mellitus and evaluated the prevalence of periodontal disease in Type 2 Diabetes Mellitus (DM). They have done assessment of Periodontitis in all by Community Periodontal Index (CPI) modified, Simplified Oral Hygiene Index (OHI-S) and Mobility.

Periodontitis is a possible early indicator of diabetes mellitus. Oral cavity with particular focus on patients with severe Periodontitis, seems be apt place for screening for (pre)diabetes, and in particular many patients of suspected new diabetes cases were recognised. So, the early diagnosis and treatment of (pre)diabetes help to prevent more severe complications and benefit the treatment of periodontitis.

A deviation of glucose metabolism, a change in cells like monocyte/macrophage phenotype leads to excess pro-inflammatory markers — cytokines due to periodontal infection, in diabetic patients.The cytokine-Tumour Necrosis Factor—(TNF-alpha) is the villain of periodontal disease and diabetes. The rise of TNF-a induces fibroblasts causing production of matrix-degrading enzymes and osteoclasts resulting active bone resorption.

DM and Periodontitis association seems to be not only bidirectional but also cyclical. Thus diabetes predisposes to oral disease and also periodontitis once diagnosed accelerates diabetes and worsens.So screening and managing DM is vital to prevent Periodontitis and complications.

Apart from Periodontitis, DM and HT are a deadly Duet of Tom and Jerry. There is a also study by Marta Czesnikiewicz-Guzik, *et al* and they noticed a casual relationship between periodontitis and BP, as evident from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. So, it is better to screen the patients of Periodontitis for not only Diabetes but also for HT.

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End TB by 2025 : Difficult Mission, but Not Impossible
JIMA, Vol 187, No 1, January, 2020

Sir, — At the outset congratulations for giving a new shape to the JIMA.

The editorial by Dr Surya Kant gives a positive approach to make India TB free.

May I suggest to add quiz corner where you can have ECG quiz, Imaging quiz etc. Please include updates in Medicine including Digital Medicine and Artificial Intelligence etc.

Keep up your good work.

Thank you.

With Best Regards

MD, FICP, FRCP (Glasg, London, Ireland), **Dr A Muruganathan**
FACP (USA), FPCP (Philippines),
Governor - American College of Physicians India Chapter

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Thank you for your positive response. From February issue we will start Mediquiz and Pictorial CME. For Digital Medicine and Artificial intelligence, Please contribute for the same.

Hony Editor, JIMA

Prevalence of anaemia in school going adolescents in a municipality town of West Bengal
JIMA, Vol 118, No 1, January, 2020

Sir, — The authors have rightly enlightened us regarding the current situation of prevalence of anaemia in adolescent school going children.

The study has rightly pointed out that – the female adolescents suffer from anaemia more than their male counterparts.

I would like to suggest the comparison of prevalence of anaemia in female students who has attained menarche and those who have not attained menarche yet, against their male counterparts (age matched) – separately.

Since in both the male & the female adolescents are exposed to sex hormones which have an important role on erythropoesis which will help us to reveal the increased prevalence of anaemia in this population further[1,2].

Moreover, this would also help us to compare the results of the study with that of Ludhiana study.

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Kolkata 700004

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IMA Hqs.- Extended Action Committee Meeting

Shillong - 5th NE IMA Conclave

Thodupuzha - Annual Kerala State Conference

MP - World Cancer Day

Dhule - Maha MLCON

Kottakkal, WDW

Bodhan - Installation Ceremony

Thane, Annual Conference

Thrissur - Leprosy Day Observation

Palakkad - CME

Kannur - CME

Ernakulam - Small and Medium Hospitals Meeting

Sullia - CME


Thiruvananthapuram, WDW


Gangavathi - Mega Health Camp


Siliguri - Workshop on Corono Virus


Muvattupuzha - GB


Kerala State WDW Conference

Novel Coronavirus (2019-nCoV): Wuhan Virus: Facts and Figures

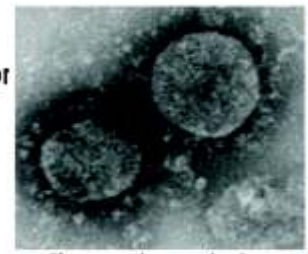
Issued in public interest by JIMA

Prof. Jyotirmoy Pal and Dr Rudrajit Paul

Avoid non-essential travel to China

Common symptoms: -

- Starts with cough, fever, myalgia, fatigue
- Later, dyspnea and desaturation
- Non-respiratory symptoms: Diarrhea, nausea
- Severe illness: bilateral pneumonia, ARDS, shock



Electron microscopic view

Diagnostic tests:

- ❑ Nasopharyngeal and oropharyngeal swab, urine and stool in specific situations
- ❑ Specimen to be collected on first suspicion of illness
- ❑ Tested by RT-PCR

Who should be tested?

Anyone with confirmed or suspected travel to geographical areas known to have viral transmission

Anyone in close contact with a person as described above

Who can be affected?

Anyone with epidemiological risk factor, including newborn babies

No age is exempt

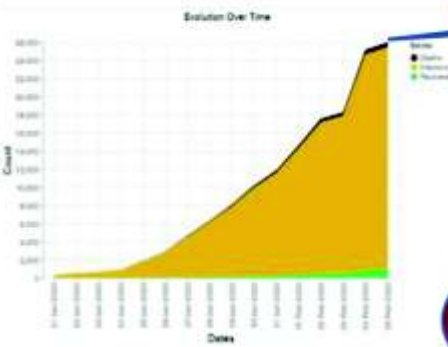


Figure showing epidemic curve till now

Case fatality: 2%

First case: 31/12/2019

Potential source: bats

Rapid human-to-human spread

Mask etiquette:

Do not reuse

Proper disposal of used masks

Cover both nose and mouth

Hand washing before using mask

Healthcare workers should take adequate precautions for droplet infection

Precautionary measures:

Face mask only near suspected cases; General community use not recommended

Maintain one mt distance from suspected cases; any contact should preferably be less than 10 minutes

Quarantine (14 days)

People with known or suspected infection may be in home isolation

Myth buster:

- Letters or other items received from China are not infectious
- There is no diet or vaccine or herb for prevention

Further information: WHO, CDC websites for daily updates; Lancet Journal website

Two Feathers in the Cap of Team JIMA in 2019

JIMA goes SMART

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