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AHA/ASA: Treat All Patients with Suspected CVST Due to a COVID-19 Vaccine with Nonheparin Anticoagulants

The American Heart Association (AHA)/American Stroke Association (ASA) Stroke Council leadership has issued guidelines on the management of cerebral venous sinus thrombosis (CVST) with vaccine-induced immune thrombotic thrombocytopenia (VITT), which have been published in the journal *Stroke*.

Let's first understand the definitions of these terms.

- CVST is formation of clots in the veins (*cf.* in most cases of stroke, clots are formed in the arteries of the brain).
- CVST and thrombocytopenia together are called thrombosis-thrombocytopenia syndrome (TTS).
- When TTS is linked to receiving a coronavirus disease 2019 (COVID-19) vaccine, it is called vaccine-induced immune thrombotic thrombocytopenia (VITT).

CVST may be roughly divided into four syndromes:

- Isolated headache or increased intracranial pressure
- Focal neurological presentations
- Subacute encephalopathy
- Cavernous sinus syndrome/multiple cranial neuropathies.

CVST is not easy to diagnose as its symptoms resemble several other neurological disorders and can include severe headache, blurry vision, fainting or loss of consciousness, weakness, sensory changes, confusion or trouble speaking, seizures, abdominal pain, leg pain, difficulty breathing or shortness of breath.

If associated with the COVID-19 vaccine, cases of TTS/VITT occurred several days up to 2½ weeks after being vaccinated with the Johnson & Johnson (Janssen) COVID-19 vaccine in the US, or up to 3½ weeks after receiving the AstraZeneca COVID-19 vaccine in Europe. All patients who present to the emergency room (ER) with a suspected clot should be screened for a recent history of COVID-19 vaccine. However, the risk of CVST blood clots was 8-10 times higher following a COVID-19 infection as compared to the risk associated with a COVID-19 vaccine. The guideline also says that whether an association between the vaccine and platelet factor 4 (PF4) antibody, thrombocytopenia and thrombosis exists or not is not definitive as at present there is no data about people who did not develop CVST, TTS or VITT after a COVID-19 vaccine for comparison.

Key Recommendations

- All patients with suspected CVST due to a COVID-19 vaccine should be treated with nonheparin anticoagulants such as argatroban, bivalirudin, danaparoid, fondaparinux or a direct oral anticoagulant (DOAC). No heparin products in any dose should be given.
- Magnetic resonance imaging with a venogram (MRI/MRV) or computed tomography with venogram (CT/CTV) is recommended to accurately detect and diagnose CVST.
- Blood tests should include a CBC (complete blood count) plus: Platelet count, peripheral smear, prothrombin time, partial thromboplastin time, fibrinogen test, D-dimer test and PF4 antibody enzyme-linked immunosorbent assay (ELISA) test (PF4 antibodies are sometimes formed in the blood to fight against the anticoagulant heparin).
- Anticoagulation treatment doses may need to be tailored if platelet counts are extremely low (<20,000/mm^3) or if there is low fibrinogen.
- Anticoagulants should be used to treat CVST even if there is a secondary hemorrhage in the brain in order to prevent progressive thrombosis and to control bleeding.
- Platelet transfusion should be avoided.
- Once platelet counts return to normal (1,50,000-4,50,000/mm^3), most patients can be transitioned to an oral anticoagulant if there are no contraindications.
- Individual patient factors should be considered regarding the use of a DOAC or a vitamin K agonist (VKA) after there is full platelet count recovery.
- All cases of thrombosis after a COVID-19 vaccine should be reported to the US Department of Health and Human Services Vaccine Adverse Event Reporting System. This data will be important to understanding the incidence of CVST, TTS and VITT. *In our country, such ADRs (or any other) can be reported to PvPI.*

Source: AHA Press Release, April 29, 2021

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Fully Vaccinated Adults Aged 65 and Above 94% Less Likely to be Hospitalized with COVID

A new CDC assessment has found that both Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines protect against COVID-19-related hospitalization among adults aged 65 years and above.

It was found that fully vaccinated adults aged 65 and older had a 94% lesser likelihood of being hospitalized with COVID-19 compared to individuals of the same age who were not vaccinated. Furthermore, individuals aged 65 and above who were partially vaccinated had a 64% lesser likelihood of hospitalization for COVID-19 compared to those who were not vaccinated.

People were considered partially vaccinated 2 weeks following their first dose of mRNA vaccine and fully vaccinated 2 weeks following their second dose… (*CDC*)

Pfizer Pill for COVID-19 Symptoms could be Ready by Year End: Company CEO

Pfizer CEO Albert Bourla has said that an oral drug that the company is developing to treat COVID-19 symptoms could be available by the end of this year.

Currently, the only antiviral drug authorized for use in COVID-19 is remdesivir which needs to be administered by injection in a healthcare setting. An oral drug like the one being developed by Pfizer could be taken at home and might help people keep out of hospitals. Getting the pill at home could be a game-changer.

The drug might be effective against the emerging variants as well, said Bourla. The oral drug works by blocking protease, an enzyme needed by the virus to replicate… (*Medscape*)

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Acute Seizure in Hyponatremia

AMIT KUMAR*, VN JHA†

ABSTRACT

Introduction: Acute and severe electrolyte imbalances can manifest with seizures, which may be the sole presenting symptom. Seizures are more frequently observed in patients with sodium disorders (especially hyponatremia), hypocalcemia and hypomagnesemia. An accurate and prompt diagnosis should be established for successful management of seizures, as rapid identification and correction of the underlying electrolyte disturbance (rather than an antiepileptic treatment) are of crucial importance in the control of seizures and prevention of permanent brain damage. **Aims and objectives:** To study the incidence of seizure in hyponatremia. **Material and methods:** Two hundred patients were chosen from indoor settings and studied for seizure among hyponatremic patients. **Results and Conclusion:** Seizure generally occurred in severe hyponatremia with the incidence being 4%.

Keywords: EEG, electrolyte, epilepsy, seizures, hyponatremia

Acute and/or severe electrolyte imbalances can manifest with rapidly progressive neurologic symptoms or seizures, which may be the sole presenting symptom. Seizures are more frequently observed in patients with sodium disorders (especially hyponatremia), hypocalcemia and hypomagnesemia. Epidemiological data show that electrolyte disturbances (especially hyponatremia) represent a frequent cause of acute symptomatic nonfebrile seizures in patients of any age. Electrolyte disturbances may cause diffuse brain dysfunction that can be assessed by means of EEG recording. In general, the most prominent feature of the EEG record in metabolic encephalopathies is a slowing of the normal background frequency. EEG evolution generally correlates well with the severity of encephalopathy; more specifically, the degree and severity of EEG abnormalities correlate with the rate of change of electrolyte balance rather than with the absolute level of a specific electrolyte or metabolite.

Hyponatremia is defined as a serum sodium level of <135 mEq/L and is considered severe when the serum level is <125 mEq/L.

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The major clinical complications from acute hyponatremia are brain cell swelling and herniation with neurologic symptoms being evident when hyponatremia approaches 120 mEq/L. The risk of cerebral edema and neurologic manifestations is minimized if the decline in serum sodium occurs slowly and gradually (≥48 h), even in case of a marked absolute reduction of serum sodium values. Conversely, in case of a rapid decrease in serum sodium (acute hyponatremia), cerebral edema with neurologic symptoms are likely to occur.

The neurological symptoms of hyponatremia therefore go in parallel with the severity of cerebral edema, and are less frequently induced by chronic than by acute hyponatremia: approximately half of the patients with chronic hyponatremia are asymptomatic, even with serum sodium concentration <125 mEq/L. In these patients, symptoms are rarely noted until the serum sodium is <120 mEq/L and are more frequently seen with values of ≤110 mEq/L.

Hyponatremia represents a frequent cause of epileptic seizures, as shown in a prospective observational multicenter study where acute epileptic seizures and focal neurological deficits were identified in 5% of patients each, with severe (<125 mEq/L) hyponatremia.

MATERIAL AND METHODS

A total of 200 indoor patients were chosen and routine blood tests were done and serum electrolytes were assessed, especially for serum sodium.

Table 1. Patients with Hyponatremia

Total patients with hyponatremia	Mild hyponatremia (Na 130-134 mEq/L)	Moderate hyponatremia (Na 125-129 mEq/L)	Severe hyponatremia (Na <125 mEq/L)
50	35	5	10

Table 2. Patients with Seizure and Altered Sensorium

Hyponatremic	With seizure	With altered sensorium
50	2 (4%)	7 (14%)

RESULTS

Fifty patients were found to have serum sodium <135 mEq/L (Table 1). Among 50 hyponatremic patients, 10 had sodium level <125 mEq/L, and among these, 2 patients developed seizure and 7 had altered sensorium (Table 2). Seizure did not occur in patients with serum sodium >125 mEq/L.

DISCUSSION AND CONCLUSION

Hyponatremia is a frequent cause of epileptic seizures. In our study, the incidence of seizure disorder in patients with hyponatremia was found to be 4%.

The neurological symptoms in these patients are rarely seen until the serum sodium is <120 mEq/L. Particularly, the children are at high risk of developing symptomatic hyponatremia, because of their larger brain-to-skull size ratio. Severe and rapidly evolving hyponatremia may cause seizures, which are usually generalized tonic-clonic, and generally occur if the plasma sodium concentration rapidly declines to <115 mEq/L.

Early identification and correction of these disturbances are necessary to control seizures and prevent permanent brain damage, as antiepileptic drugs (AED) alone are generally ineffective if the electrolyte disorder persists. In fact, treatment of seizures secondary to electrolyte imbalances is largely driven by the underlying cause of the disturbance, and in most cases, administration of AED is not necessary as long as the underlying disturbance is corrected.

We physicians should be vigilant to recognize and treat acute electrolyte imbalance in the best possible way so that irreversible brain damage can be prevented and patient recovers completely.

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Indian Journal of Clinical Practice, Vol. 31, No. 12, May 2021

Efficacy of Modified Bleach Concentration Method for Demonstration of Acid-fast Bacilli in Fine Needle Aspiration of Lymph Nodes with Clinical Suspicion of Tuberculosis

PARWINDER KAUR*, SILKY MAHAJAN†, KANWAL MASIH‡

ABSTRACT

Background: Tuberculous lymphadenitis is the most common form of extrapulmonary tuberculosis. Fine-needle aspiration cytology of lymph node for its diagnosis is simple and safe. Conventional Ziehl-Neelsen (ZN) method for acid-fast bacilli plays a key role in the diagnosis; however, it has variable sensitivity due to low bacterial load. We evaluated the role of bleach concentration method before performing ZN method for the detection of mycobacterium in clinically suspected cases of tuberculous lymphadenitis. **Method:** A total of 103 samples of fine-needle aspirates were collected from clinically suspected cases of tuberculous lymphadenitis as part of routine diagnosis. All the samples were processed for cytology, conventional ZN staining, bleach concentration followed by ZN staining. **Results:** As per cytomorphological diagnosis of aspirates, 50.50% cases were categorized as reactive hyperplasia, 43.68% cases as tubercular lymphadenopathy and 5.82% cases of suppurative lymphadenitis. The detection rates of conventional ZN method and bleach concentrated ZN method were 28.15% and 33%, respectively. The bleach method has 100% sensitivity and specificity while conventional ZN method showed 85.29% and 100%, respectively. **Conclusion:** Bleach concentrated method can be done before conventional ZN staining for detection of tubercle bacilli, as it has a higher case detection rate than that of the conventional ZN method.

Keywords: Bleach method, ZN staining, tubercular lymphadenitis, fine-needle aspiration cytology

Tuberculosis (TB) is one of the top 10 causes of death and the leading cause from a single infectious agent (above human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS]). Overall, 1.4 million people died from TB in 2019 (including 2,08,000 people with HIV) globally. Major suffering due to TB is attributable to appearance of virulent strains, resistance to multiple drugs and steady increase in HIV infection. When TB is bacteriologically confirmed or clinically diagnosed in other parts of the body other than the lung, such as the abdomen, meninges, genitourinary tract, joints, bones, lymph nodes and skin, it is classified as extrapulmonary tuberculosis (EPTB). The most common extrapulmonary sites of TB infection include the lymph nodes, the pleura, the genitourinary system, the gastrointestinal tract, the bones and the central nervous system. Tuberculous lymphadenitis is seen in nearly 35% of EPTB. The methodology for diagnosis of EPTB can divided into: (a) Primary diagnostic studies and (b) Ancillary diagnostic studies. The primary diagnostic studies are fine-needle aspirate cytology (FNAC), lymph node biopsy, culture and molecular tests which are based on nucleic acid amplification for detecting *Mycobacterium tuberculosis* namely polymerase chain reaction, line probe assays. The ancillary diagnostic studies are tuberculin skin test and interferon-gamma release assays. Molecular methods are rapid and sensitive but expensive for routine use in the developing countries. The usefulness, priority and scope of various techniques used in TB diagnosis depend on the epidemiological situation prevailing in individual countries and on the resources available. In our setup, the only practically available

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bacteriological method for diagnosing EPTB is direct smear microscopy of material obtained from FNAC. FNAC of lymph node offers early availability of results since the test is simple, safe, quick and causes minimal trauma for the diagnosis of lymph node TB. The collection of material by FNAC is suitable for the patients as it is relatively painless procedure. Cytomorphology and mycobacterial visualization of smears using Ziehl-Neelsen (ZN) staining method plays a key role in the diagnosis and monitoring of treatment in TB. However, the sensitivity of this technique is low (22-43%). If the sensitivity of detection of acid-fast bacilli (AFB) by any staining method can be improved, it has the potential to become the most valuable tool for TB detection and control programs around the world. Over the years, several improvements have been done to increase the microscopic detection of AFB in sputum specimens. In late 1940s, sputum liquefaction with household bleach, i.e., sodium hypochlorite (NaOCl) and concentration by centrifugation prior to ZN staining was done to improve the AFB detection. Several studies showed that the use of bleach, in concentrations of 2-5%, digests the sputum and inactivates the bacteria without altering its structure. This method is simple, requires no expertise and cost-effective. Majority of the studies have been done on sputum and body fluid samples for detecting TB bacilli by using bleach method, but very few of them are there on lymph node aspirate samples.

The present study has been undertaken to find out the efficacy of modified staining using bleach technique in comparison to conventional ZN staining technique for detection of AFB on lymph node aspirates of patients suspected to have tubercular lymphadenitis in our hospital.

MATERIAL AND METHODS

A prospective study was conducted in the Dept. of Pathology, Punjab Institute of Medical Sciences, Jalandhar. The proposed study duration was 1 year, from April 2016 to March 2017. The 103 patients of clinically suspected tuberculous lymphadenitis belonging to all the age groups, who were referred for FNAC, were included in this study. Exclusion criteria were the patients on antitubercular drugs within previous 3 months and elderly patients with known primary malignancy.

FNAC was done by using 22-gauge needle and 20 mL syringe. All the aspirates yielded whitish, pus or pus-mixed material, which was expressed on to the glass slide. Smears were made from the expressed material. The remaining material in the hub was washed with 1 mL normal saline and collected in conical test tube and subjected to centrifugation. Three smears were prepared, of which, 2 were air-dried and one was subjected to wet fixation. One of the air-dried smear was stained with Giemsa stain for routine cytology and another smear was stained with conventional ZN stain. The wet fixed smear was stained with hematoxylin and eosin stain.

The bleach method was performed with the remaining aspirated material in the needle hub or syringe, which was rinsed with 1 mL normal saline and transferred into 5 mL sterile conical screw-capped test tube and mixed with 2 mL of 5% NaOCl. After thorough mixing, the mixture was incubated at 37°C for 15 minutes by shaking at regular intervals. An equal amount of distilled water was added, mixed and then centrifugation done at 3,000 g for 15 minutes. The supernatant was discarded, and the sediment was transferred to a clean slide. The slide was air-dried, heat fixed and stained by ZN method. As a control, 2 mL of distilled water was centrifuged, and the sediment was stained by ZN staining to rule out any error due to contamination while testing each specimen. Cytological smears were examined under light microscope. The smears, one with conventional ZN technique and the other with bleach concentration techniques, were examined under oil immersion lens for the presence of AFB. At least 100 fields were scanned for AFB, which is a standard procedure. The data were processed and the sensitivity, specificity and positive and negative predictive values were calculated.

RESULTS

The present study was undertaken to emphasize the role of bleach concentration method over the conventional ZN direct smear microscopy for the detection of tubercle bacilli in FNAC material of lymph nodes. In the 1 year duration, a total of 103 patients were evaluated. As per sex distribution of patients, 59.22% were female patients and 40.78% were male patients. Male-to-female ratio was 1:1.45. The age range of the suspects was between 1 and 70 years with a mean age of 26.43 years. As per age group, 41% patients were in the age group of 21-40 years and 0-20 years each, respectively, 15% were in the age group of 41-60 years and 3% were above 60 years of age. The most common lymph node group involved was cervical 66.99% (69/103), followed by axillary 7.76% (8/103), supraclavicular and submandibular 6.79% (7/103) each, inguinal and submental 4.85% (5/103) each and postauricular 1.94% (2/103). Enlarged single lymph node was the most common mode of presentation seen in 72.81% (75/103) cases.

According to cytomorphological diagnosis of lymph node aspirate, reactive hyperplasia was seen in 52 (50.49%) cases, followed by granulomatous inflammation with necrosis in 31 (30.1%), granulomatous inflammation without necrosis in 09 (8.73%) cases, nonspecific inflammatory pathology in 6 (5.82%) cases and necrosis alone without granuloma formation in 5 (4.85%) cases (Table 1).

Among the 45 cases suggestive of tuberculous lymphadenopathy, the cytological patterns were as follow:

- Pattern 1: Granulomatous inflammation with necrosis 68.88% (31)
- Pattern 2: Granulomatous inflammation without necrosis 20% (09)
- Pattern 3: Necrosis alone without granuloma formation 11.11% (05) (Table 2).

In Pattern 1, 24/31 (77.41%) were positive for AFB by conventional ZN technique, while bleach method detected AFB in 26/31 (83.87%) cases. Hence, 2 cases missed by the conventional ZN staining method were picked up by the bleach method. In Pattern 2, 03/09 (33.33%) were positive for AFB by conventional ZN staining, while, the bleach method detected AFB in 04/09 (44.44%) cases. Here also, 1 case missed by the conventional ZN method was picked up by the bleach method. In Pattern 3, positivity for AFB with both the conventional ZN method and bleach method was 40% (02/05). Out of 06 nonspecific inflammatory pathology smears tested for AFB, none was AFB positive by conventional ZN method but 2 cases were positive for AFB by bleach method. All the cases cytologically diagnosed as reactive hyperplasia were negative for AFB by both the methods (Table 3).

The smear positivity for AFB on conventional ZN staining method was 28.15% (29/103), while the positivity increased to 33.01% (34/103) when the bleach method was used. Thus, the bleach method detected AFB in additional 5 cases, which was statistically significant.

The direct smear microscopy for ZN staining showed sensitivity 85.29%, specificity and positive predictive value (PPV) 100% and negative predictive value (NPV) 95.15%, whereas bleach method showed sensitivity, specificity, PPV and NPV 100%, respectively (Table 4).

Table 1. Cytomorphological Pattern Observed on Lymph Node Aspirates

Cytomorphological pattern	Number of cases (n = 103)
Reactive hyperplasia	52
Granulomatous inflammation with necrosis	31
Granulomatous inflammation without necrosis	09
Nonspecific inflammatory pathology	06
Necrosis alone	05

Table 2. Pattern of Cases in Various Cytomorphological Tubercular Lymphadenopathy

Pattern	Types of tubercular lymphadenopathy	Number of cases (n = 45)
Pattern 1	Granulomatous inflammation with necrosis	31 (68.88%)
Pattern 2	Granulomatous inflammation without necrosis	09 (20%)
Pattern 3	Necrosis alone without granuloma formation	05 (11.11%)

Table 3. Correlation of Cytomorphological Diagnosis with the Bleach Method and the Conventional ZN Method

Cytomorphological diagnosis	Bleach method		Conventional ZN method		Total
	Positive	Negative	Positive	Negative	
Reactive hyperplasia	Nil	52	Nil	52	52
Nonspecific inflammatory pathology	02	04	Nil	06	06
Granulomatous inflammation with necrosis	26	05	24	07	31
Granulomatous inflammation without necrosis	04	05	03	06	09
Necrosis alone	02	03	02	03	05
Total	**34**	**69**	**29**	**74**	**103**

Table 4. Comparison of Sensitivity, Specificity, Positive and Negative Predictive Values in Conventional ZN Method and Bleach Method

Values	ZN method (%)	Bleach method (%)
Sensitivity	85.29	100
Specificity	100	100
Positive predictive value	100	100
Negative predictive value	95.15	100

DISCUSSION

In developing countries like India, the diagnosis for tubercular lymphadenitis mainly relies on FNAC and aspirate direct smear microscopy. The microscopy of the specimen is by far the fastest, cheapest and most reliable method for the detection of AFB. In the late 1940s, sputum liquefaction with NaOCl (readily available at low cost as household bleach) and then concentration by centrifugation before acid-fast staining was implemented to improve the smear positivity for the detection of AFB. The increased sensitivity by bleach method is probably due to the fact that NaOCl removes debris and leaves the microscopic field free for easy examination. The present study was carried out on lymph node aspirates to know and compare the sensitivity of bleach method over conventional ZN staining.

In our study, the patients showed a wide age group ranging from 1 to 70 years with the mean age being 26.43 years. Most of the patients (41%) were in the age group of 21-40 years and 0-20 years. The male-to-female ratio was 1:1.45. Our study is in accordance with the study done by other workers that reported maximum number of cases (36.65%) in the age group of 21-30 years and male-to-female ratio of 1:1.21. However, other workers reported male predominance.

In the present study, most common lymph node group involved was cervical (66.99%) followed by axillary (7.76%), supraclavicular and submandibular (6.79% each), inguinal and submental (4.85% each) and postauricular (1.94%), and enlarged single lymph node was the most common mode of presentation (72.81%). These findings are almost similar with a study done by other workers, which also reported greater involvement of cervical lymph node and supraclavicular lymph nodes (66% and 8.6%, respectively) and 61% of enlarged single lymph nodes.

The cytomorphological features were analyzed based on the nature of aspirate and microscopy. In the present study, as per cytological pattern, 43.68% cases (45/103) were diagnosed as tubercular lymphadenopathy.

In this study, all reactive hyperplasia lymph node aspirates were negative for AFB by both routine ZN staining and bleach method. Whereas other workers reported AFB in few cases of reactive hyperplasia by bleach method which were initially negative for AFB by ZN staining, 24.4% and 22.2%, respectively.

In our study, a total of 6 (5.82%) cases showed nonspecific inflammatory pathology (suppurative lymphadenitis). None of these cases were positive for AFB by conventional ZN staining. Later on, 2 cases (33.33%) of suppurative lymphadenitis were diagnosed as tuberculous lymphadenitis based on the detection of AFB in bleach method. Similar findings were reported by Bhardwaj et al. They reported 11.2% cases of suppurative inflammation and all of these cases were negative for AFB by conventional ZN staining, whereas 21.4% positivity was reported by bleach method. Other workers reported 42.8% positivity by conventional method and 82.1% positivity by bleach method in the suppurative lymphadenitis. The diagnosis of nonspecific inflammatory pathology was based on cytological picture showing numerous degenerated polymorphs, lymphocytes and plasma cells along with cellular debris. Two of these cases had foci of necrosis.

In our study, cytomorphological features of TB were seen in 45 (43.68%) cases. It was further categorized under 3 patterns as shown in Table 2. Three cases which were initially negative for AFB by the routine ZN smear in Pattern 1 and 2 were then reported positive for AFB by the bleach method. This increase in positivity could be due to increased number of the bacilli per field and clean background due to digestion of cellular elements by bleach method. The morphology of AFB also appeared to be better preserved, and they were thicker and longer than the routine ZN smears. This could probably be due to swelling of bacilli in the solution. The above mentioned observations were also noted by other workers in their studies. In the present study, we observed that bleach method has 100% sensitivity and specificity compared to conventional ZN method, which showed sensitivity and specificity of 85.29% and 100%, respectively.

CONCLUSION

The use of bleach method prior to ZN staining helps in liquefaction of lymph aspirate and concentration of

bacilli by centrifugation helps in increased positivity of direct microscopy, making the screening process easier, faster and less laborious. The implementation of the bleach method can be a useful contribution to routine cytology examination for detection of AFB in FNAC aspirate.

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Thyroid Disease in Pregnancy

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ABSTRACT

Thyroid disease is the second most common endocrine disorder affecting women of reproductive age, and when untreated during pregnancy, is associated with an increased risk of miscarriage, placental abruption, hypertensive disorders and growth restriction. Current guidelines recommend targeted screening of women at high risk, including those with a history of thyroid disease, type 1 diabetes mellitus or other autoimmune disease; current or past use of thyroid therapy or a family history of autoimmune thyroid disease. Appropriate management results in improved outcomes, demonstrating the importance of proper diagnosis and treatment. In women with hypothyroidism, levothyroxine is titrated to achieve a goal serum thyroid-stimulating hormone level <2.5 mIU/L. The preferred treatment for hyperthyroidism is antithyroid medications, with a goal of maintaining a serum free thyroxine level in the upper one-third of the normal range. Postpartum thyroiditis is the most common form of postpartum thyroid dysfunction and may present as hyper- or hypothyroidism. Symptomatic treatment is recommended for the former; levothyroxine is indicated for the latter in women who are symptomatic, breastfeeding or who wish to become pregnant. Thyroid disease is second only to diabetes mellitus as the most common endocrinopathy that occurs in women during their reproductive years. Symptoms of thyroid disease often mimic common symptoms of pregnancy, making it challenging to identify. Poorly controlled thyroid disease is associated with adverse outcomes during pregnancy, and treatment is an essential part of prenatal care to ensure maternal and fetal well-being.

Keywords: Hyperthyroidism, hypothyroidism, postpartum thyroiditis, levothyroxine

The thyroid gland is important during pregnancy as it regulates the production of hormones triiodothyronine (T3) and thyroxine (T4), each of which plays a critical role in the development of the baby's brain and nervous system.

During the first trimester, the fetus depends on the mother's supply of thyroid hormone, which is delivered through the placenta. In order to meet this need, the mother's thyroid production will typically go into overdrive, resulting in an enlargement of the gland itself.

Diseases of thyroid hormone (hyperthyroidism and hypothyroidism) are quite commonly seen in pregnancy (2-3%) and 1 in 10 women of childbearing age group will have some indication of reduction of functional reserve of thyroid function.

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THYROID GLAND AND ITS ADAPTION DURING NORMAL PREGNANCY

Thyroid gland is a butterfly-shaped endocrine gland located in front of the neck and releases hormones that regulate the metabolism, heart, nervous system, weight, body temperature and many other processes in the body.

For diagnosing thyroid disease in pregnancy, we need to understand the changes in thyroid physiology and changes in the values of thyroid function tests that occur during pregnancy.

Pregnancy poses various metabolic changes in the body and to meet the increased metabolic needs, thyroid physiology and thyroid function change (Reflected as altered thyroid tests).

There is an increase in serum thyroxine-binding globulin (TBG) and stimulation of thyrotropin (TSH) receptors by hCG (human chorionic gonadotropin) in pregnancy. The serum TBG levels rise almost double because of estrogen (increased TBG production and TBG sialylation). This causes slowing and decrease in TBG clearance.

In response, the total T4 and T3 increase in first half of pregnancy up to 20 weeks, plateauing at 20 weeks of gestation.

The production of thyroid hormones T3 and T4 returns to pre-pregnancy levels at approximately 20 weeks. hCG β-subunit is similar to thyroid-stimulating hormone. Hence, hCG has a weak thyroid-stimulating activity.

1 micro U of hCG = 0.0013 micro U of TSH.

THYROID FUNCTION TESTS IN PREGNANCY

Several population studies have demonstrated that it is normal for TSH in pregnancy to be below the classic lower limit of normal. Therefore, use of non-pregnant reference ranges result in the overdiagnosis of hyperthyroid states and under-recognition of hypothyroid states. Laboratories should provide trimester-specific reference ranges but if these are not available, the trimester-specific TSH ranges indicated in Table 1 are recommended.

Because normal thyroid function is different during pregnancy, TSH values will change as the mother progresses from the first to third trimester. Under normal circumstances, the normal TSH value would range from 0.2 to 4.0 mIU/L.

The lower reference range of TSH can be reduced by approximately 0.4 mIU/L, in first trimester and upper reference range is reduced by approximately 0.5 mIU/L. This corresponds to a TSH upper reference limit of 4.0 mIU/L. This should be applied beginning with the late first trimester, Weeks 7-12, with a gradual return towards the nonpregnant range in the second and third trimesters. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake and negative thyroid-peroxidase antibody (TPOAb) status.

There is an increase in total T4 concentration from 7 to 16 weeks of gestation, ultimately reaching 50% above the pre-pregnancy level. This level is then sustained through pregnancy. Upper range determination can be calculated by shifting the nonpregnant limit 50% higher.

Table 1. Recommended Trimester-specific Reference Ranges for TSH

Trimester	TSH range
First	0.1-2.5 mIU/L
Second	0.2-3.0 mIU/L
Third	0.3-3.0 mIU/L

This can only be used after 16 weeks of pregnancy. If a T4 measurement is required before that time (i.e., 7-16 weeks of pregnancy), a calculation can be made for the upper reference range based on increasing the nonpregnant upper reference limit by 5% per week, beginning with 7 weeks. Accurate estimation of the free T4 (FT4) concentrations can also be done by calculating a FT4 index. Table 2 summarizes thyroid evaluation.

TSH and FT4 are useful for diagnosis of and monitoring thyroid dysfunction in pregnancy. T3 levels are only ordered if a suspicion of T3 predominant thyrotoxicosis is there.

THYROID DISEASES

- Hypothyroidism (Overt and Subclinical)
- Hyperthyroidism (Overt and Subclinical)
- Postpartum thyroiditis
- Thyroid nodule/Goiter

Hashimoto's disease, also known as Hashimoto's thyroiditis, is an autoimmune disease which attacks and gradually destroys the thyroid gland. Hypothyroidism is a common outcome of the disorder and is treated in the same manner using hormone replacement therapy. Typically speaking, a woman with Hashimoto's should maintain her TSH under 3.0 mIU/L.

The provisions for treatment during pregnancy are the same as for other forms of hypothyroidism, although additional attention should be made to keeping the TSH under 2.5 mIU/L as higher levels are associated with a two-fold increase in the risk of miscarriage.

Hypothyroidism

Hypothyroidism in pregnancy is usually due to Hashimoto's disease (3 to 5 out of 1,000 pregnancy). Hashimoto's disease is chronic inflammation of thyroid

Table 2. Basic Thyroid Evaluation

	TSH		
	Low	**Normal**	**High**
FT4			
High	Primary hyperthyroid	Nonthyroid illness-(NTI) or Patients on levothyroxine	Secondary hyperthyroid
Normal	Subclinical hyperthyroid	Euthyroid	Subclinical hypothyroid
Low	Secondary hyperthyroid	NTI	Primary hypothyroid

gland (Hashimoto's thyroiditis is an autoimmune disorder). Euthyroid patients who are antithyroid Ab positive, post-hemithyroidectomy or treated with radioactive iodine have an increased propensity for the development of hypothyroidism in gestation and should be monitored regularly.

Overt hypothyroidism is when there is an elevated TSH and low FT4. This is clearly associated with adverse pregnancy outcomes (Lower IQ) and miscarriages, prematurity, low birth weight and stillbirths. Frequently, elevated maternal TSH is detected when FT4 concentrations are normal. Conversely, low FT4 concentrations can be detected despite normal TSH concentrations, called as isolated hypothyroxinemia.

Symptoms

- Extreme tiredness
- Weight gain
- Constipation
- Difficulty in concentration
- Memory problems
- Sensitivity to cold temperature
- Muscle cramps

Adverse outcomes with overt maternal hypothyroidism include increased risks of premature birth, risk of gestational hypertension, low birth weight, pregnancy loss and lower offspring IQ.

Overt hypothyroidism should be urgently treated by L-thyroxine (LT4) replacement. In severe cases, a loading dose for 3-4 days of 150-200 μg should be given, followed by titration with TSH levels.

In patients with pre-existing hypothyroidism already on replacement therapy, the dose needs to be increased by about 30% (Increase 2 additional doses per week or 7-9 doses per week) on suspicion or confirmation of pregnancy.

T4 and TSH should be checked every 4 weeks in first half of pregnancy and at least once in between 26 and 32 weeks. The aim is to keep TSH within trimester-specific ranges (Table 1).

After delivery, the dose can be reduced to pre-pregnant levels and should be monitored with a serum TSH measurement approximately every 4 weeks until mid-gestation and at least once near 30 weeks of gestation. Adjustment of LT4 dosage when affected women become pregnant and also for the timing of follow-up interval for TSH in treated patients is suggested. Increased requirement for thyroxine (or exogenous LT4) occurs as early as 4-6 weeks of pregnancy. Requirements gradually increase up till 16-20 weeks of pregnancy and plateau thereafter until the time of delivery. Following delivery, maternal LT4 dosing should be reduced to pre-pregnancy levels, and a serum TSH assessed 6 weeks thereafter. However, a study demonstrated that more than 50% of women with Hashimoto's thyroiditis required an increase in the pregestational thyroid hormone dose in the postpartum period, presumably due to an exacerbation of autoimmune thyroid dysfunction postpartum. In women started on LT4 during pregnancy for thyroid autoimmunity in the absence of TSH elevation, the LT4 can be stopped at delivery, with serum TSH assessment at 6 weeks postpartum. A maternal serum TSH concentration <2.5 mIU/L is a reasonable goal. Even lower preconception TSH values (<1.5 mIU/L) could reduce the risk of TSH elevation during the first trimester, but a lower treatment target may not improve outcomes because the LT4 dose can be immediately increased upon a positive pregnancy test. Achieving a TSH concentration at the lower end of the reference range could induce subnormal TSH concentrations in some patients.

Though generally safe for any developing fetus, potential effects upon conception and/or successful implantation are unknown.

If TSH is well-controlled in pregnancy and treatment is adequate, neonatal thyroid function screening is not necessary.

Subclinical hypothyroidism (SCH) is also associated with some adverse outcomes like miscarriage but not proven to cause fetal impaired cognitive functions.

Any pregnant woman with an elevated TSH concentration must also be evaluated for TPOAb status. A dose of only 50 μg/day is typically required for effective treatment of subclinically hypothyroid women.

- LT4 therapy is recommended for:
  - TPOAb-positive women with a TSH greater than the pregnancy-specific reference range
  - TPOAb-negative women with a TSH >10.0 mU/L.
- LT4 therapy may be considered for:
  - TPOAb-positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range
  - TPOAb-negative women and TPOAb-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L.

- LT4 therapy is not recommended for:
  - TPOAb-negative women with a normal TSH <4.0 mU/L.

A clear association has been demonstrated between thyroid antibodies and spontaneous pregnancy loss; however, it does not prove causality and the underlying mechanisms are not known. All women with overt and subclinical hypothyroidism should be treated irrespective of TPOAb positivity with LT4 during pregnancy to maintain serum TSH in the trimester-specific goal range. It has been recommended to check serum TSH every 4 weeks during pregnancy so that appropriate dose adjustments can be made, but our routine practice is to check every 6 weeks. The recommended therapy is with oral LT4, which should be taken on an empty stomach (45 minutes before consumption of food, beverages or other medications). In addition, calcium, iron and prenatal vitamin supplements should be avoided within 4 hours of ingestion of LT4, as these can decrease the absorption of thyroxine.

Immediately after delivery, the requirement of thyroxine drops and women who were taking thyroxine prior to pregnancy will shift to their pre-pregnancy dose, and those who started their thyroxine in pregnancy will require half the dose they were taking just before delivery. In women who had started their thyroxine in pregnancy for subclinical hypothyroidism, the medication can be stopped after delivery and thyroid balance re-assessed again after 6 weeks and decision taken regarding continuation of treatment.

Monitoring of euthyroid women who are thyroid antibody (Ab)-positive during pregnancy

TPOAb are able to cross the placenta. At the time of delivery, cord blood TPOAb levels strongly correlate with third-trimester maternal TPOAb concentrations.

However, maternal passage of either TPOAb or thyroglobulin (Tg)Ab is not associated with fetal thyroid dysfunction.

Euthyroid pregnant women who are TPOAb or TgAb positive should have measurement of serum TSH concentration performed at time of pregnancy confirmation and every 4 weeks through mid-pregnancy. LT4 administration in low dosage (25-50 μg/d) is safe. Therefore, its use among patients with recurrent pregnancy loss may be reasonably considered in the setting of early gestation, especially when no other known cause of prior pregnancy loss has been identified.

Two randomized clinical trials are currently ongoing. One of them is the Thyroid Antibodies and LevoThyroxine study (TABLET) trial in the United Kingdom. There is a greater risk for adverse events in women who are TPOAb-positive versus TPOAb-negative, even when thyroid function is identical.

The recommended treatment of maternal hypothyroidism is oral LT4. Other thyroid preparations, such as T3 or desiccated thyroid, should not be used in pregnancy.

Hyperthyroidism

Pregnancy hyperthyroidism is often due to Grave's disease (GD). It has an incidence of about 1 in 500 pregnancies (0.4%). Hyperthyroidism in pregnancy is also termed gestational thyrotoxicosis.

Pregnant women with GD should be monitored monthly. No prior history of thyroid disease, no stigmata of GD (goiter, orbitopathy), a self-limited mild disorder and symptoms of emesis favor the diagnosis of gestational transient thyrotoxicosis.

Rarely severe vomiting (Hyperemesis gravidarum) can cause dehydration and weight loss; this may be triggered by high levels of hCG and causes temporary hypothyroidism that settles in second trimester.

Symptoms

- Irregular heart beat
- Nervousness
- Severe nausea or vomiting
- Slight tremor
- Trouble sleeping
- Weight loss or low weight gain
- Eye problems (irritation, bulging and puffiness)

Uncontrolled hyperthyroidism in pregnancy can lead to:

- Congestive heart failure
- Pre-eclampsia
- Thyroid storm
- Miscarriage
- Premature birth
- Low birth weight.

Hyperthyroid in newborns can cause:

- Rapid heart rate
- Heart failure
- Early closure of soft spot of skull

- Poor weight gain
- Irritability
- Enlarged gland, causing problem in breathing.

Diagnosis is made on testing for thyroid if there is a suspicion on account of the symptoms. Tests include:

- TSH/Ultra TSH
- T3 and T4
- Thyroid-stimulating immunoglobulin (TSI).

TSH receptor antibody (TRAb) and maternal TT3 may prove helpful in clarifying the etiology of thyrotoxicosis. Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy.

Mild hyperthyroidism in which TSH is low but T4 is normal does not need any treatment. Treatment of choice is PTU (propylthiouracil). If patient is on carbimazole (CM), then it is advisable to change to PTU (CM can cause rare embryopathy). If liver function is compromised, then PTU should be stopped and carbimazole should be started. Titration of treatment should be guided by TSH and free T4 levels.

Moderate doses of antithyroid drugs (ATDs) (carbimazole 25-30 mg or PTU <300 mg/day) are recommended during breastfeeding.

Thyroid function should be monitored in mothers on high doses during the postpartum period. Gestational or hCG triggered thyrotoxicosis usually does not require antithyroid treatments; this is self-limiting. Sometimes symptomatic treatment may be needed in these cases.

If the patient opts for radioactive iodine ablative therapy prior to pregnancy, the following recommendations should be provided:

First, TRAb levels tend to increase following ^{131}I therapy and may remain elevated formany months following ^{131}I therapy. Therefore, patients with high TRAb levels or severe hyperthyroidism may favor consideration of other therapeutic options, such as surgery.

Second, a subset of young patients with severe GD may not become stably euthyroid within the first year after ^{131}I therapy.

Third, if ^{131}I therapy is planned, a pregnancy test should be performed 48 hours before ^{131}I ablation to confirm absence of unexpected pregnancy.

Fourth, conception should be delayed for 6 months and until a stable euthyroid state is reached after ablation and initiation of LT4 replacement therapy.

If the patient chooses ATD therapy, the following recommendations should be given:

First, the increased risk of birth defects associated with both PTU and methimazole (MMI) use during early pregnancy should be reviewed. ATDs should be avoided in the first trimester of pregnancy, but when necessary, PTU is generally favored. PTU after the first trimester should be switched to MMI to decrease the risk of liver failure in the mother.

In thyrotoxic patients, the possibility of future pregnancy should be discussed. Women with GD seeking future pregnancy should be counseled regarding the complexity of disease management during future gestation and birth defects with ATD use. In preconception counseling, the risks and benefits of all treatment options and the patient's desired timeline to conception should be discussed.

Thyrotoxic women should be rendered stably euthyroid before attempting pregnancy. Treatment options are associated with risks and benefits. These include ^{131}I ablation, surgical thyroidectomy or ATD therapy.

Management of patients with Graves' hyperthyroidism during pregnancy

In some cases, a woman may experience an overactive rather than underactive thyroid. This is known as hyperthyroidism, commonly referred to as GD.

Obstetric and medical complications are directly related to control of maternal hyperthyroidism, and the duration of the euthyroid state throughout pregnancy.

Poor control of thyrotoxicosis is associated with pregnancy loss, pregnancy-induced hypertension, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm and maternal congestive heart failure. Moreover, some studies suggest fetal exposure to excessive levels of maternal thyroid hormone may program the offspring to develop diseases such as seizure disorders and neurobehavioral disorders in later life.

During pregnancy, GD is typically treated with an antithyroid medication such as PTU during the first trimester and another called MMI for the remainder.

Thionamide ATDs (MMI, CM and PTU) are the mainstays of treatment for hyperthyroidism during pregnancy. They reduce iodine organification and coupling of monoiodotyrosine and diiodotyrosine, therefore inhibiting thyroid hormone synthesis. The thyroid function tests return to normal gradually over weeks.

Initial doses of ATDs during pregnancy are: MMI, 5-30 mg/day (typical dose in average patient 10-20 mg); CM, 0-40 mg/day and PTU, 100-600 mg/day (typical PTU dose in average patient 200-400 mg/d). The equivalent potency of MMI to PTU is 1:20. PTU dosing should be split into 2-3 daily doses. MMI can be given in one daily dose.

Postpartum Thyroiditis

About 1 in 20 women may get postpartum thyroiditis (PPT).

- 48% are hypothyroidism.
- 22% biphasic where there is hyperthyroidism followed by hypothyroid.
- 30% have isolated hyperthyroidism.

During the thyrotoxic phase of PPT, symptomatic women may be treated with β-blockers. These are safe for lactating women, such as propranolol or metoprolol, at the lowest possible dose to alleviate symptoms; it is the treatment of choice. Therapy is typically required for a few weeks.

ATDs are not recommended for the treatment of the thyrotoxic phase of PPT.

Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4-8 weeks (or if new symptoms develop) to screen for the hypothyroid phase.

Treatment is on the basis of the presenting disease and long-term follow-up with annual thyroid function tests is recommended. All patients with depression, including postpartum depression, should be screened for thyroid dysfunction.

Thyroid Nodule and Cancer

If thyroid nodules are seen is prepregnant period, it is advisable to delay pregnancy by 1 year after ablation.

If detected in pregnancy after 20 weeks, then a biopsy (FNAC) can be done. For malignancy, surgery is delayed till second trimester. Special care is needed during labor and delivery due to anesthesia complications.

In postnatal period, radioactive iodine is contraindicated if patient is breastfeeding.

UNIVERSAL SCREENING

It is still controversial whether to do universal screening of all pregnant women or apply case finding approach.

Table 3. High Risk Attributes for Thyroid Dysfunction

- A history of thyroid dysfunction or surgery
- Family history of thyroid disease
- Goiter
- Antithyroid antibodies present
- Symptoms or signs of hypothyroidism
- Women with type 1 diabetes
- History of miscarriage or preterm delivery
- Autoimmune disorder
- Infertility
- Prior head or neck irradiation
- Morbid obesity
- Age 30 years or older
- Treatment with amiodarone
- Treatment with lithium
- Recent exposure to iodinated contrast

American Thyroid Association guidelines do not support universal screening but recommend ordering a TSH test at first antenatal visit for women with high risk attributes (Table 3).

KEY POINTS

- Pregnancy-specific reference ranges should be used to guide diagnosis and monitoring of thyroid conditions in pregnancy.
- The World Health Organization (WHO) recommends a daily intake of iodine 250 μg during pregnancy and lactation.
- Hypothyroid states should be treated with thyroxine aiming for TSH <2.5 prior to conception and in the first trimester and TSH <3.0 for the second and third trimesters.
- Thyroxine should be increased by two additional doses per week (or 30%) on suspicion or confirmation of pregnancy in women already taking thyroxine.
- It is important to separate thyroxine intake from preparations that may reduce absorption.
- Women with high risk attributes for thyroid dysfunction are appropriate for antenatal screening with TSH.
- Gestational thyrotoxicosis needs to be differentiated from Graves' disease and rarely requires thioamide treatment.
- It is important to maintain a high index of suspicion for postpartum thyroiditis, especially in those with known thyroid antibodies or autoimmune conditions.

Pearls of Practice – Thyroid Dysfunction

Hypothyroidism

- T4 essential for early fetal development
- Little T4 crosses placenta after first trimester
- Adequate treatment - good outcome

Postpartum Thyroiditis

- Occurs 3-4 months postpartum
- Autoimmune disorder
- Phases of hyper- and hyporecovery
- Annual thyroid function tests

Hyperthyroidism

- Careful D/D at early weeks
- Untreated poor pregnancy outcome
- Drug cross placenta: lowest optimal dosage
- Cord blood - thyroid function

Thyroid Nodule and Cancer

- Defer pregnancy for 1 year after treatment with radioactive iodine
- Nodule identified beyond 20 weeks - biopsy after delivery
- Large goiter - anesthetic complications

FIGO RECOMMENDS THE FOLLOWING

- Screening for thyroid function is recommended in the first trimester particularly in countries with a deficient iodine diet and in symptomatic patients.
  - TSH is the superior method for screening. FT4 and TPOAb testing are not recommended for screening. The best reliable tests for TSH are by chemiluminescence immunoassay (CIA) or third-generation radioimmunoassay (RIA). Notably, normal thyroid test values change in pregnancy.
- Treatment for hypothyroidism is recommended when TSH levels are >2.5 and >3.0 mIU/L during the first and second/third trimesters, respectively. The only replacement therapy is LT4. Treating subclinical hypothyroidism, in the presence of negative thyroid autoantibodies, is still debatable. Importantly, women on LT4 before pregnancy should increase their dosage by 30-50% when they first recognize the pregnant state.
- Treatment of hyperthyroidism due to GD is by ATDs (PTU/CM/MMI). It is not recommended to change drugs during pregnancy. Symptomatic treatment with β-blockers for short-term may be needed.
- Primary prevention of hypothyroidism is by a healthy diet and iodized fortified salt (especially in iodine deficient areas).
- If the patient has a thyroid nodule, she should be evaluated and treated during pregnancy. The first steps are performance of a thyroid ultrasonogram and a fine needle aspiration (FNA), as needed. Surgery should be preferably deferred to the postpartum period.
- Follow-up and postpartum TSH evaluation and reduction of LT4 dose to pre-pregnant levels in patients with hypothyroidism.

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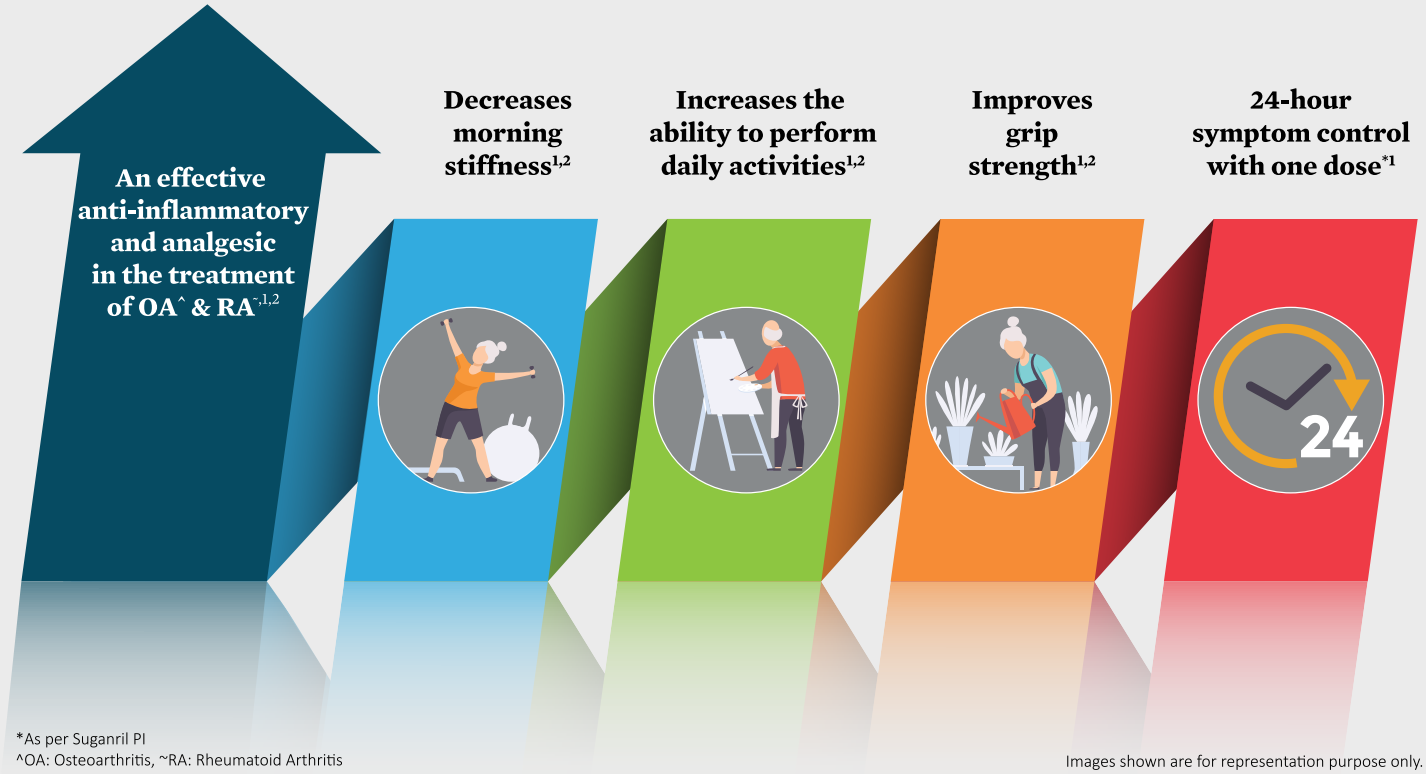

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Understanding Evolution of Resistant Strains in Recent Decades and Approach Towards Antibiotic Therapy

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ABSTRACT

Developing resistance to antibiotics is a natural process, and a rising threat to human society. These emergent strains have worsened the burden on existing regimen of antibiotic therapy. Resistance, classified under multidrug resistance (MDR), extensively drug-resistance (XDR) and pandrug-resistance (PDR), is widely seen in hospital setup. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), *Escherichia coli* and Klebsiella (Resistant to third-generation cephalosporins), carbapenem-resistant Enterobacteriaceae (CRE) are currently spread infectious agents which call for careful and proper antibiotic management. Antibiotic control programs, better hygiene, antibiogram-based empirical therapy with improved antimicrobial activity are needed to limit bacterial resistance.

Keywords: Antibiotics resistance, mechanisms, biofilm resistance, multidrug resistance, extensively drug-resistance, pandrug-resistance

Discovery of antibiotic was a milestone in the history of medical science, which revolutionized clinical world. The antibiotics are wonder drugs which have immense role in health sector by reducing morbidity as well as mortality. They are the main weapons against infectious diseases which is a serious issue on a global level, and save countless lives. The antibiotic era started in the 1940s, which changed the profile of infectious diseases and human demography. With due course of time, there evolved a large variety of pathogens and discovery of new antibiotics became necessary. However, as antibiotics served as magical bullets, equally infectious agents challenged by rapid appearance of resistance through unbelievable molecular mechanisms emerged. Over a period of 65 years, newer antibiotics were introduced in the market, which was followed by emergence of resistant strains. Due to increased concern of change in resistance, this is an attempt to point out how far our chemotherapy with antibiotics has reached, emerging resistant strains, mechanisms, multidrug resistance (MDR), extensively drug-resistance (XDR) and pandrug-resistance (PDR) and how intense use of reserve antibiotics will affect in future.

EVOLUTIONARY CHANGE OF ORGANISMS AFTER ANTIBIOTIC DISCOVERY

The extensive use and misuse of antibiotics are the major factors driving the high numbers of resistant pathogenic bacteria worldwide, which is a rising threat to the society. The introduction of new antibiotics to counter those pathogens has frequently been closely followed by the emergence of resistant strains. These emergent strains have worsened the burden on existing regimen of antibiotic therapy in both clinical and economical aspects. Some of the examples are *Staphylococcus aureus* isolates resistant to β-lactams due to β-lactamase as well as extensive spectrum β-lactamase and many of these are also resistant to β-lactamase-resistant penicillins. Methicillin-resistant *S. aureus* (MRSA) isolates are one of the most challenging resistant pathogens now-a-days. Evolutionary pattern of resistant strains of *S. aureus* is given in Figure 1. They are usually associated with hospitals and require implementation of appropriate control measures, which usually reduces prevalence

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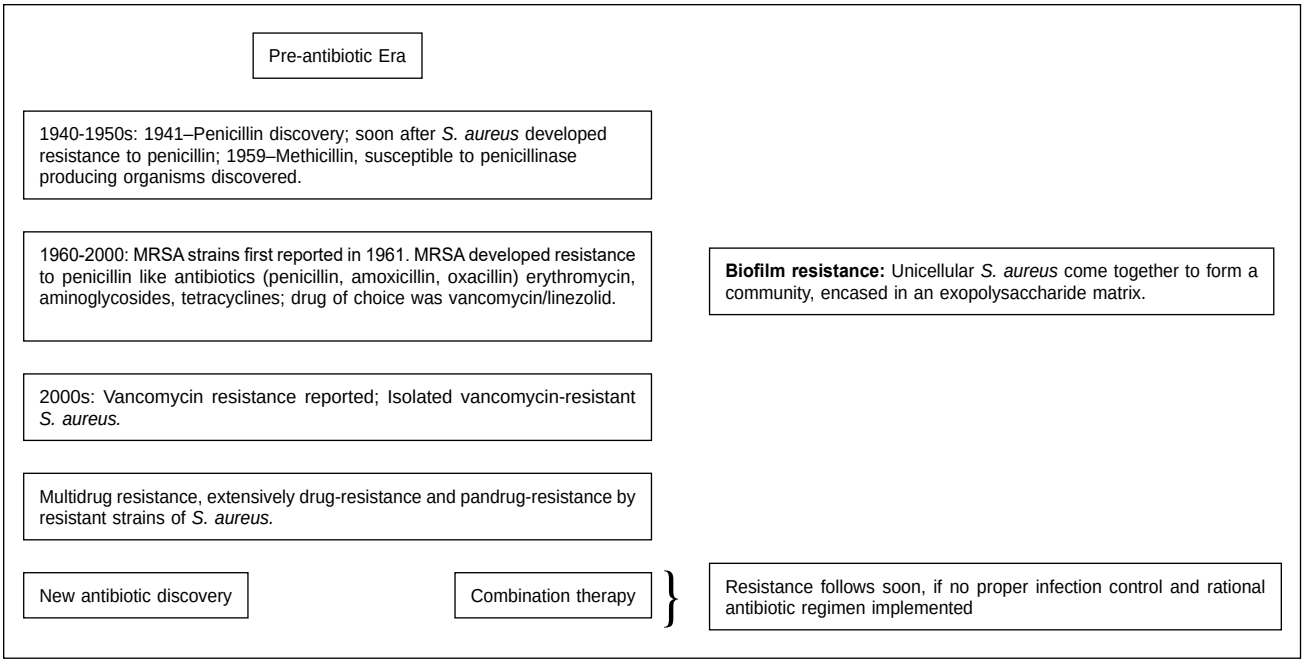

Figure 1. Evolutionary pattern of resistant *S. aureus* strains.

to sporadic levels. Antibiotic resistance often results in failures of empirical therapy. These conditions call for the need for the revolutionary change by either discovery of new antibiotics or combination antibiotic therapy in future. But it is not a rational solution to the problem because resistance follows with these approaches. In short, antibiotic resistance is the major challenge associated with chemotherapy against infectious diseases. Resistant pathogens developed are more virulent, so as a first step, knowledge of etiological agents of infections, antibiotic resistance mechanisms, pattern of developing resistance and sensitivities to available drugs is of immense value for the rational empirical therapy of antibiotics and to slow down the process of antibiotic resistance.

RESISTANT STRAINS IN RECENT DECADES

The susceptible populations of bacteria may become resistant to antimicrobial agents through mutation and selection, or by acquiring from other bacteria, the genetic information that encodes resistance. The infectious agents may get intrinsically resistant to more than one class of antimicrobial agent, or may acquire resistance by *de novo* mutation or via the acquisition of resistance genes from other organisms. These spontaneous mutations may cause resistance by: a) altering the target protein to which the antibacterial agent binds by modifying or eliminating the binding site; b) up regulating the production of enzymes that inactivate the antimicrobial agent; c) down-regulating or altering an outer membrane protein channel that the drug requires for cell entry; or d) up regulating pumps that expel the drug from the cell (Table 1).

However, acquisition of new genetic material by antimicrobial-susceptible bacteria from resistant strains may occur by means of conjugation, transformation or transduction, with transposons often facilitating the incorporation of the resistance genes into the host's genome or plasmids. Some of the important or recently developed resistant strains in our community and its mechanisms are discussed below.

E. coli and Klebsiella: Resistance to Third-generation Cephalosporins

Escherichia coli is a common cause of urinary tract infections (UTI) and bacteremia in humans. It has been observed that there is a generalized decrease in bacterial susceptibility of common oral antibiotics to community-acquired UTI, which is frequently resistant to aminopenicillins, such as amoxicillin or ampicillin and narrow-spectrum cephalosporins. Resistance is typically mediated by the acquisition of plasmid-encoded β-lactamases. But the third-generation cephalosporins are broad-spectrum drugs with intrinsic activity against Gram-negative species. Resistance to third-generation cephalosporins and monobactams (aztreonam) occurs through the acquisition of extensive spectrum beta-lactamases (ESBLs). ESBL are strong bacterial enzymes that raise the burden of resistance to even highly

Table 1. Common Resistance Mechanisms and Examples

Common resistance mechanisms	Example	Antibiotics
a) Altering the target protein to which the antibacterial agent binds	Change in penicillin-binding protein 2b in pneumococci, which results in penicillin resistance	Penicillin G, ampicillin, amoxicillin, ticarcillin, piperacillin, methicillin
b) Up regulating the production of enzymes that inactivate the antimicrobial agent	Erythromycin ribosomal methylase in staphylococci	Penicillins, monobactams, carbapenems and cephalosporins, aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc.)
c) Down-regulating or altering an outer membrane protein channel that the drug requires for cell entry	OmpF in *E. coli*	β-lactams, carbapenems, fluoroquinolones, chloramphenicol have specific porins
d) Up regulating pumps that expel the drug from the cell	Efflux of fluoroquinolones in *S. aureus*	Aminoglycosides, ampicillin, ciprofloxacin, chloramphenicol, clindamycin, cephalosporin, erythromycin, fluoroquinolones, macrolides, nalidixic acid, novobiocin, norfloxacin, streptogramin B, tetracycline, tigecycline, trimethoprim, vancomycin

effective antibiotics. The problem of resistance due to ESBL, even though more reported on Klebsiella, now-a-days has a similar pattern for *E. coli*. Different studies showed that ESBL-producers are also resistant to fluoroquinolone, trimethoprim-sulfamethoxazole and aminoglycoside. However, resistance to cephamycins and other β-lactams may arise as a result of changes in the porins in the outer membrane.

Methicillin-resistant *S. aureus*

Methicillin, the first of the semi-synthetic penicillinase-resistant penicillins, was introduced to target strains of penicillinase-producing *S. aureus*. However, resistance to methicillin was reported very quickly after its introduction in 1960s and detection of MRSA has been associated with more severe clinical presentation of community-acquired pneumonia and it is a leading pathogen in skin infection. It was the beginning of global outbreaks of community-associated MRSA infection. MRSA is a common cause of infection among hospitalized patients. Consequently, treatment of these infections has become more difficult and is a healthcare burden. The studies show that MRSA bacteremia is linked with significantly higher mortality rate compared to methicillin-susceptible *S. aureus* (MSSA) bacteremia. Resistance occurs following the chromosomal acquisition of novel DNA, resulting in the production of a new penicillin-binding protein (PBP2a), with a low-binding affinity for methicillin. PBP2a substitutes for all other penicillin-binding proteins, and because of its low affinity for all β-lactam antibiotics, it confers resistance to all β-lactam agents, including cephalosporins. Vancomycin is currently the gold standard for the treatment of MRSA bacteremia, but over the last decade, there has been increasing concern about the development of MRSA strains with reduced susceptibility to vancomycin.

Vancomycin-resistant *S. aureus*

Another major concern after the emergence of MRSA is the vancomycin-resistant strains (VRSA), that is, evolution of strains resistant to vancomycin, which is the typical treatment for MRSA infection. However, the therapeutic failure of vancomycin therapy is explained by the reduced susceptibility of glycopeptides rather than using the term resistance in clinical world and is associated with minimum inhibitory concentration (MIC). *S. aureus* strains with reduced susceptibility to glycopeptides can be divided into three categories - vancomycin-resistant strains (VRSA; MIC, ≥16 μg/mL); vancomycin-intermediate strains (VISA; MIC, ≥4 μg/mL) and heterogeneous vancomycin-intermediate strains (hVISA; MIC <4 μg/mL). Reduced susceptibility versus resistance of vancomycin is controversial, as the term resistance is reserved for those with MIC ≥16 μg/mL. However, the prevalence of hVISA among MRSA is rising.

The exact mechanism of vancomycin resistance remains unclear, but it probably involves thickening of the organism's cell wall due to the accumulation of cell wall fragments capable of binding vancomycin extracellularly, thereby preventing them from reaching their bacterial target. High-level vancomycin resistance occurs because of expression of vanA, which is

associated with alteration of the vancomycin-binding site in the cell wall. Expression of vanA and other genes made the affinity of vancomycin 1,000 times lower than for the native peptidoglycan precursor and resulted in high resistant density.

E. coli, *S. aureus*, *Streptococcus pyogenes*: Biofilm Resistance

Bacterial biofilm is an emerging mechanism of resistance, as it succeeded in explaining the reason of chronic infectious diseases that ends in treatment failure. Biofilms are communities of microorganisms attached to a surface. Bacterial biofilms are formed when unicellular organisms come together to form a community that is attached to a solid surface and encased in an exopolysaccharide matrix. Example-biofilm development in both commensal and pathogenic *E. coli* - the polysaccharide matrix contributes to the development of phenotypic resistance of pathogenic *E. coli* biofilms and leads to persistent infections. Biofilm bacteria show much greater resistance to antibiotics than their free-living counterparts. Its mechanisms is entirely different from familiar mechanisms of resistance such as familiar plasmids, transposons and mutations. This emerging mechanism has grabbed the attention of clinical world and calls the need for potential antibiotic therapies.

It has been suggested that this matrix prevents the access of antibiotics to the bacterial cells embedded in the community. However, *Staphylococcus epidermidis* biofilms formed allowed for the diffusion of rifampicin and vancomycin. These results suggest that inhibition of diffusion cannot always explain resistance to antimicrobial compounds and other mechanisms must be in place to promote biofilm cell survival. Some organisms in biofilms have been shown to express biofilm-specific antimicrobial resistance genes that are not required for biofilm formation. The 38% of the *E. coli* genome is affected by biofilm formation (ompR gene, csgD gene involved in bacterial adhesion). However, the exopolysaccharide matrix does act as an initial barrier that can delay penetration of the antimicrobial agent. Phenotypic and genotypic characteristics associated with biofilm formation of *E. coli*, *S. aureus, Streptococcus pyogenes* have been widely studied. Pharyngitis treatment failure has been seen in patients with isolates of *S. pyogenes* having a biofilm-positive phenotype and increased minimum biofilm eradication concentration (MBEC) for all contemporary antibiotics that are used to treat acute pharyngitis cases. *S. epidermidis* infections on indwelling medical devices point towards biofilm formation. *S. aureus* infections, such as osteomyelitis, specifically cases of juvenile osteomyelitis, periodontitis and peri-implantitis, wound infection, endocarditis, are types of biofilm infection. Device-mediated infections are also common and such devices need to be replaced more frequently than those infected with *S. epidermidis*. Biofilm infections must be either prevented from forming or be surgically removed once formed in order to resolve the infection, together with potential antimicrobial therapy.

Carbapenem-resistant Enterobacteriaceae

The difficult situation has not ended with the emergence of broad-spectrum third-generation cephalosporins, carbapenems (example: *E. coli*-resistant to imipenem). These entered the clinical world with extreme potency and broad-spectrum of activity, but are also showing resistance now-a-days. This may have serious public health consequences, resulting in the elimination of many effective antimicrobial drug treatments against the most common human bacterial pathogens. Many studies support the use of carbapenem as an empirical antibiotic for patients with community-onset bacteremia and those with high risk of resistance. Increased consumption of carbapenems after rise of third-generation cephalosporin-resistant *E. coli* and *Klebsiella pneumoniae* may be the reason for emergence of carbapenem-resistant strains of organisms. Resistance density of carbapenem-resistant *K. pneumonia*e is also increasing along with third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*.

Carbapenemases are powerful enzymes that inactivate carbapenems. Bacterial acquisition of carbapenemases has a role in the emergence of carbapenem-resistant Enterobacteriaceae (CRE). It also led to resistance to all cephalosporins, aztreonam and β-lactamase inhibitors including clavulanic acid and tazobactam. CRE isolates are increasingly reported as multidrug-resistant, extensively drug-resistant or pandrug-resistant. In a short time, isolates of *E. coli*, Klebsiella, Enterobacter, Serratia, and Salmonella species have reported carbapenem resistance and it globally changed the epidemiology of resistance. Combination regimen or monotherapy of agents such as polymyxins (such as colistin), aminoglycosides, tigecycline and fosfomycin are the available therapeutic options.

Multidrug Resistance, Extensively drug-resistance and Pandrug-resistance

Multidrug resistance, extensively drug-resistance and pandrug-resistance have been defined differently in medical literatures. The standardized international

terminology was created by group of international experts that came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) defines these terms as follows: MDR is defined as nonsusceptibility to at least one agent in three or more antimicrobial categories; XDR is defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (bacterial isolates remain susceptible to only one or two categories). PDR is defined as nonsusceptibility to all agents in all antimicrobial categories (no agents tested as susceptible for that organism). The pictorial representation of relation between MDR, XDR and PDR is shown in Figure 2.

Emerging and spreading of MDR (emerged strains are referred as 'super bugs') is a natural phenomenon, followed by the inappropriate use of antimicrobial drugs, inadequate sanitary conditions, inappropriate food-handling and poor infection prevention and control practices. XDR ('extreme drug resistance', 'extensive drug resistance') was the term created initially to describe drug-resistant *Mycobacterium tuberculosis.* Eventually, the condition changed and the resistance profile of non-Mycobacterium that compromised most standard antimicrobial regimens was also described by same term. Pandrug-resistant (pan-'all') means 'resistant to all antimicrobial agents'. The management of pandrug-resistant Gram-negative bacterial infections is very difficult. Only few drugs, including colistin, in combination with β-lactam antibiotics, polymyxins, an old class of antibiotics, are recommended. Now the time has been reached where there are only limited therapeutic options. Even though many antibiotics are in our hand, it's time to focus on careful handling of antibiotics.

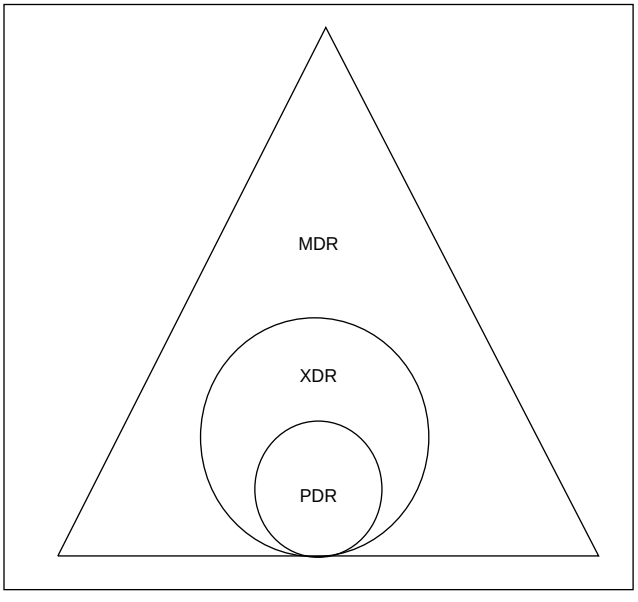

Figure 2. Relation between MDR, XDR and PDR.

MANAGEMENT OF ANTIBIOTIC RESISTANCE

Most of the antibiotic drug resistance is nosocomial or of hospital origin. In India, 1 in 4 patients admitted into hospital acquire nosocomial infection. So, for adequate management of critically ill patients and patients undergoing various operative procedures and other medical interventions, hospital antibiotic policies need to be revisited. In the management of infectious diseases, initially more care should be given in the selection of antibiotics based on hospital antibiogram in empirical therapy. More rational selection of antibiotics based on the most likely pathogens for a given infection and the susceptibility profiles of these pathogens that are specific to each institution will reduce density of resistance in and around institution. Antibiogram considerably helps in proper empirical selection of antibiotics. Each practitioner should have updated knowledge about evolutionary stage of resistant isolates in the hospital, while prescribing each antibiotic. Proper infection control should be employed in hospitals. In short, antibiotic control programs, better hygiene, antibiogram-based empirical therapy and synthesis of agents with improved antimicrobial activity are needed to limit bacterial resistance. In a developing country like India, there is an urgent need to develop and strengthen antimicrobial policy and standard treatment guidelines at the national, community and hospital level.

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CDC Issues New Guidance on What Vaccinated People can Safely Do

Fully vaccinated individuals in the US can now safely enjoy more pre-pandemic activities without wearing a mask, suggest new guidelines from the US CDC. Fully vaccinated individuals are defined as those for whom at least 2 weeks have passed since the second dose of the Pfizer/BioNTech or Moderna vaccines, or at least 2 weeks have passed since the single-dose J&J vaccine. These people can now avoid a mask while dining at an outdoor restaurant with friends from several households, stated the CDC. They can also avoid wearing a mask at small outdoor gatherings with other fully vaccinated family members and friends, or where there is a mix of fully vaccinated and unvaccinated individuals. CDC Director Dr Rochelle Walensky stated that an increasing amount of data suggest that most of the transmission is happening indoors rather than outdoors, and that less than 10% of the transmission in many studies has taken place outdoors… (*CNN*)

Covishield, Covaxin Effective Against Indian Strain of Coronavirus, Says Study

Covishield and Covaxin are effective against the Indian strain of the coronavirus and show milder illness if infection is contracted after vaccination, reported a senior scientist citing preliminary results of a study.

Anurag Agrawal, Director of the Institute of Genomics and Integrative Biology (IGIB), stated that the study on effectiveness of the vaccines currently available on the B.1.617 variant indicates that the infections are milder following vaccination. The B.1.617 variant has been termed as ''double mutant'' or the ''Indian strain'' as well.

Another study by the CCMB noted that early results using *in vitro* neutralization assay suggested that both convalescent sera and Covishield-vaccinated sera were protective against the B.1.617 variant… (N*DTV – PTI*)

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Study of Demographic Profile, Comorbidities, Role of Hydroxychloroquine Prophylaxis and Outcomes of COVID-19 Positive Healthcare Workers at a Tertiary Care Center in Southern Rajasthan

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ABSTRACT

Background: In December 2019, a new respiratory tract infecting agent emerged in Wuhan city of China, known as the coronavirus. There are limited studies regarding coronavirus disease 2019 (COVID-19) in healthcare workers (HCWs). Therefore, the present study was aimed to determine the demographic profile, comorbidities, hydroxychloroquine as prophylaxis and outcomes of reverse transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 HCWs. **Material and methods:** This study was an observational retrospective study carried out over a period of 10 months from 15th March, 2020 to 15th January, 2021 in 350 RT-PCR confirmed COVID-19 HCWs who were in home isolation or admitted in dedicated COVID hospital. **Results:** We observed that majority of HCWs were in the age group 20-39 years (66.58%), were males (69.14%) and from urban areas (72.86%). Only few had comorbidities (3.42%), took hydroxychloroquine as prophylaxis (5.71%) and mortality was 0.57%. About 46.29% of the HCWs were doctors and 28.40% of the doctors were from Medicine. **Conclusion:** From the present study, we conclude that HCWs affected by COVID-19 are mainly young adult male physicians from urban areas, without significant comorbidities. The outcome in COVID-19 positive HCWs is favorable due to better awareness, prompt diagnosis and treatment. The results of this study will be useful in knowing the most vulnerable section of HCWs.

Keywords: COVID-19, healthcare workers, hydroxychloroquine

In December 2019, a new respiratory tract infecting agent emerged in Wuhan city of China, known as the coronavirus. It was later named coronavirus disease 2019 (COVID-19). Full-genome sequencing and phylogenetic analysis indicated that 2019-nCoV is a form of beta-coronavirus which include human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses.[1] The World Health Organization (WHO) declared COVID-19 as a pandemic on 11th March, 2020, and from India, the first case was reported on 30th January, 2020 from Kerala. Transmission of the coronavirus is usually via respiratory droplets in closed environments and through close contact between people and touching contaminated surfaces, with incubation period of 2-14 days and a reproductive number noted in early studies as 2.2.[2] COVID-19 has various clinical presentations that range from asymptomatic to mild symptoms such as fever, myalgia, sore throat, cough and cold to severe symptoms like acute respiratory distress syndrome, myocarditis, acute renal failure and multi-organ failure.[3-5]

According to WHO, healthcare workers (HCWs) are defined as all people engaged in actions whose primary intent is to enhance health.[6] In this pandemic, to manage COVID-19, many people came together and worked

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as HCWs. In our study, HCWs included consultants and postgraduates from clinical as well as nonclinical departments, interns, undergraduate students, nursing staff, nursing students, paramedical staff and lab technicians. HCWs have exposure to COVID-19 patients directly or indirectly or to the infectious materials. Secondary transmission from HCWs is a possibility among patients, family members and the community.

Therefore, the present study was aimed to determine the demographic profile (age, sex, residence), comorbidities, role of hydroxychloroquine as prophylaxis and outcomes of reverse transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 HCWs who were in home isolation or admitted in dedicated COVID hospital, a tertiary care institute attached to RNT Medical College, Udaipur, Rajasthan over a period of 10 months (15th March, 2020 to 15th January, 2021).

AIMS AND OBJECTIVES

- To study the demographic profile (age, sex, residence) of COVID-19 positive HCWs.
- To study the comorbidities in COVID-19 affected HCWs.
- To study the role of hydroxychloroquine as prophylaxis in COVID-19 affected HCWs.
- To study the outcomes of COVID-19 positive HCWs.

MATERIAL AND METHODS

This study was an observational retrospective study which was carried out over a period of 10 months from 15th March, 2020 to 15th January, 2021 in 350 RT-PCR confirmed COVID-19 HCWs who underwent home isolation or were admitted in dedicated COVID hospital, a tertiary care center attached to RNT Medical College, Udaipur, Rajasthan. We have analyzed the demographic profile, associated comorbidities, role of hydroxychloroquine drug as prophylaxis and outcomes of these HCWs.

Inclusion Criteria

All RT-PCR confirmed COVID-19 positive HCWs who were in home isolation or admitted in wards and intensive care unit (ICU) of our dedicated COVID hospital, irrespective of age and gender were included. HCWs included consultants and postgraduates from clinical as well as nonclinical departments, interns, undergraduate students, nursing staff, nursing students, paramedical staff and lab technicians.

Exclusion Criteria

HCWs who did not give written consent for the study.

Methodology

HCWs who were suspected to be COVID-19 positive on the basis of their clinical history, contact history and travel history as per the Indian Council of Medical Research (ICMR) guidelines, underwent RT-PCR testing for COVID-19 and those who came out positive were admitted in COVID Dedicated Hospital (wards and ICU) or underwent home isolation and were enrolled in our study after written consent. The following parameters were used for our study:

- Demographic profile – which includes age-wise, sex-wise and area-wise distribution.
- Comorbidities – which include diabetes mellitus, hypertension, ischemic heart disease, chronic respiratory illness, malignancies and hypo-thyroidism.
- Number of HCWs taking hydroxychloroquine prophylaxis – which includes collecting information from the HCWs whether he or she had completed or was taking hydroxychloroquine as prophylaxis.
- Outcome was recorded in the form of recovery or deaths.
- Amongst the HCWs, we classified them into doctors, nursing staff, paramedical staff and lab technicians. We further divided the doctors department-wise to see the distribution of affected doctors in each and every department. This will further give us a better picture of the departments at risk of getting affected by COVID-19.

OBSERVATION AND RESULTS

Table 1 shows the demographic profile in the COVID-19 positive HCWs. Among the age groups, maximum HCWs were in the 20-39 years group (66.58%) followed by 40-59 years age group (30.00%). Regarding gender, males were predominantly affected (69.14%). The disease predominantly involved the urban population (72.86%).

Table 2 shows the association of comorbidities with COVID-19 positive HCWs. Out of 350 HCWs, 12 had comorbidities (3.42%). Among comorbidities, diabetes mellitus was observed in maximum HCWs (1.42%), followed by hypertension (0.57%), chronic respiratory illness (0.57%), ischemic heart disease (0.28%), malignancy (0.28%) and hypothyroidism (0.28%).

Table 1. Demographic Profile

Characteristics	HCWs (n = 350)	Percentage (%)
Age		
0-19 y	5	1.42
20-39 y	233	66.58
40-59 y	105	30.00
>60 y	7	2.00
Sex		
Male	242	69.14
Female	108	30.86
Residence		
Urban	255	72.86
Rural	95	27.14

Table 2. Comorbidities in COVID-19 Positive HCWs

Comorbidities	HCWs (n = 350)	Percentage (%)
Diabetes mellitus	5	1.42
Hypertension	2	0.57
Chronic respiratory illness	2	0.57
Ischemic heart disease	1	0.28
Malignancy	1	0.28
Hypothyroidism	1	0.28

Table 3. Number of HCWs Taking Hydroxychloroquine Drug as Prophylaxis

Hydroxychloroquine prophylaxis	HCWs (n = 350)	Percentage (%)
Yes	20	5.71
No	330	94.29

Table 3 shows that out of the 350 HCWs affected, 20 took hydroxychloroquine prophylaxis (5.71%).

Table 4 shows the outcome of COVID-19 positive HCWs. Out of 350 HCWs, 348 got discharged (99.42%).

Table 5 shows the distribution of COVID-19 positive HCWs. Out of 350 HCWs, maximum affected were doctors (46.29%) followed by nursing staff (37.14%), lab technicians (10.86%) and paramedical staff (5.71%). The table also shows the department-wise distribution of doctors. Among 162 doctors, maximum were from Medicine (28.40%) followed by Orthopedics (10.50%), Anesthesia (8.64%), Internship (8.64%), Pediatrics (7.40%), Surgery (6.80%), Obs and Gyne (6.17%), Radiodiagnosis (4.32%), Biochemistry (2.47%), ENT (2.47%) and others.

Table 4. Outcome of HCWs

Outcome	HCWs (n = 350)	Percentage (%)
Discharged	348	99.43
Death	2	0.57

Table 5. Distribution of COVID-19 Positive HCWs According to their Field

Subtypes	HCWs (n = 350)	Percentage (%)
Doctors	**162**	**46.29**
Medicine	46	28.40
Orthopedics	17	10.50
Anesthesia	14	8.64
Internship	14	8.64
Pediatrics	12	7.40
Surgery	11	6.80
Obs and Gyne	10	6.17
Radiodiagnosis	7	4.32
Biochemistry	4	2.47
ENT	4	2.47
Pathology	3	1.85
Anatomy	3	1.85
Microbiology	3	1.85
Physiology	3	1.85
PSM	3	1.85
Psychiatry	2	1.23
Ophthalmology	2	1.23
Radiotherapy	1	0.61
Dermatology	1	0.61
FMT	1	0.61
Dentist	1	0.61
Nursing staff	130	37.14
Paramedical staff	20	5.71
Lab technicians	38	10.86

DISCUSSION

The present study was an observational retrospective study which was done over a period of 10 months

(15th March, 2020 to 15th January, 2021) on 350 RT-PCR confirmed COVID-19 HCWs who underwent home isolation or were admitted in a dedicated COVID hospital attached to RNT Medical College, Udaipur, Rajasthan. These HCWs were analyzed in respect to demographic profile, comorbidities, role of hydroxychloroquine drug as prophylaxis and outcomes.

In the present study, we observed that COVID-19 affects all age groups. Out of 350 HCWs, maximum were from 20 to 39 years group (66.58%) followed by 40-59 years (30.00%), whereas the disease was less commonly seen in >60 years (2.00%) and 0-19 years (1.42%) age groups. Lai et al and Sikkema et al also observed similar results and calculated median age of COVID-19 positive HCWs as 36.5[7] and 49 years,[8] respectively. The possible explanation of higher COVID-19 positivity in the age group 20-59 years (96.58%) may be due to the fact that this age group of HCWs may be actively involved in management of this pandemic. Regarding gender, males were predominantly involved (69.14%). This may be because the majority of HCWs at our center are males and in the Indian society, males are more habituated in smoking, drinking alcohol, outdoor activities and tendency of removal of face masks frequently. The study done by Mahajan et al[9] found similar results (57%). This study also shows that the disease has a predominantly urban preponderance (72.86%). The possible explanation might be that the study was conducted at a tertiary care center, which in itself is in urban area.

In the present study, comorbidities were seen in 3.42% HCWs. Among comorbidities, diabetes mellitus was observed in maximum HCWs (1.42%), followed by hypertension (0.57%), chronic respiratory illness (0.57%), ischemic heart disease (0.28%), malignancy (0.28%) and hypothyroidism (0.28%). In contrast to our study, Mahajan et al[9] reported 19% comorbidities in COVID-19 positive HCWs. This significant difference in comorbidities may be due to the fact that the maximum HCWs in our study were in younger age groups. They also observed that hypertension and diabetes mellitus were the most common comorbidities, which resembles the present study.

The present study shows that only 5.71% of HCWs took hydroxychloroquine drug as prophylaxis as it was advocated to have a role in the early phase of the pandemic. But, the drug did not seem much efficacious, hence, HCWs stopped taking it as prophylaxis in the later half. Therefore, majority of the HCWs did not take hydroxychloroquine as prophylaxis. Jha et al[10] also stated that hydroxychloroquine did not have a role in prophylaxis. Multiple systematic reviews[11] also concluded that there is no pertinent data to support the use of hydroxychloroquine drug outside that of research, and there is lack of clinical data to actually support its efficacy.

Among the 350 COVID-19 positive HCWs, deaths occurred in only 2 HCWs (0.57%). Mahajan et al[9] and Lai et al[7] reported similar results in their studies (1%, 0.9%). This can be explained by several reasons. In our study, most of the HCWs were young adults which accounts for better immunity. Early symptoms were more easily noticed by HCWs which led to early diagnosis, treatment and better outcome. Also, the proper use of personal protective equipment (PPE) kits and face masks by them may be responsible for decreasing the severity of infection and death.

In the present study, out of 350 COVID-19 affected HCWs, maximum were doctors (46.29%) followed by nursing staff (37.14%), lab technicians (10.86%) and paramedical staff (5.71%). The study by Mahajan et al[9] showed involvement of 29% doctors, 26% nursing staff and 46% healthcare assistants and other staff. The result of the present study is contradictory to the above mentioned study. In the present study among HCWs, doctors were maximally affected (46.29%). This may be explained by the fact that doctors were the frontline warriors and were actively involved in the management of COVID-19 positive cases.

Amongst the 162 doctors affected, maximum were from Medicine department (28.40%), followed by Orthopedics (10.50%), Anesthesia (8.64%) and Internship (8.64%). The possible explanation of this higher involvement (28.40%) of doctors from Medicine department may be due to the fact that these doctors were actively and directly engaged in patient care in COVID-19 positive wards, ICU as well in severe acute respiratory illness (SARI) wards. In this pandemic, there were a lot of patients presenting with bilateral atypical pneumonias but their COVID-19 RT-PCR was repeatedly negative and they were admitted in various general medical wards, where improper use of PPE and exposure of these Medicine residents to highly suspected clinical COVID-19 patients might be one of the cause of higher involvement of doctors of this department. Orthopedicians are often involved due to operating on emergency cases of trauma without knowing the COVID-19 status of the patient. The surgeries are for longer hours and thus, increase the chances of exposure of the doctors. Anesthetists are involved in aerosol generating procedures like mechanical ventilation and noninvasive ventilation, which can lead to their increased chances of exposure.

Also, Interns are primarily affected because at our center, they are doing the job of sampling of COVID-19 suspect and positive cases, which leads to increased risk for them.

CONCLUSION

From the present study, we conclude that HCWs affected by COVID-19 are mainly young adult males from urban areas, without significant comorbidities. The outcome in COVID-19 positive HCWs is favorable due to better immunity, awareness, prompt diagnosis and treatment. We recommend that all HCWs as well as their family members and close contacts should be regularly tested for COVID-19 as they are the most precious resource for every country. Special attention needs to be paid to protect HCWs from cross infection from other HCWs. HCWs are at higher risk of being exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and could potentially have a role in hospital transmission. Among HCWs, doctors are most prone to develop the infection, especially the ones from departments of Medicine, Orthopedics, Anesthesia and Interns.

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ICMR Advises Against NSAIDs, Says Certain Painkillers can Worsen COVID-19

Some of the painkillers, such as ibuprofen, can worsen COVID-19, are known to be detrimental to patients with heart failure and may heighten the risk of kidney damage, stated the ICMR, advising against the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and recommended taking paracetamol, if required, during the disease. Listing some of the frequently asked questions (FAQs) for patients with hypertension, diabetes and heart diseases, the ICMR also stated that there is no evidence to state that the BP medications, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), increase the susceptibility or severity of COVID-19. The apex health research body said that around 80% of people diagnosed with COVID-19 will have mild symptoms of a respiratory infection, such as fever, sore throat, cough and will recover completely… (*ET Healthworld – PTI*)

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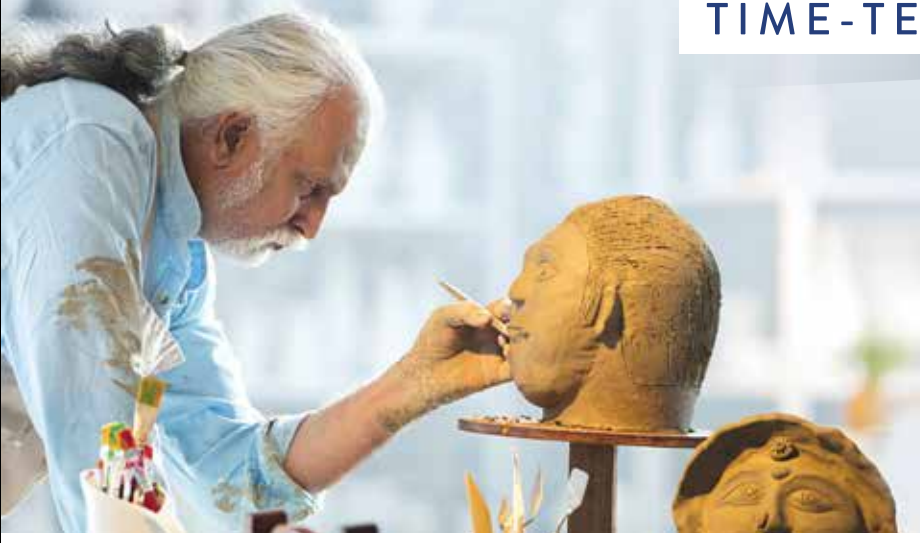

NCDC~ guidelines, 2016

- Recommends gentamicin as an empirical treatment option for acute pyelonephritis and pneumonia[1]
- Recommends gentamicin for neonatal sepsis[1]

Spectrum

- Broadest spectrum against Gram-negative bacilli[3]

Cure rate

- Microbiological cure rate in UTI^ is 94%$[4]

Gentamicin achieves maximum concentration in urine within 1 hour[2]

Available as 20 mg ▸ 60 mg ▸ 80 mg

#RTI: Respiratory Tract Infection, ^UTI: Urinary Tract Infection, ~NCDC: The National Centre for Disease Control,
$Pooled microbiological cure rate for 13 studies, n = 13804

Images shown are for representation purpose only.

References: 1. National Treatment Guidelines for Antimicrobial Use in Infectious Diseases. Version 1.0 (2016). National Centre For Disease Control; Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. Available from: https://ncdc.gov.in/WriteReadData/l892s/File622.pdf. Accessed on 12 December 2020. 2. Labovitz E, et al. Single-dose daily gentamicin therapy in urinary tract infection. Antimicrob Agents Chemother. 1974;6(4):465-70. 3. Serio AW, et al. Aminoglycoside revival: Review of a historically important class of an microbials undergoing rejuvenation. EcoSal Plus. 2018;8(1). 4. Goodlet KJ, et al. A systematic review of single-dose aminoglycoside therapy for urinary tract infection: Is it time to resurrect an old strategy?. Antimicrob Agents Chemother. 2019;63(1):e02165-18.

Abridged Prescribing Information:

COMPOSITION: For 80mg Injection: Each 2ml contains: Gentamicin Sulphate IP eq to Gentamicin bas 80mg, Methylparaben IP 0.18% w/v (as preservative), Propylparaben IP 0.02% w/v (as preservative) Water for Injection IPq.s. For 60mg Injection: Each 1.5 ml contains: Gentamicin Sulphate IP eq to Gentamicin base 60mg, Methylparaben IP 0.18% w/v (as preservative), Propylparaben IP 0.02% w/v(as preservative), Water for Injection IPq.s. For 20mg Injection (2ml ampoule): Each ml contains: Gentamicin Sulphate IP eq to Gentamicin base 10mg, Methylparaben IP 0.18% w/v (as preservative), Propylparaben IP 0.02% w/v (as preservative), Water for Injection IPq.s. INDICATIONS: Pneumonia; cholecystitis; peritonitis;septicaemia; acute pyelonephritis;prostatitis; skin infections; pelvic inflammatory disease; endocarditis;meningitis; listeriosis; tularaemia;brucellosis; plague; surgical prophylaxis;ocular bacterial infection DOSAGE AND ADMINISTRATION: Gentamicin injection is given intramuscularly every 8 hourly to provide a total dose of 3-5 mg /kg. In the prophylaxis and treatment of streptococcal and enterococcal endocarditis, a dose of 1 mg/kg every 8 hours with a penicillin or vancomycin has been suggested .A recommended dose for prophylaxis in high risk patients is 120 mg before induction of anesthesia with a penicillin or vancomycin or teicoplanin. For urinary tract infections if renal function is not impaired, 160 mg once a day may be administered. CONTRAINDICATIONS: In patients with a history of hypersensitivity to Gentamicin, other aminoglycoside or any constituents of the injection. In patients who have experienced serious toxic reactions (ototoxicity or nephrotoxicity) to Gentamicin or to other aminoglycoside therapy. WARNINGS AND PRECAUTIONS: Cross allergenicity among aminoglycosides has been known to occur; Neurotoxicity;cautious use in Premature and neonatal infants; Neuromuscular blockade and respiratory paralysis, Ototoxicity. PREGNANCY AND LACTATION: Pregnancy Category D. Gentamicin should not be administered to lactating women unless the benefit clearly justifies the potential risks ADVERSE REACTIONS: Neurotoxicity; Neuromuscular blockade and respiratory paralysis, ototoxicity, nausea, vomiting, increased salivation and stomatitis, decreased appetite, transient hepatomegaly and splenomegaly, myasthenia gravis-like syndrome. increased levels of serum transaminase. ISSUED ON: SOURCE: Prepared based on full prescribing information, version 1.0 – dated 31/12/2015 TM / * Trademark of the Abbott Group of Companies. For full prescribing information, please contact: Medical Sciences Division, Abbott Healthcare Pvt. Limited, Floor 17, Godrej BKC, Plot No. C – 68, BKC, Near MCA Club, Bandra (E), Mumbai – 400 051.

DISCLAIMER: Emergence of Antimicrobial Resistance (AMR) in pathogens has become a matter of great public health concern as it is leading to increased morbidity, mortality, and healthcare costs. AMR has been reported to develop due to improper and irrational use of antimicrobials. Antibiotics should be prescribed judiciously after appropriate diagnosis and understanding the local resistance patterns. (NCDC Guidelines for Infectious Diseases, 2016) [Kumar SG, et al. Antimicrobial resistance in India: A review. J Nat Sci Biol Med. 2013;4(2):286–91.]

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Reasons for Default among Patients Receiving Antitubercular Treatment in Eastern Uttar Pradesh

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ABSTRACT

Objective: To study the reasons for nonadherence to antituberculosis treatment (ATT) in Eastern Uttar Pradesh. **Methods:** This retrospective analysis was done among a cohort of 670 patients attending BRD Medical College, Gorakhpur, Uttar Pradesh during 2014. Defaulters were interviewed using semi-structured questionnaire to elicit reasons of treatment default. Statistical analysis was done by using Chi-square test. **Results:** Out of the total 670 patients enrolled in the study, 87 (16.35%) pulmonary, 7 (6.08%) extrapulmonary and 2 (8.69%) both pulmonary as well as extrapulmonary, defaulted ATT. Overall default rate was 14.32%. Major reasons for treatment interruption were early improvement (24.19%), high cost of treatment (16.12%) and ATT-induced side effects (11.29%). Maximum treatment interruption occurred between second and third month of ATT. More than one reason was often reported for discontinuation of treatment. **Conclusion:** Noncompliance was found to be mainly due to early improvement, high cost of treatment and side effects of medicine. So, information on disease and treatment should be intensified and appropriate to the level of education of population, in order to promote adherence to treatment and counter the spread of multidrug-resistant tuberculosis.

Keywords: Noncompliance, antituberculosis treatment

Tuberculosis (TB) is a major public health concern in the South-East Asia region, with the region accounting for 39% of the global TB burden in terms of incidence. India alone accounts for 26% of the global TB burden. India is the second-most populous country in the world and is home to a quarter of the global TB cases annually. Of the estimated global annual incidence of 8.6 million TB cases in the year 2012, 2.3 million cases were estimated to have occurred in India.

World Health Organization (WHO) has recommended Directly Observed Treatment, Short-course (DOTS) strategy for global TB control, which is accepted worldwide. Direct observation and regular home visit by treatment providers are provisions to increase treatment completion under DOTS. Based on DOTS strategy, India's Revised National Tuberculosis Control Programme (RNTCP) was launched in 1997. Though treatment completion rate reported by RNTCP is satisfactory, recently there is growing concern of emergence of drug-resistant strains of TB bacillus. Incomplete antituberculosis treatment (ATT) is the reason for emergence of multidrug-resistant (MDR) strains of TB bacillus that emerged in the early 1990s. Extensively drug-resistant (XDR) strains emerged in 2006 and totally drug-resistant strains emerged in 2011 in India.

Further poor adherence to treatment leads to emergence of MDR bacilli. So, ensuring compliance is of utmost importance to control TB and halt the MDR-TB epidemic at its beginning. There is continuing need to sustain and further intensify the action being undertaken to reduce default. The focus must remain on dealing with important reasons of default and timely retrieval of patients who interrupt treatment. The aim of this study was to determine the reasons for nonadherence to ATT in Eastern Uttar Pradesh.

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METHOD

The present study was conducted over a 6-month period from March to August 2014 and consists of an analysis of the data of pulmonary as well as extrapulmonary TB patients, indoor and outdoor, of BRD Medical College, Gorakhpur, Uttar Pradesh. After obtaining consent, patients were interviewed using a semi-structured questionnaire. Information recorded in the questionnaire included personal data, socio-demographic data, past and present history of ATT and reasons for discontinuation of ATT.

Definition – *Defaulter*: As per RNTCP guidelines, defaulter is defined as a patient who has not taken antitubercular drugs for 2 or more consecutive months, any time after registration.

Patients who gave a history of treatment interruption as defined above were enrolled for the study. All these patients were then interviewed in detail using a pre-tested semi-structured questionnaire. In addition to the personal and socio-demographic data, treatment history was recorded in detail.

Statistical analysis was performed by using the Chi-square test and a 'P' value of <0.05 was considered as significant.

RESULT

The study was conducted among patients of BRD Medical College, Gorakhpur, Uttar Pradesh, who were admitted and attended OPD in the Dept. of TB and Chest. A total 670 patients suffered from TB. Among the 670 TB patients, 96 (14.32%) were found to have history of ATT interruption and were included in study. Biosocial characteristics of the patients were studied and the effect of various factors on patients' compliance to treatment was observed.

In the present study, 78 (16.95%) males and 18 (8.5%) females defaulted. The highest number of defaulter were in the age group of 25-45 years [69 (18.15%)] while 15 (11.71%) defaulted in the age group of >45 years. In all, 12 (7.4%) defaulted in age group of below 25 years (Table 1).

On analyzing the religion, 76 (14.84%) Hindus and 16 (12.30%) Muslims defaulted, while among others (i.e., Christian, Sikh), 4 (14.28%) defaulted. Analysis of marital status revealed that 34 (12.97%) married patients had history of treatment interruption while among others (unmarried, widow, divorced), 62 (15.19%) patients defaulted.

Table 1. Factors Associated with Noncompliance to Treatment

Factors	Total no. of patients (n = 670)	Non-compliance (%) n = 96	P value
Age (years)			
<25	162	12 (7.40)	<0.05
25-45	380	69 (18.15)	
>45	128	15 (11.71)	
Sex			
Male	460	78 (16.95)	<0.05
Female	210	18 (8.5)	
Religion			
Hindu	512	76 (14.84)	NS
Muslim	130	16 (12.30)	
Others	28	4 (14.28)	
Marital status			
Married	262	34 (12.97)	NS
Others	408	62 (15.19)	
Education level			
Illiterate	260	59 (22.69)	<0.05
Literate	410	37 (9.0)	
Smoking			
Smokers	215	35 (16.27)	NS
Ex- or nonsmokers	455	61 (13.40)	
Occupation			
Employed	68	5 (7.35)	<0.01
Laborer	276	58 (21.01)	
House wives	180	15 (8.33)	
Unemployed	146	18 (12.32)	
Type of disease			
Pulmonary	532	87 (16.35)	<0.05
Extrapulmonary	115	7 (6.08)	
Both	23	2 (8.69)	

On analyzing the effect of education and occupation level, 59 (22.69%) illiterate and 37 (9.0%) literate patients had history of noncompliance to treatment, while 58 (21%) laborers, 18 (12.32%) unemployed, 15 (8.33%) house wives and 5 (7.3%) employed defaulted.

On analyzing the effect of smoking, 35 (16.27%) patients defaulted who were smokers while 61 (13.4%) patients defaulted, who were nonsmokers.

Among 670 patients, 87 (16.35%) pulmonary, 7 (6.08%) extrapulmonary and 2 (8.69%) both pulmonary as well as extrapulmonary patients defaulted. Eighty-one of the

Table 2. Reasons for Default (186)

Reasons	No. of patients who interrupted treatment (n = 186)	Percentage (%)
Early improvement	45	24.19
High cost of treatment	30	16.12
ATT-induced side effect	21	11.29
Alcoholism	20	10.75
No improvement or deterioration	16	8.6
Advised to stop treatment by physician	13	6.98
Unaware about long duration of treatment	12	6.45
Long distance travel to center	11	5.91
Lack of faith in treatment	8	4.30
Personal reasons	10	5.37
a. Family problem	6	3.22
b. Went to village	4	2.15
Total	**186**	

patients interviewed had no comorbidities and among the remaining 15 patients had history of comorbidities (e.g., diabetes mellitus, hypertension).

Among the 96 patients interviewed, 51 (53.12%) had defaulted treatment only once and 32 (33.3%) had interrupted treatment twice, while rest of patients had interrupted treatment more than two times (i.e., three or four). Thus, the 96 patients included in the study had interrupted treatment 157 times. Among 157 treatment interruption episodes, 102 (64.96%) occurred when the prescribing source of ATT was private practitioner, 50 (31.84%) took place while on treatment under DOTS therapy and remaining 5 (3.18%) interruptions took place while on non-DOTS treatment from a Government source.

Among the 96 patients interviewed, 38 (39.58%) stated only one reason for defaulting their treatment, 34 (35.4%) patients stated two reasons and 16 (16.66%) and 8 (8.33%) gave three and four reasons, respectively. Thus, 186 reasons for treatment interruption were obtained from 96 patients.

Maximum interruptions were found to occur between second and third month of ATT and 61 (64%) had defaulted treatment by the end of second month.

On analyzing the reasons of default among defaulters (Table 2), early improvements following medications were found to be the most common reason 45 (24.19%). Next important reasons were high cost of treatment and ATT-induced side effects (16.12% and 11.29%, respectively).

Alcoholism, no relief of symptoms and advised to stop by physician were other important reasons behind the default (10.75%, 8.6% and 6.98%, respectively). Some other reasons such as unaware about long duration of treatment, long distance travel to center, lack of faith and personal problem were also found to be important reasons for treatment interruption (6.45%, 5.91%, 4.30% and 5.37%, respectively).

DISCUSSION

Among the 670 TB patients, indoor and outdoor, during the study period, 96 (14.32%) had history of treatment interruption, of which 90.62% patients had pulmonary TB while 7.29% extrapulmonary and 2.08% had both pulmonary as well as extrapulmonary TB.

In the present study, out of 157 treatment interruptions, 102 (64.96%) interruptions occurred on private treatment, while 50 (31.84%) interruptions took place on DOTS and remaining 3.18% treatment interruptions occurred on non-DOTS government treatment. This emphasizes the need to provide DOTS to all as it is the only path to minimize treatment interruption.

In our study, default to treatment was found to be more in the 25-45 years age group of patients (18.15%), while good compliance to treatment was observed among less than 25 years (7.40% default). Similar results were

also observed in a study conducted by Chandrasekaran et al where the odds of default were higher in those aged >45 years. In another study, Kumar et al observed maximum default in 35-44 years age group (25.4%), followed by the patients aged above 45 years (18.1%). Further, comparatively more default in the 25-45 years of age group is mainly due to the subjects being economically productive members of the family, which led them to the skip treatment rather than to leave their earning of the day.

Another risk factor for default is sex. Males defaulted more (16.95%) as compared to female (8.5%). More default among males is supposed to be due to being on job frequently; while in contrast, DOTS centers are present in most of the localities, so females can visit the center regularly. Similar results were also found in a study by Jaggarajamma et al in which male and female defaulters were 24% and 8%, respectively.

Another risk factor for default is education. Illiterate defaulted more as compared to literate (22.69% vs. 9.0%). Similar results were also found in the study by Jaggarajmma et al.

Persons involved in various occupations, especially the laborer (21%), defaulted more as compared to housewives, unemployed (students, retired) and employed. Mittal et al observed that more people defaulted among businessman (30.6%), unemployed/ retired (25%) and laborer (18.2%) groups. While few others did not find any association between patient's occupation and response to treatment. The main reason behind the difference in compliance among persons with occupation seems to be loss of wages and lack of time.

In our study, 64% patients had interrupted treatment by the end of second month and other studies have also reported that maximum number of patients interrupted their treatment by the end of second or third month. Kaona et al reported up to 29.8% patients stopped taking their medication within the first 2 months of commencing treatment. Oliveira et al from Brazil found 43.3% of the defaulters in the first 2 months of treatment.

The present study identified early improvement following medication as the most common reason of default. So, the most common reason was a feeling of early improvement as stated by 45 patients (24.19%). Kaona et al also found that 29.8% of TB patients interrupted treatment once they start feeling better. In another survey by Tissera at Colombo Chest Clinic, relief from symptoms emerged as the most common reason for treatment interruption (13%).

The next most common reason for default was high cost of treatment cited by 30 (16.12%) patients in our study. This was exclusively reported by patients who took ATT from outside the government sources, i.e., purchased their medicine from the market. It is thus necessary that all TB patients should be registered under DOTS for treatment, so as to reduce the number of interruption occurring due to high cost of treatment.

Third common reason for default was ATT-induced side effects, in the present study, stated by 21 (11.29%) patients. Wares et al found the most common reason for stopping treatment being the adverse effects of ATT. A study from Bihar and West Bengal reported that improvement in symptoms (40% and 56%), intolerance to drugs (20% and 9%) and other illness causes in some patients. O'Boyle et al have also reported similar finding.

In the present study, 20 (10.75%) patients blamed alcoholism as the reason for their treatment interruption and 35 (16.27%) patients who smoked defaulted. Jakubowiak et al found alcohol use among the commonest reasons (30%) for treatment default. Sophia et al stated in their study that alcoholism can also predict poor treatment adherence.

Sixteen (8.6%) patients stopped treatment due to no improvement and 12 (6.45%) patients defaulted because they were unaware about long duration of treatment. Mittal et al have found similar finding.

Eleven (5.91%) patients had defaulted treatment due to long distance of travel to their DOTS center and 5.37% patients interrupted treatment due to personal reasons. In a study by Chatterjee et al, an important reason for default was distance from the treatment center. Mishra et al reported that the risk of nonadherence to treatment was significantly associated with cost of travel to the TB treatment facility.

CONCLUSION

There were many reasons reported for discontinuation of treatment and maximum interruption was found in the end of second and third month. The default could be a result of inadequate pre-treatment health education and counseling and poor defaulter tracing mechanism resulting from overworked healthcare personnel, feeling better after medication for a while and socioeconomic factors, including inadequate food and opportunity costs. Multiple factors influence default.

Keeping in mind all the important reasons of default, initial counseling by the health personnel explaining the

treatment plan before starting of the treatment, periodic motivation of patient, increased number of DOTS centers and prompt action to tackle any problem will enhance compliance. Adequate health education and information about TB has been demonstrated to be most effective when given as one to one counseling. Such measures are likely to increase the therapeutic success rate, impacting on global disease burden attributable to TB and thus MDR-TB can be decreased.

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■■■■

Wear a Mask Even at Home, Advises Center

With COVID-19 cases spreading rapidly, the Center has advised people to wear masks even inside homes, more so when using a common space and added that it would be good not to invite visitors. Dr VK Paul, a NITI Aayog member and head of the government's group on vaccinations, said that people should start wearing masks inside their homes also, particularly when all the members are sitting together. Dr Paul added that mask protocol should also be followed when there is a person isolated due to COVID-19 at home in order to limit the risk of infection. The government also stressed that improper use of masks and lack of physical distancing can heighten the risk of transmission by 90%. The risk is reduced to 30% if the unaffected person is wearing a mask… (*ET Healthworld – TNN*)

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  Exhibits aphrodisiac, antidepressant, and anxiolytic actions

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2 capsules once daily, one hour before sexual intercourse. It is necessary to continue the treatment for a minimum of 6 weeks without interruption for satisfactory correction of erectile dysfunction.

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Role of Tentex Royal in Erectile Dysfunction of Various Etiologies: A Randomized Double-blind Placebo-controlled Clinical Study

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ABSTRACT

Introduction: Erectile dysfunction (ED) is the failure to achieve or maintain the penile erection for sufficient satisfactory sexual performance. It is the most common male sexual disorder, with 44% of men aged between 60 and 69 years old and up to 70% of men aged ≥70 years old being affected. **Objectives:** To evaluate the safety and efficacy of Tentex Royal for ED caused by various etiologies. **Methods:** The study included 30 patients with a history of ED. The patients were randomized into two groups: 15 patients in Tentex Royal group and 15 patients in placebo group. Each patient was given Tentex Royal or similar looking placebo, 2 capsules once daily at night for 6 weeks. **Results:** The IIEF-5 (International Index of Erectile Function) score and EHS (Erection Hardness Score) Likert scale were used to evaluate ED. In Tentex Royal group, at study entry, 66.67% patients had severe ED and 33.33% patients had moderate ED. After treatment with Tentex Royal, 13.33% patients got completely relieved of ED and 40% patients showed improvements, who shifted from severe or moderate ED to mild ED. Overall 53.33% patients showed improvements in ED as compared to placebo. In the placebo group, only 20% patients showed improvements in ED. Adverse event was neither observed nor reported during the study period in both groups. The IIEF-5 score and EHS Likert scale also showed significant results, in Tentex Royal group. About 53% patients showed improvement in hardness as compared to placebo, while only 20% patients showed improvement in hardness in the placebo group. Hence, Tentex Royal was considered effective and safe for the management of ED. **Conclusion:** The results of this trial clearly demonstrate that Tentex Royal capsule is safe and effective for ED in comparison with placebo.

Keywords: Tentex Royal, erectile dysfunction, IIEF-5, EHS

Erectile dysfunction (ED) is the inability to attain or maintain penile erection, sufficient for satisfactory sexual performance and is the most common male sexual disorder, with 44% of men aged between 60 and 69 years of age and up to 70% of men aged ≥70 years old being affected.[1]

Approximately 150 million men worldwide suffer from some degree of ED.[2] The combined prevalence of minimal, moderate and complete impotence was 52%.[3] In one study, amongst men aged 40 to 70 years, the prevalence of "mild ED" was found to be 27%, "moderate ED" was found to be 25% and "severe ED" was found to be 10%.[4] The prevalence of ED is age-dependent and increases with advancing age (among men aged 40 years, it is 5%, while among those aged 70 years the same is 15%).[3]

In the past, ED was thought to be a purely psychogenic disorder in most of the cases; however, now the current evidence suggests that more than 80% of cases have an organic etiology. Erectile dysfunction is a multifactorial disease and is influenced by increasing age, hypertension, diabetes, cardiovascular disorder, dyslipidemia and lifestyle factors (cigarette smoking and excess alcohol use).[5-9]

Erectile dysfunction occurs at an earlier age in men with diabetes than in men in the general population,[10] The prevalence of ED among diabetic men varies

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between 35% and 90%.[11] It has been estimated that >50% of diabetic men develop ED within 10 years of being diagnosed with diabetes and the incidence of ED increases from 9% in diabetic men in the age group 20 to 29 years to 95% in men >70 years of age.[12]

The risk for ED increases progressively with advancing age. The causes of ED are divided into 3 broad categories, viz. "Psychogenic ED", "Organic ED" and "Mixed ED". Psychogenic factors are involved alone, or combined with organic causes, in a considerable number of cases. Organic ED results from neurologic, hormonal and vascular pathologies.[13-15]

Erectile dysfunction is also commonly associated with several other diseases frequently occurring in aging men, like benign prostatic hyperplasia, hypertension, ischemic heart disease, peripheral vascular disease, atherosclerosis, dyslipidemia and diabetes mellitus. In men with diminished libido, an endocrine mechanism (hypogonadism, hyperprolactinemia or dehydroepiandrosterone [DHEA] deficiency) may be at work. Neurologic origins of ED include peripheral autonomic (cavernous nerve) or somatic (dorsal and pudendal nerve) neuropathy associated with diabetes, alcoholism, vitamin deficiencies, infectious diseases and spinal cord injury.[16]

The incidence of ED increases with diabetes, hypertension, hypercholesterolemia, cardiovascular disease and renal failure, and all these conditions are associated with endothelial dysfunction. Increased inactivation of nitric oxide (NO) by superoxide leads to and impairment of penile NO transmission and smooth muscle relaxation. The propagation of endothelial dysfunction by reactive oxygen species may cause chronic impairment of penile vascular function, a process comparable to early atherogenesis. In one study, erectile function was evaluated by measuring the increase in intracavernous pressure following supplementation with antioxidants and the penile tissue was evaluated for neuronal NO synthase, smooth muscle alpha-actin, nitrotyrosine and endothelial cell integrity. The study showed that adequate concentrations of the oxygen free radical scavenger vitamin E, enhanced levels of circulating NO and improved the erectile function.[17,18] "Tentex Royal", a polyherbal formulation, which was found to be beneficial in the management of the ED in some preclinical and clinical studies, was used in this study. Principal ingredients of this formulation include extracts of *Tribulus terrestris* and powders of *Asteracantha longifolia, Prunus amygdalus, Blepharis edulis, Curculigo orchioides, Crocus sativus*, processed in *Curculigo orchioides* and *Piper betle.* Further, one more study was planned in Indonesian population with an objective to evaluate the efficacy and safety of "Tentex Royal" this formulation in patients with ED due to various etiologies.

AIM OF THE STUDY

To evaluate the safety and efficacy of Tentex Royal for ED caused by various etiologies.

MATERIALS AND METHODS

This randomized placebo-controlled study was approved by the Research Ethics Committee, Udayana University, Sanglah Hospital Denpasar, Bali, Indonesia (IEC approval no. 1949/UN14.2.2.VII.14/LP/2018) dated on September 03, 2018.

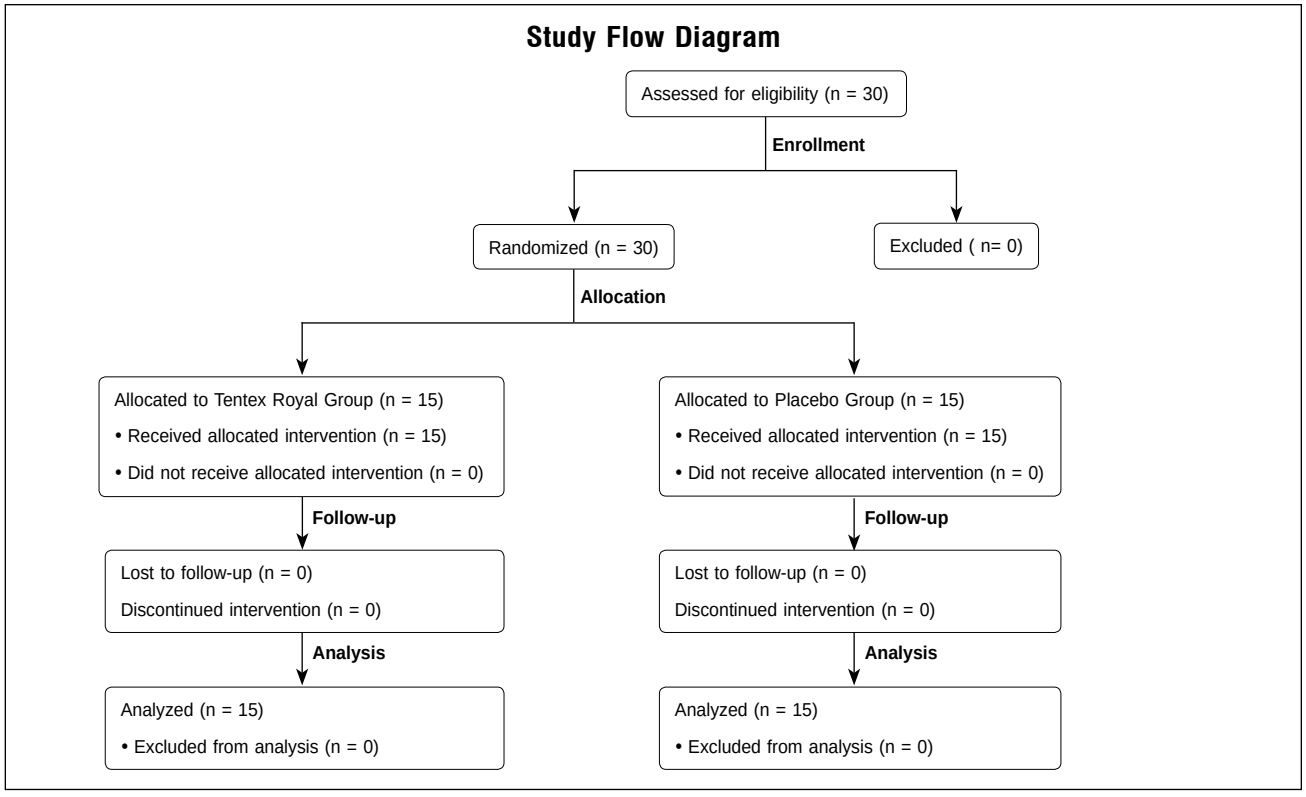
The study was carried out in accordance with the principles of Declaration of Helsinki from October 2018 to March 2019. Native male patients in the age group of 40 to 70 years, who were suffering from ED caused by various etiologies and who visited the site for treatment for a period of at least past 3 months, were recruited in this study. Patients were included in the study only after obtaining written informed consent from them.

Subject Selection Criteria

A total of 30 male patients, as per the eligibility criteria of the study, aged between 40 and 70 years with ED, who agreed to take treatment for ED, and those who were willing to give informed consent, agreed not to use any other medicine for ED, were included in study.

Study Procedure

Patients were recruited as per the diagnosis of ED by International Index of Erectile Function (IIEF-5) questionnaires and as per the subject selection criteria. Potential patients who agreed to participate in the study signed the informed consent document before any study related screening procedure. Eligible patients as per inclusion/exclusion criteria were then divided randomly into two groups - control group and treatment group. Patients received either Tentex Royal or similar looking placebo at a dose of 2 capsules once daily at night for 6 weeks. Patients visited the site at every 2 weeks of treatment for the period of 6 weeks for assessment of IIEF-5, Erection Hardness Score (EHS) and physical examination.



Statistical Analysis

Descriptive statistics was used to summarize the number of subjects for the category of IIEF-5 scale and for Erection score. Significance was fixed at <0.05. Statistical analysis was carried out using GraphPad Prism, Version 6.07 for windows, GraphPad Software, San Diego, California, USA.

All adverse events, either reported or observed by patients, were recorded with information about severity, date of onset, duration and action taken regarding the study medication. The causal relationship between the investigational product and the adverse event would be established using the criteria of Certain, Probable, Possible, Unlikely and Conditional/Unclassified, Unassessable/Unclassifiable (WHO-UMC Causality Categories).

Patients could voluntarily withdraw from the study for any reasons. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Noncompliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for noncompliance were noted.

RESULTS

A total of 30 patients were enrolled in this study. The efficacy analysis data set consisted of 30 patients: Tentex Royal group (n = 15) and Placebo group (n = 15) with the confirmed diagnosis of ED. All patients completed the study in both the groups.

In Tentex Royal group, at study entry 66.67% of patients had severe ED and 33.33% of patients had moderate ED as per IIEF-5 scoring system. However, after treatment in the study, 13.33% of patients got completely relieved of ED and 40% of patients shifted from severe and moderate ED to mild ED. Overall 53.33% of patients showed improvements in ED as compared to placebo, where only 20% patients showed improvements in ED. Effect of Tentex Royal capsules and placebo on IIEF-5 is shown in Table 1 and Figure 1.

The detailed analysis of IIEF-score is summarized in Table 2. In Tentex Royal group, pre-treatment score was 7.67 ± 2.82 as compared to post-treatment value of 13.73 ± 7.41, which showed statistical significance with p value <0.0078. In placebo group, there was no significance observed after the treatment. However, in the between group comparison, outcome was not statistically significant.

EHS Score (Table 3) also showed significant result, similar to IIEF-5. In Tentex Royal group, about 53% patients showed improvement in hardness as compared to placebo, where only 20% patients showed improvement.

Table 1. Summary of IIEF-5: International Index of Erectile Function-5 (n, %)

Scale	Tentex Royal (n = 15)		Placebo (n = 15)	
	Pre-test	Post-test	Pre-test	Post-test
21-25 (No ED)	0 (0.0%)	2 (13.33%)	0 (0.0%)	0 (0.0%)
16-20 (Mild ED)	0 (0.0%)	6 (40%)	0 (0.0%)	3 (20%)
11-15 (Moderate ED)	5 (33.33%)	1 (6.67%)	3 (20%)	4 (26.67%)
5-10 (Severe ED)	10 (66.67%)	6 (40%)	12 (80%)	8 (53.33%)

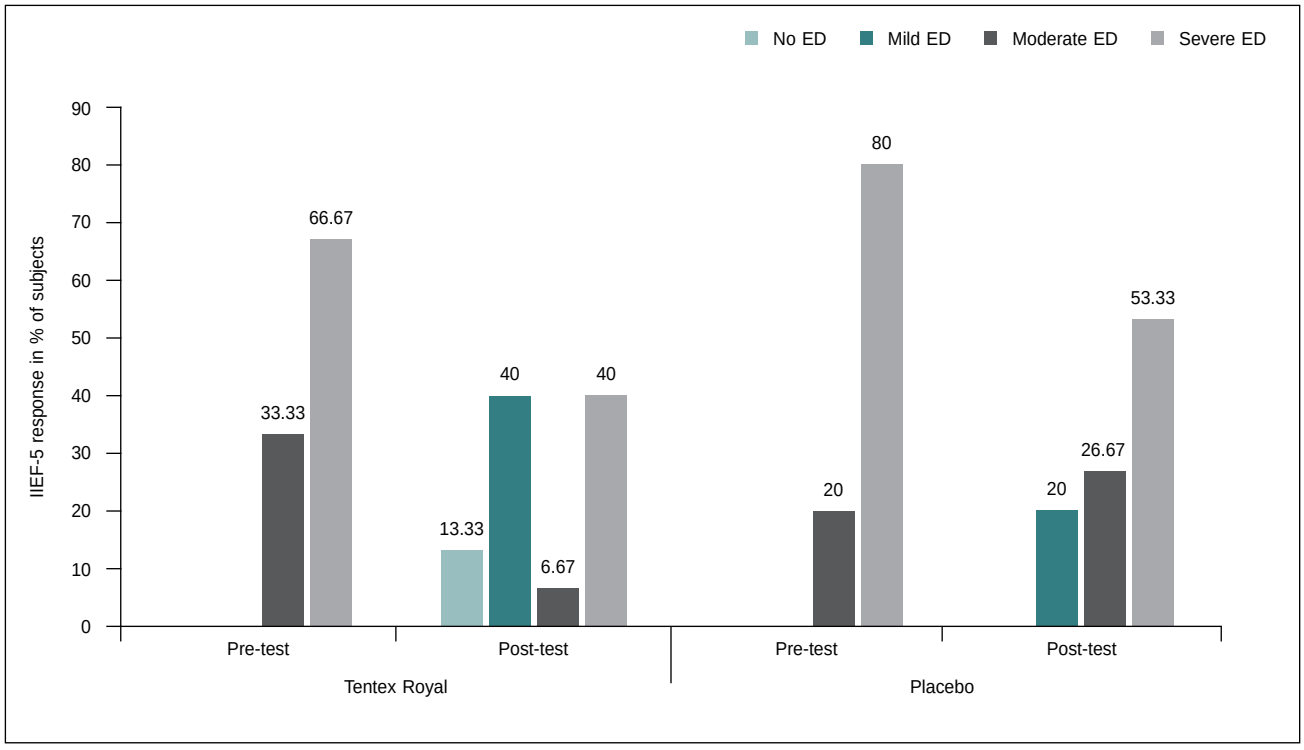


Figure 1. Graphical representation for IIEF-5.

Table 2. International Index of Erectile Function-5 (IIEF-5) Score

IIEF-5	Tentex Royal (n = 15)		Placebo (n = 15)	
	Pre-test	Post-test	Pre-test	Post-test
Mean (SD)	7.67 (2.82)	13.73 (7.41)	6.4 (2.44)	9.73 (6.03)
P value within group		P < 0.0078		NS
P value between group		NS (0.0716)		NS
Median	6	20	5	5
Range (Min to Max)	5 to 12	5 to 21	5 to 11	5 to 20
Lower 95% CI	6.105	9.629	5.047	6.394
Upper 95% CI	9.228	17.84	7.753	13.07

Statistical test: Wilcoxon matched pairs signed rank test, Mann-Whitney test.
Significance was fixed at < 0.05, NS: Not significant.

Table 3. Effect of Intervention on Erection Hardness Score (EHS)

Frequency Table of EH	Tentex Royal (n = 15)		Placebo (n = 15)	
	Pre-test	Post-test	Pre-test	Post-test
Scale	N (%)	N (%)	N (%)	N (%)
1	10 (66.67)	6 (40)	12 (80)	8 (53.33)
2	5 (33.33)	1 (6.67)	3 (20)	4 (26.67)
3	0 (0)	6 (40)	0 (0)	3 (20)
4	0 (0)	2 (13.33)	0 (0)	0 (0)

Likert scale: 0 – Penis does not enlarge, 1 – Penis is larger, but not hard, 2 – Penis is hard, but not hard enough for penetration, 3 – Penis is hard enough for penetration, but not completely hard, 4 – Penis is completely hard and fully rigid.

Safety Evaluation

There were no adverse events or serious adverse events, neither reported nor observed, during the study period, which shows that Tentex Royal was well-tolerated and safe to be used.

DISCUSSION

Erectile dysfunction is a potentially devastating ailment that is affecting men. The Massachusetts Male Aging Study revealed that age is the single most important variable associated with erectile difficulty.[3] There has been an increased understanding of the physiology of erection and the pathophysiology of ED over the past few years. We are beginning to understand the events leading to tumescence and detumescence at the cellular and molecular level. Combined with the advent of sophisticated diagnostic modalities, more and more of these patients are diagnosed with treatable organic causes of ED. Currently, there are a multitude of treatment options available, ranging from oral to injectable medications and various surgical treatments. A thorough understanding of penile physiology as well as current diagnostic and treatment modalities is necessary for proper evaluation and treatment of patients with ED.[19]

There are various treatment options available for ED such as oral agents (sildenafil, tadalafil, vardenafil, trazodone, yohimbine, apomorphine, phentolamine, L-arginine, testosterone), vasoactive intracavernosal injections (phentolamine mesylate, papavarine, vasoactive intestinal peptide, forskolin, alprostadil), intraurethral therapy (alprostadil), transdermal therapy (testosterone, nitroglycerine, minoxidol), vacuum constriction devices, penile prosthesis and reconstructive surgeries.[20]

Even though phosphodiesterase 5 (PDE-5) inhibitors are most commonly used medications for ED, they are known to cause common adverse effects like headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision.[21]

This current study observed significant improvement in the mean score for "Ability to achieve erections", "Ability to maintain erections", "Frequency of orgasm" and "Satisfaction with sexual relationship". Also, there were no clinically significant changes in the hematological and biochemical parameters and there were no clinically significant adverse reactions, which is reflected in the excellent patient compliance to the treatment. These beneficial effects of Tentex Royal might have been possible due to the synergistic action of all the ingredients present in Tentex Royal capsule, which are well researched and documented by various researchers.

Tentex Royal has constituents which have a known role in the management of ED. Tentex Royal contains an extract of *T. terrestris* and powders of *A. longifolia*, *P. amygdalus*, *B. edulis* and *C. sativus*. These herbs mentioned above have been conventionally used in the management of ED for centuries. *T. terrestris* has been clinically proven to improve sexual desire and enhance erection.[22] The pharmacological properties of *T. terrestris* extracts have been studied on the rabbit corpus cavernosum muscles. The extract showed increase in relaxation of cavernosum smooth muscles in a dose-dependent manner.[23] *P. amygdalus* extract is associated with a significant increase in the sperm content and the motility in the epididymis and vas deferens. *P. amygdalus* has been used as an aphrodisiac in Arab Medicine.[24] *C. sativus*, or saffron, is used in medicine as an aphrodisiac and antioxidant agent.[25]

A preclinical study was conducted in rat experimental models to assess the efficacy of Tentex Royal in

enhancing the male sexual function. A significant improvement was observed in all the parameters of sexual indices and Tentex Royal the formulation was found to enhance erectile capacity.[26]

Following are the various other studies conducted on Tentex Royal this formulation in ED. The brief details of each study on Tentex Royal are summarized here. Study conducted by Garg et al: The study included 45 patients with a history of ED. Each patient received 2 capsules of Tentex Royal daily at night for 6 weeks. All patients were followed-up to assess the effect of the drug and to rule out any side effects after the second week and then every week for further 4 weeks. Among the 45 patients, 40 completed the treatment. Thirty-two patients (80%) exhibited significant clinical improvement, 18 patients (45%) were cured in 3 weeks and 14 patients (35%) showed improvement in 6 weeks. Thus, study concluded that Tentex Royal is effective and well-tolerated in the treatment of patients with ED.[27]

A clinical study was conducted in 50 diabetes patients with ED. Tentex Royal was advised at a dose of 2 capsules once every evening for 6 weeks. All the patients were evaluated once every week. The study revealed that Tentex Royal yielded considerable improvement in penile erection in diabetics with a history of ED. None of the patients reported any noticeable adverse reactions during the study.[28]

A study conducted to evaluate efficacy and safety of Tentex Royal in the management of ED in 30 patients: This study observed significant improvement in the mean score for "Ability to achieve erections" from the 3rd week onward, and a highly significant improvement in the mean scores for "Ability to maintain erections", "Frequency of orgasm" and "Satisfaction with sexual relationship" from the 4th week onward, as compared to the baseline mean score. These effects might be attributed to the synergistic actions of the ingredients of Tentex Royal and it was concluded that Tentex Royal is clinically effective and well-tolerated in the management of ED.[29]

A clinical study assessed the efficacy, safety and tolerability of Tentex Royal capsules administered once daily in subjects with ED. Thirty-four men with a mean age of 48.91 ± 10.47 years completed the study. IIEF score increased significantly after Tentex Royal treatment. The study concluded that Tentex Royal is clinically effective and safe in the management of ED.[30]

All these effective actions are attributed to synergistic action of polyherbal ingredients in Tentex Royal. The principal active ingredients of *T. terrestris* are saponins (terrestrinins A and B) and galactopyranosides.[31] The active ingredients of *P. amygdalus* are polyphenols, flavonoids, anthocyanins, chlorogenic acid and quercetins.[32]

The principal ingredient of *C. sativus* is a carotenoid (crocetin) and is characterized by a diterpenic and symmetrical structure with seven double bonds and four methyl groups. The active ingredients of *C. orchioides* are triterpene glycosides (Curculigo saponins G, H, J and I).[33] Dehydroepiandrosterone has been demonstrated to have an antiatherosclerosis effect in animal models.[34] Protodioscin, a phytochemical derived from *T. terrestris,* is converted to DHEA,[22] and it has been observed that DHEA improves flow-mediated dilation of the artery (a function dependent on endothelium-derived NO). *T. terrestris* enhances the relaxant effect on corpus cavernosum due to an increase in the release of NO from the endothelium and nerve endings.[23] *C. orchioides* also has androgen-like action.[35] *C. sativus*[36] is a potent antioxidant agent and reduces the lipid peroxidation with a concomitant increase in enzymatic activity of superoxide dismutase, catalase and glutathione peroxidase.

The efficacy could therefore be due to the synergistic actions of the potent herbs in the formulation.

CONCLUSION

This was a randomized, two-arm comparative clinical study to evaluate the efficacy and safety of Tentex Royal capsule in ED. A total of 30 patients (15 patients in Tentex Royal and 15 patients in placebo group) participated in the study.

This study demonstrates the clinical efficacy of Tentex Royal capsules as compared to placebo treatment. The results of this trial clearly demonstrate that Tentex Royal capsule is effective for ED as compared to placebo. No serious adverse events were observed or reported during the study. In Tentex Royal group, 53% patients showed improvement compared to only 20% subjects in placebo group in terms of the IIEF-5 score and EHS Likert scale response. Results of the study showed that Tentex Royal is effective, safe and well-tolerated in the treatment of ED due to varied etiology.

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Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

HEART CARE FOUNDATION OF INDIA
A Not-For-Profit Organisation

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

E-219, Greater Kailash, Part I, New Delhi - 110048 E-mail: heartcarefoundationfund@gmail.com Helpline Number: +91 - 9958771177

"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

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Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

Padma Shri, Dr BC Roy National & DST National Science Communication Awardee

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This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

http://heartcarefoundationfund.heartcarefoundation.org

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A Cross-sectional Study on Prescribing Pattern for Children at Primary Healthcare Clinics

ARCHANA JORIGE*, LOHITHA B, LAVANYA SL

ABSTRACT

Background: Rational prescribing for children is very essential as there is increased risk from the use of medicines in them due to multiple reasons ranging from altered pharmacokinetics to long-term side effects. Drug-related needs of children must be assessed on individual basis to meet appropriate healthcare outcomes. **Aim:** This cross-sectional descriptive study aims at assessing drug use pattern and rationality in prescribing pattern as per World Health Organization (WHO) core prescribing indicators. **Material and methods:** A cross-sectional and prospective study was carried out in private primary healthcare clinics of Hyderabad, Telangana State. A total number of 300 prescriptions for children were reviewed. Patients' demographic characteristics, diagnosis and drugs prescribed were recorded in a prestructured and validated data collection form. **Results:** Average number of drugs per prescription were 1.92. Fever and upper respiratory tract infections were found to be common complaints in this age group. Paracetamol was the most commonly prescribed medication and among prescribed antibiotics, fluoroquinolones occupied the major part. About 67.3% of drugs were from the WHO Model List of Essential Medicines for Children. The percentage of drugs prescribed with generic names was very less. **Conclusion:** In this study, it was found that the prescription pattern in the selected primary healthcare centers in Hyderabad was in compliance with the WHO prescribing indicators, except the generic prescribing practice.

Keywords: Pediatrics, prescribing indicators, antibiotics, demographic characters

The availability and affordability of good quality drugs and their rational use are needed for effective healthcare. Rational prescribing is an essential component of healthcare system. Inappropriate prescribing negatively impacts the health of an individual and the economy of the society. Especially in children, irrational prescribing may increase the risk of developing health complications in the later stages of their life. It was reported that the use of antibacterial at young age can develop respiratory problems, allergic manifestations and may increase the risk of obesity. Thus, medicine safety issues in children, especially rational prescribing, is an essential component of healthcare system.

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For the rational prescribing of medicines in children, the first model list of essential drugs for children (less than 12 years) was released in October 2007. It is aimed to serve as a guideline for rational prescribing in this age group. Now the 7th edition of list was released in 2019 by WHO.

MATERIAL AND METHODS

A descriptive cross-sectional study was carried out in the primary healthcare pediatric clinics for evaluation of drug prescribing patterns starting from 20th January 2019 to 23rd March 2019. The study protocol was approved by RBVRR Women's College of Pharmacy Institutional Research Board (IRB). Only prescriptions with legible handwriting, demonstrating all the essential components of prescriptions were included. The data was collected from 5 private practitioners from chosen areas of Hyderabad. Five practitioners were randomly chosen each month from a pool of 10 practitioners enrolled for the study. Prescriptions were selected by random sampling method.

The study population included was under 13 years of age. Patients' demographic characteristics (age, gender), chief complaints and medicines prescribed were recorded. Class of medicines prescribed, dose,

route of drug administration, frequency and duration of treatment was recorded in data collection form. WHO specifies drug use indicators for adoption in drug utilization studies.

The following basic drug use indicators (core indicators) were used in the study to describe the prescribing pattern: (a) Average number of drugs per encounter; (b) Percentage of drugs prescribed by a generic name; (c) Percentage of encounters with an antibiotic prescribed; (d) Percentage of encounters with an injection prescribed and (e) Percentage of drugs prescribed from the essential drug list. Based on this collected data, the WHO prescribing indicators were assessed.

Data collection was carried and supervised on a daily basis by the investigators involved in the study. Completeness of data was checked every day during the data collection period. Data was analyzed descriptively and summarized using tables and charts.

RESULTS

Total 300 prescriptions were analyzed; 162 male and 138 female patients visited the clinic during assessment period. Among 300 patients, 35% were below 4 years, 56% were 4-10 years of age and 9% were above 10 years. The major complaint was fever with or without upper respiratory tract infections. Thirty-two percent of prescriptions were found to be with one drug and 44% of prescriptions had two drugs. Only 22% of prescriptions had three drugs and 2% had more than three drugs (Table 1).

Average number of drugs prescribed was 1.92. Nonsteroidal anti-inflammatory drugs (NSAIDs) occupied 30% of the total medications prescribed. Twenty-four percent of the medications were mucolytics and antitussives (Fig. 1). Most frequently prescribed drug was found to be paracetamol followed by mucolytic agents. Together they contributed to more than 50% of the prescribed drugs. Only 10% patients received antibiotics and the overall percentage of antibiotics prescribed was also 10%. The most frequently prescribed antibiotics were fluoroquinolones followed by macrolides (Fig. 2).

Table 1. Summary of Drugs per Prescription

No. of drugs per prescription	Total prescriptions
One	96
Two	132
Three	66
More than three	6

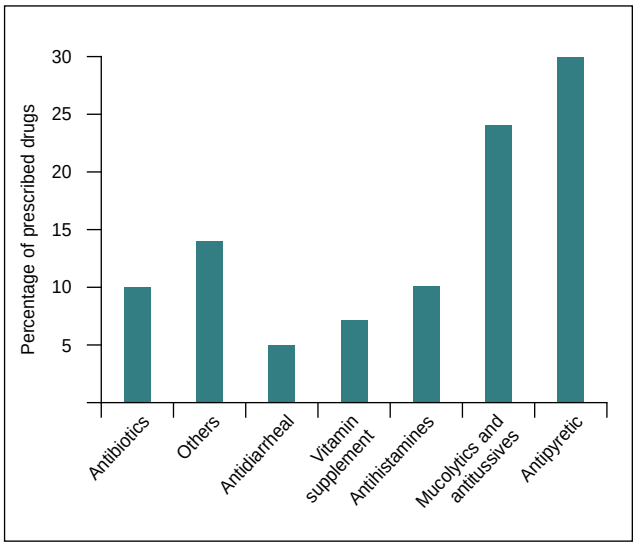

Figure 1. Percentage of prescribed drugs from various therapeutic classes.

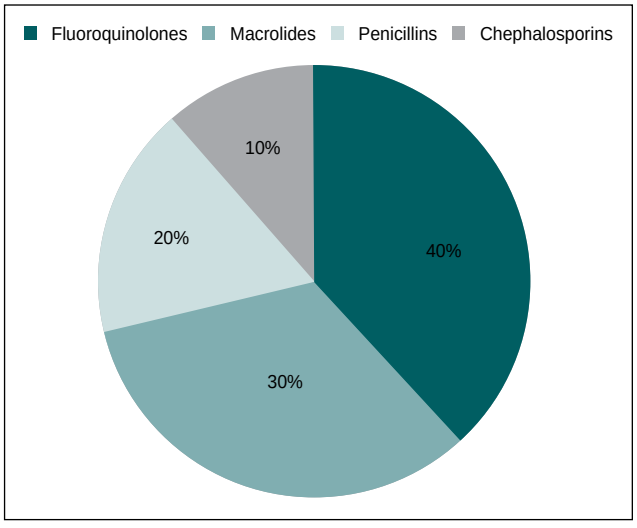

Figure 2. Relative percentage of prescribed antibiotics.

Table 2. Analysis of Prescriptions According to the WHO Core Prescribing Indicators

WHO prescribing indicator	Reported (%)	WHO Standard (%)
Average number of drugs per encounter	1.92	2
Percentage encounters with one or more antibiotics	10	20-26.8
Percentage of drugs prescribed by generic name	13	100
Percentage encounters with an injection prescribed	1.67	13.4-24.1
Percentage of drugs from essential drug formulary list	67.3	100

The percentage of drugs prescribed from the essential drugs list was 67.3%.

Out of 300 prescriptions, only 5 (1.67%) patients had been prescribed with injections. Percentage of drugs prescribed by a generic name was only 13% (Table 2).

DISCUSSION

There are only few published studies in India on prescribing practices for children to conclude about this practice. Especially, there is a need to study prescribing practices in rural areas of India. However, findings of our study highlighted few areas of prescribing that should be intervened appropriately.

Antipyretics, cough and cold preparations and vitamins were the commonest categories of drugs prescribed, as reported in some similar studies. Fever and respiratory disorders are very common outpatient complaints in this age group. The average number of drugs prescribed is within the limits of WHO indicators. The total number of drugs from essential list in this study was better compared to the studies in other cities.

Percentage encounter with injection was only in 1.67% patients, indicating a rational practice as previously reported. Generics prescription was very poor which was in line with other reports, which needs to be improved.

CONCLUSION

Hence, the present study concludes that the prescribing pattern in children in selected areas of Hyderabad city was found to be rational in most of the aspects of WHO guidelines. We also found some areas of concern regarding prescribing practices. Low usage of generic drugs in prescription writing was the main drawback. So, there is an immediate need of encouraging physicians towards generic prescriptions. The number of drugs prescribed from model EDL can also be improved by continuing education on rational drug use and development of easy to use treatment guidelines by the physicians.

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We are thankful to Principal and Management of RBVRR Women's College of Pharmacy for supporting us to carry out this research.

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Effectiveness of Counseling in the Management of Infertile Patients Undergoing Treatment with Assisted Reproductive Technologies

SUNITA CHANDRA*, SUHANI CHANDRA†

ABSTRACT

Background: The objective of this study was to appraise counseling intervention for infertile patients. **Methods:** One hundred sixty-three couples enrolled in the Rajendra Nagar Hospital & IVF Centre, Lucknow, Uttar Pradesh, were asked to participate in this study. Seventy-six couples agreed and were randomized according to a computer-generated random-numbers table into either a routine-care control group or an intervention group. The intervention consisted of three sessions with a counselor: one before, one during and one after the first cycle. **Results:** Significant improvement in the pregnancy rate was observed in the intervention group. **Conclusions:** The results of this study suggest that counseling increases infertile women's chance of becoming pregnant.

Keywords: Stress, distress, effectiveness, counseling, IVF, ART, infertility, pregnancy rates

Two hundred fourteen million women of reproductive age in developing countries who want to avoid pregnancy are not using a modern contraceptive method, still 10-14% of couples suffer from infertility. Infertility is akin to crisis situation, and to any newcomer, the field of assisted reproductive technology (ART) can be confusing and alarming. It could invoke several emotional, spiritual, moral, cultural and ethical issues for the patient. It is possible that the emotional impact of infertility is disregarded and the issue is reduced merely to a biological or medical one. For years altogether, patients have asked for psychosocial support through consumer advocacy organizations, and the same also been suggested by professionals and has been legislated for. Irrespective of a consensus for the need for infertility counseling, patients have largely had to depend on their spouse and family in times of distress, rather than on more formal support resources. There are varied factors that prevent patients from initiating counseling, with the less distressed patients using their existing resources, while the more distressed ones failing to initiate contact with the counseling service possibly because of not knowing how to do so and also due to cost implications.

Evidence estimates an average rate of 20% for uptake of counseling within the field of infertility. A higher uptake has been noted among participants with higher levels of education, and among those from the middle and upper classes as compared to those from lower social classes. When psychosocial infertility counseling is included in fertility treatment, and its goals and course are explained prior to initiation, acceptance rates can be as high as 80%.

Table 1 summarizes a formula to monitor infertility prevalence in women.

Table 1. Monitoring Infertility Prevalence in Women

Numerator: Number of women of reproductive age (15-49 years) at risk of becoming pregnant (not pregnant, sexually active, not using contraception and not lactating) who report trying unsuccessfully for a pregnancy for 2 years or more x 100
Denominator: The number of women of reproductive age (15-49 years) at risk of becoming pregnant (not pregnant, sexually active, not using contraception and not lactating) who report trying for a pregnancy for 2 years or more

Source: World Health Organization. Sexual and reproductive health. Available at: https://www.who.int/reproductivehealth/topics/infertility/burden/en/

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With the introduction of ART, such as *in vitro* fertilization (IVF), the need for counselors in fertility clinics was kindled. Counselors possessed the expertise to conduct pre-treatment psychological assessments that were deemed necessary while selecting the most suitable patients to undergo IVF. At the outset, the role of the counselors focused on pre-treatment screening and social workers with experience in pre-adoption assessment and welfare of child issues took care of the same.

The effect of psychological symptoms on fertility continues to be dubious. It is widely recognized that infertility leads to psychological distress, whether distress contributes to infertility is still debatable. Data suggest that psychological issues adversely affect fertility and a decline in such issues could increase pregnancy rate. Studies have reported lower pregnancy rate with elevated anxiety and depression levels. Standard psychological interventions such as counseling could go a long way in helping infertile couples. The need for psychosocial counseling by a skilled professional in order to ensure comprehensive care in ART was first recognized in the 1980s. Latifnejad Roudsari and Allan suggested in their study that infertility is an issue with many sides to it. Therefore, professionals working with infertile couples need to employ a holistic approach such as counseling that covers all psychological, social and cultural needs of individuals.

METHODS

Inclusion Criteria

Study participants had to be infertile women and men or infertile women only. They must be undergoing treatment with ART such as IVF, intracytoplasmic sperm injection (ICSI), embryo transfer (ET) and intrauterine insemination (IUI).

Interventions consisted of counseling as a psychological face-to-face intervention: (i) designed to influence psychological functioning and (ii) incorporating psychological strategies through interaction. The counseling could be provided using different methods (individual, couple or group) in a variety of settings.

Between February 2016 and January 2018, a total of 163 couples enrolled in the Rajendra Nagar Hospital & IVF Centre, Lucknow, Uttar Pradesh, were asked to participate in this study. Seventy-six agreed and were randomized according to a computer-generated random-numbers table into either a routine-care control group or an intervention group. Reasons for nonparticipation are depicted in Table 2.

Study Design

Two groups were prepared by a computer-generated random-numbers table. Thirty-six couples were randomized in a routine-care control group, 37 couples into an intervention group, 3 couples did not turn up. During the first week visit, the record chart was completed daily by the women (baseline) and again daily during their first IVF cycle: depending on the ovarian stimulation protocol used, women started monitoring on either the first day of down-regulation (gonadotropin-releasing hormone [GnRH] agonist long protocol co-treatment) or the first day of ovarian stimulation (mild ovarian stimulation using GnRH antagonist co-treatment). Monitoring ended 2 weeks after the day of the pregnancy test and after the third counseling session. On that same day, all participants completed the stress parameter sheet for the second time. Since previous studies have shown that men experience lower levels of distress during IVF treatment than women, male participants did not fill in the record chart.

Interventions

In the intervention group, couples were given three counseling sessions, ranging from 1 hour to 1.5 hours. Similar to a previous study, a pre-treatment (1 week before the first day of pituitary down-regulation or the first day of ovarian stimulation in the case of GnRH antagonist co-treatment), and a post-treatment session took place approximately 2 weeks after the day of the pregnancy test. Additionally, patients received a counseling session 6-9 days after the embryo was transferred. The waiting period is associated with more uncertainty and lack of control than other treatment stages. During the nondirective sessions, couples were invited to discuss their feelings and thoughts on topics related to infertility and IVF treatment. Depending

Table 2. Reasons for Nonparticipation

Motivation	n	%
Lack of awareness	30	34.48
No time for counseling	11	12.64
No need for counseling	18	20.69
Fear	19	21.84
Overly stringent protocol	9	10.34

on the needs of the clients, the counselor alternately used the four basic aspects of infertility counseling: information gathering and analysis, implications and decision-making counseling, support counseling and therapeutic counseling. Counseling was provided by a trained counselor. Instead of being an objective observer, the counselor expresses her own feelings and ideas about the client in order to create new interpersonal experiences for the client. It is assumed that through these personal experiences with the counselors, clients learn how to cope with (inter)personal problems.

Outcome Measure

The outcome measure in this study was pregnancy rate, which was measured through β-human chorionic gonadotropin (β-hCG) test, sonography or both of them. The stress appraisal measure (SAM) was developed and monitored at regular interval and analyzed.

RESULTS

Counseling was initiated to all couples as psychological intervention or cognitive-behavioral therapy in which couples received relaxation training, cognitive restructuring, methods for emotional expression and nutrition and exercise information techniques of stress control.

The couples who completed the program differed significantly from the couples who dropped out in demographics and stress as measured by the record chart at baseline. The biochemical pregnancy rate after the first IVF treatment cycle was 35% for the intervention group and 19% for the control group. This difference was significant.

DISCUSSION

Counseling makes an impact through stress reduction mechanism. Distress is associated with a significant reduction in the probability of conception. Counseling could possibly exert a decreasing impact on stress and enhance the possible chance of pregnancy. This conforms with the results from study by Boivin and de Liz and Strauss that investigated the efficacy of psychological interventions for infertile patients.

Psychological interventions include counseling, educational interventions, relaxation and psycho-dynamic or analytic interventions. The beneficial impact of such interventions on pregnancy rates needs to be viewed with caution as there is no clear explanation for this effect.

Sexual activity seems to be disturbed in over half of the couples suffering from infertility. Psychological interventions could have a positive impact on sexual behavior and enhance a couples' chances of pregnancy. An increased rate of sexual intercourse following psychological interventions may be associated with an increased rate of pregnancy.

Most women in this study seemed to be able to cope with the procedural distress of their first IVF treatment with the help of a counselor.

In order to draw an inference, it is required to assess the infertile patient's sexual behavior and their mental distress to determine their relative impact on the pregnancy rate. Future studies should determine the association between a couple's frequency of sexual activity and sexual satisfaction and the pregnancy rates.

Clinical Implications

Counseling should be integrated in the treatment of infertility as the present study indicates that counseling is effective in increasing pregnancy rate.

CONCLUSION

The findings of the present study provide some evidence in support of integrating counseling as an early remedial strategy for infertile patients. Counseling appears to increase infertile women's chances of becoming pregnant. On the basis of the results, counseling is beneficial for infertile patients, but more randomized controlled trials are needed.

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More Americans are Missing Second Dose of COVID-19 Vaccines: CDC Data

An increasing number of Americans have missed their second dose of a COVID-19 vaccine, suggest data from the US CDC. The Pfizer/BioNTech and Moderna COVID-19 vaccines require two doses, to be given at a gap of 3 and 4 weeks, respectively, to be considered fully effective. However, data indicate that nearly 8% of Americans have missed their second dose, rising from about 3.4% in March.

However, this is not an exact count. If a person received the two doses from different reporting entities, the two doses may not have been linked together, stated a CDC spokesperson. If an individual received the first dose at a state-run clinic, and the second dose at a tribal health clinic, they might not be linked and it could reflect as the second dose was missed… (*CNN*)

Immunization Services Start Slow Recovery from Pandemic Disruptions, Millions of Children at Risk from Deadly Diseases

While immunization services begin to have a slow recovery from disruptions due to COVID-19 pandemic, millions of children are still susceptible to deadly diseases, stated the WHO, UNICEF and Gavi, the Vaccine Alliance, emphasizing the urgent need for improved global commitment toward improving vaccination access and uptake. According to a WHO survey, despite progress in comparison with the situation in 2020, over a third of respondent countries (37%) continue to report disruptions to their routine immunization services. Updated data suggest that 60 of the life-saving immunization campaigns are postponed in 50 countries, which has put nearly 228 million people, most of them children, at risk for diseases such as measles, yellow fever and polio… (*WHO*)

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Acute Encephalitis Syndrome: A Rare Presentation of Scrub Typhus in Adults

VIRENDRA KR GOYAL*, JITESH AGGARWAL†, MANAN DAVE‡, ROOTIK PATEL‡

ABSTRACT

Scrub typhus or bush typhus or tsutsugamushi disease is a mite-borne acute febrile illness caused by Gram-negative intracellular organism *Orientia tsutsugamushi* (which belongs to the family of Rickettsiaceae). Common presentation of scrub typhus includes fever, headache and inoculation eschar and lymphadenopathy. In severe forms, pneumonia, myocarditis, azotemia, shock, gastrointestinal bleeding and meningoencephalitis are known to occur. Central nervous system (CNS) involvement may be a complication of scrub typhus, which ranges from meningitis to frank meningoencephalitis. Here we are describing a case of acute encephalitis syndrome (AES), following scrub typhus infection in an adult patient. Patient didn't have concurrent infection with any other tropical fever diseases, like malaria, chikungunya, typhoid and dengue fever. Patient was put on injection ceftriaxone, capsule doxycycline, tablet azithromycin, tablet levetiracetam and symptomatic treatment with multivitamin support. By Day 3, patient's sensorium improved and he started to follow verbal commands. Patient was hospitalized in our tertiary care medical college and hospital (AIIMS, Udaipur) for 7 days and recovered completely.

Keywords: Scrub typhus, eschar, thrombocytopenia, acute encephalitis syndrome, Rickettsiaceae

Scrub typhus or bush typhus or tsutsugamushi disease is a mite-borne acute febrile illness caused by Gram-negative intracellular organism, *Orientia tsutsugamushi* (which belongs to the family of Rickettsiaceae). Although the disease has a worldwide distribution, most of the cases are reported from the so-called "tsutsugamushi triangle", which is a wide area bounded by Pakistan, India, Nepal in the West; Siberia, Japan, China and Korea in the North and Indonesia, Philippines, Australia and the Pacific Islands in the South and is mostly related to agriculture and outdoor activities. There is an estimated 1 million new scrub typhus infections each year and over 1 billion people around the world are at risk of this potentially fatal tropical illness.

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It is a common, zoonotic disease in South-East Asia and on account of rapid urbanization of rural and forested areas, it is becoming increasingly common in India. Common presentation of scrub typhus includes fever, headache and inoculation eschar and lymphadenopathy. In severe forms, pneumonia, myocarditis, azotemia, shock, gastrointestinal bleeding and meningoencephalitis may occur. Central nervous system (CNS) involvement may be a complication of scrub typhus which ranges from meningitis to frank meningoencephalitis. The name "typhus" itself, is derived from the Greek word "typhos", which means stupor. Other neurological complications include seizure, cranial nerve deficits, vasculitic cerebral infarct, brain hemorrhages, polyneuropathy, sensorineural hearing loss, meningitis or meningoencephalitis. Here we are describing a case of acute encephalitis syndrome (AES), following scrub typhus infection in an adult patient. The patient did not have concurrent infection with any other tropical fever diseases, like malaria, chikungunya, typhoid and dengue fever.

CASE SUMMARY

A 25-year-old male resident of Southern Rajasthan presented in our hospital with complaints of fever with chills and rigors for 7 days, decreased

appetite and altered sensorium, unable to speak for 2 days and involuntary movements of all four limbs with frothing from the mouth and up rolling of eye balls. On examination, patient was running a high-grade temperature of 101.4°F. Blood pressure 90/80 mmHg in supine position, pulse 120/min, SpO_2 98%. Patient was unconscious, disoriented with time, place and person. Patient was not following any verbal commands. For these complaints, patient was admitted in medical intensive care unit (MICU) in our hospital. On general physical examination of the patient, eschar was found (Fig. 1). Tongue bite was present. CNS examination: Higher mental functions and cranial nerve examination could not be accessed. Pupils were normally reacting to light. There were no signs of increased intracranial pressure (ICP). Neck rigidity and hypertonia were present. Bilateral plantar were extensor. Other systems didn't show any abnormality. There was no organomegaly on per abdomen examination. Fundus examination of the patient suggested no signs of papilledema and increased ICP. Noncontrast computed tomography (NCCT) head was done to rule out hydrocephalus, and it was normal. Magnetic resonance imaging (MRI) brain could not be done due to institutional constraints. Lumbar puncture was done under aseptic precautions and cerebrospinal fluid (CSF) fluid was sent for cytological and biochemical analysis. On gross examination, CSF was drained with normal pressure and was found clear. CSF was found acellular, with proteins 22 mg/dL, sugar 66.8 mg/dL. Corresponding blood sugar was 122 mg/dL. Gram stain and Ziehl-Neelsen staining of CSF fluid was negative. X-ray chest (PA view) of the patient was normal. Complete blood count (CBC) showed mild thrombocytopenia (hemoglobin [Hb]: 13.5, white blood cell [WBC]: 5.63, platelet: 62,000) with mild derangement of liver enzymes with serum glutamic pyruvic transaminase (SGPT): 104.9, serum glutamic oxaloacetic transaminase (SGOT): 78.9. MP QBC, immunoglobulin (IgM/IgG) dengue and NS1 antigen to rule out dengue and IGM typhidot to rule out typhoid fever and enzyme-linked immunosorbent assay (ELISA) test for chikungunya of the patient were negative.

Ultrasonography of abdomen revealed biliary sludge and moderate splenomegaly (Fig. 2). ELISA test to detect IgM antibodies against *O. tsutsugamushi* antigens for scrub typhus was found positive. Patient was put on injection ceftriaxone, capsule doxycycline, tablet azithromycin, tablet levetiracetam and symptomatic treatment with multivitamin supports. By Day 3, patient's sensorium improved and he started to follow verbal commands. He was hospitalized in our tertiary care medical college and hospital for 7 days and recovered completely.

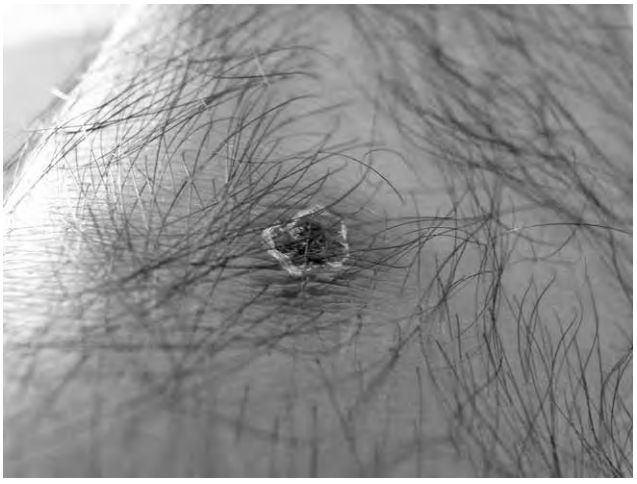

Figure 1. Eschar at left knee.

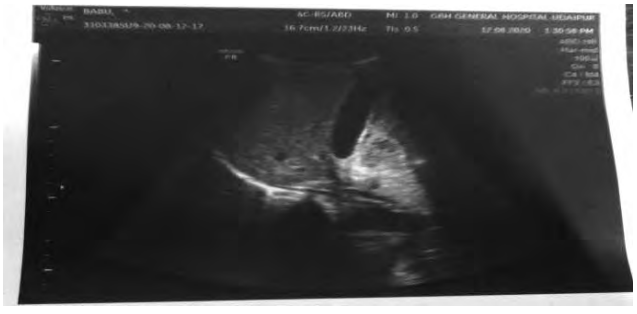

Figure 2. Ultrasonography of the abdomen indicating the presence of biliary sludge in gallbladder.

DISCUSSION

Scrub typhus is a potentially fatal infection, affecting nearly 1 million people each year. The disease first gained significance during the World War II. Several from the US, Ceylon and Burma armies were infected and succumbed to the illness due to lack of proper antibiotic treatment.

Several epidemics of scrub typhus have occurred in India, yet, the literature is still limited. *O. tsutsugamushi* is known to cause this disease and was first identified and studied in Japan in 1930. An obligate intracellular bacterium, it is transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*. The incubation period is 6-21 days with an average of 10 days. The larval mites usually feed on wild rats. There are several serotypes of *O. tsutsugamushi*, and infection with one species provides only transient cross immunity to another. When a forest is cleared, scrubs

tend to grow on those areas. These scrubs later get infested by larval mites. When man comes in contact with these scrubs, he contracts the infection. The basic pathologic changes include focal vasculitis and perivasculitis of small blood vessels in the involved organs. These occur as a result of multiplication of the organism in the endothelial cells lining the small blood vessels.

Acute encephalitis syndrome is characterized by rapid onset of febrile illness associated with convulsions, altered sensorium and focal neurological deficit such as aphasia, hemiparesis, involuntary movements, ataxia or cranial nerve involvement. In a study conducted in India, on acute febrile encephalopathy including 120 patients, the common causes included acute viral encephalitis, pyogenic meningitis, tuberculous meningitis, cerebral malaria and sepsis related encephalopathy. On the contrary, in our case, the etiology was scrub typhus. This unusual presentation of scrub typhus can be easily overlooked (in this COVID era), resulting in delay in initiating life-saving treatment.

CONCLUSION

Acute encephalitis syndrome is not an uncommon neurological presentation following scrub typhus infection in adults. It should be suspected in all patients with fever, altered sensorium and hepatic involvement. Oral azithromycin can be started as soon as possible for better outcomes.

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Mother-to-Baby COVID-19 Infection Rate Low, Indirect Risk Exists: Study

While mother-to-newborn transmission of COVID-19 is rare, newborns of expectant mothers with COVID-19 can still have indirect adverse health risks due to worsening maternal illness from the disease, suggests a study. Investigators assessed neonatal outcomes during the first month of life for babies born at 11 hospitals, and the team identified 255 neonates delivered from March 1 to July 31, 2020, to mothers with a recent positive COVID-19 test result. Of the 255 neonates assessed, 88.2% were tested for SARS-CoV-2, and just 2.2% tested positive, noted the investigators. While infection rates among newborns were relatively low, worsening maternal illness was accountable for 73.9% of preterm births… (*HT – PTI*)

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Indian Journal of Clinical Practice, Vol. 31, No. 12, May 2021

Spontaneous Intracranial Hypotension

CJ SELVAKUMAR*, SHRADDHA LAXMIDHAR MOHANTY†, V SADEESHKUMAR‡, N SHOBANA¥

ABSTRACT

Introduction: Out of all the painful conditions, headache is one of most common cause of patients coming to hospital. Usually few patients present with orthostatic headache, which signifies low cerebrospinal fluid pressure. **Case description:** A 38-year-old female presented with intense headache in upright position, relieved on lying down in supine position. She was treated with analgesics and epidural blood patch. **Discussion:** Spontaneous intracranial hypotension is one of the treatable causes of headache. It can be detected by magnetic resonance imaging, which can reduce the morbidity and improve quality of life. **Conclusion:** As there is increase in availability of MRI, spontaneous intracranial hypotension can be detected easily.

Keywords: Orthostatic headache, subdural hygroma, epidural blood patch

Spontaneous intracranial hypotension is one of the rare causes of headache. The most characteristic feature is the relative change in intensity of headache with change in posture. The intensity of headache is more in the upright and standing position, relieved in the recumbent position (orthostatic headache). The headache occurs due to lowering of intracranial pressure caused by leakage of cerebrospinal fluid (CSF).

CASE HISTORY

A 38-year-old lady presented with headache for 2 weeks, which was severe in intensity, in bitemporal and occipital region, persisting throughout the day, aggravated in sitting and standing position, relieved by supine position. The headache was associated with pain in upper part of neck and vomiting. She had past history of hypertension with regular treatment with antihypertensives. She had no history of previous lumbar puncture, spinal surgery, congenital disease, connective tissue disorders and type 2 diabetes mellitus. No significant family history obtained.

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On neurological examination, she was conscious, oriented to time, place and person; cranial nerves, motor system, sensory system, cerebellar system, autonomic nervous system were normal. No meningeal signs were present. She was initially treated with analgesics, antidepressants, antihypertensives and intravenous fluid. But her headache was not getting relieved with the medications. Neurosurgery and ear, nose and throat opinion were normal. Routine blood investigations were done (blood and radiological). Her blood parameters were hemoglobin - 11.3 g/dL, total leukocyte count - 8,400/mm^3, random blood sugar - 108 mg/dL, serum creatinine - 1 mg/dL. Magnetic resonance imaging (MRI) of brain revealed thin subdural hygroma in both the frontal convexity, prominent venous sinus and draining cortical veins, especially right transverse sinus. Left lateral ventricle narrowed at the frontal horn (slit-like frontal horn) (Figs. 1 and 2).

These findings were suggestive of intracranial hypotension. She was treated with oral analgesics tablet paracetamol and diclofenac, tablet propranolol, capsule omeprazole and intravenous fluids, but there was not significant improvement. A follow-up MRI of brain revealed increase in volume of subdural collection in right frontoparietal convexity with maximum thickness of 16 mL and left frontoparietal, occipital convexity with maximum thickness of 3 mL (Fig. 3). The lesion showed areas of blooming. Since MRI of brain did not reveal any site of leakage, MRI of whole spine with CSF sequence was done, which revealed hyperintense area at the level T7 (thoracic) vertebra suggestive of CSF leak (Fig. 4). After localization of site of CSF leak, epidural

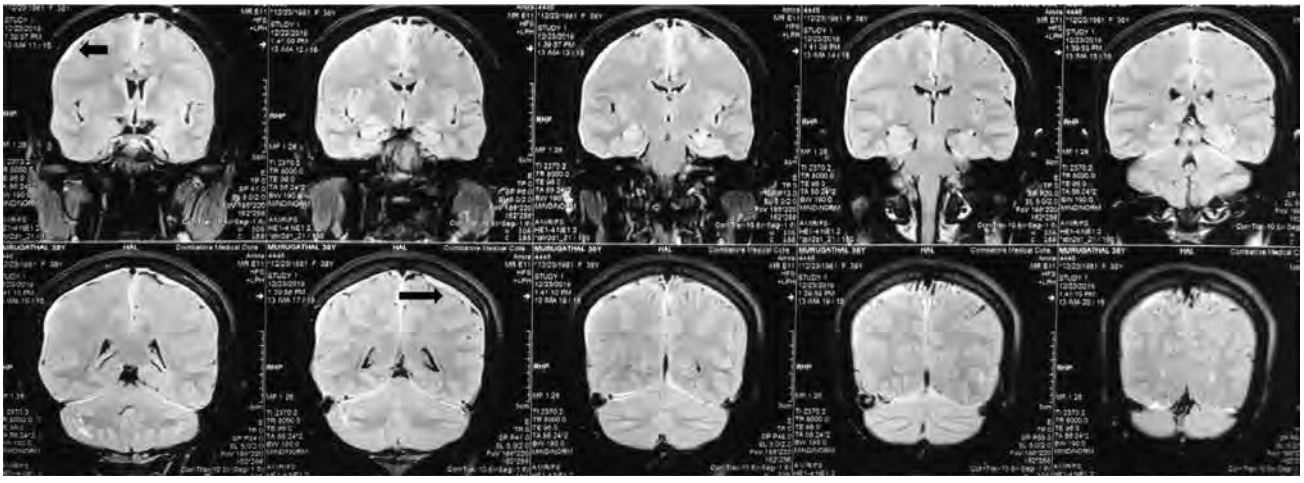

Figure 1. T2 Flair coronal section of MRI of brain - Bilateral subdural hygroma.

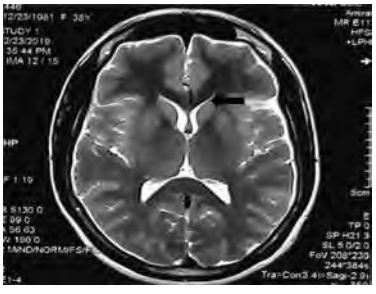

Figure 2. T1 Axial section of MRI of brain – Slit-like frontal horn of left lateral ventricle.

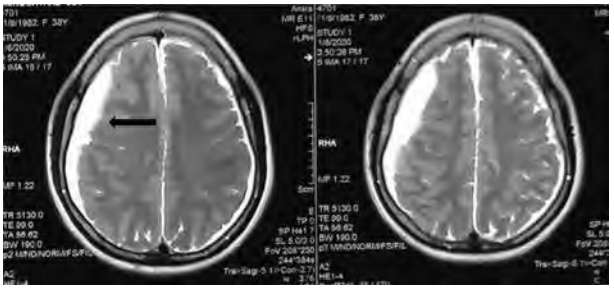

Figure 3. T2 Axial section MRI of brain - Increase in volume of subdural collection in right frontoparietal convexity and left frontoparietal, occipital convexity (follow-up scan).

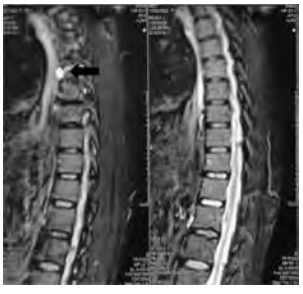

Figure 4. MRI of spine with CSF flow sequence showing leak at T7 vertebral level.

blood patch with patient's own blood was put. After the procedure, her headache reduced tremendously within 2 days.

DISCUSSION

There are various causes of intracranial hypotension. The CSF leak can be caused by lumbar puncture (CSF trickles into the paravertebral muscles), spinal surgery and spinal trauma (tear in the arachnoid surrounding a nerve root). Spontaneous intracranial hypotension can be caused due to low intracranial pressure by leakage of CSF with unknown cause. It is a rare disease occurring in 1 in 50,000 people. It is more common in women than men. The most common cause of spontaneous intracranial hypotension is the leak of CSF through a tear in spinal dura. Marfan and Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease are genetic risk factors for spontaneous CSF leak.

Orthostatic headache is cardinal presentation of spontaneous intracranial hypotension. It may be associated with diplopia (due to 6th cranial nerve palsy or self-audible bruit from turbulence in the intracranial venous system). There can be sagging of the frontal lobes in low CSF pressure caused by leakage of the CSF (brain sagging syndrome), which can lead to brainstem lesions with stupor, gaze palsies and cranial nerve palsies. Patients are apathetic and disinhibited with prominent daytime somnolence.

To localize the site of the leak, radionuclide cisternography or CT (computed tomography) myelography can be done. CT myelography is the preferred diagnostic test. Dynamic CT myelography is useful for detecting high flow leaks. As there are technological advancements and availability of MRI, MRI of brain with gadolinium contrast is done, which shows prominent dural enhancement (due to dural venous dilation) or diffuse pachymeningeal enhancement described by Fishman and Dillon et al. Other additional features seen are subdural effusions on cerebral convexities, temporal lobes, optic chiasma or cerebellar tonsils. In order to find leak, MRI of spine can be done which may show spinal fluid collection, dural enhancement, dilated epidural veins, enlarged epidural venous plexus, attenuation of spinal canal or compression of spinal cord and contrast

extravasation. MRI of spine helps us find the site of leak present in the spinal dura.

A diagnostic criteria for headache in spontaneous intracranial hypotension was framed by Schievink et al as:

- Orthostatic headache
- The presence of at least one of the following: low opening pressure (≤60 mm water), sustained improvement of symptoms following epidural blood patching, demonstration of an active spinal CSF leak, cranial MRI changes suggestive of intracranial hypotension (brain sagging or pachymeningeal enhancement)
- No recent history of dural puncture
- Not attributed to another disorder.

CONCLUSION

Our patient had orthostatic headache, with relief of headache after blood patch and MRI of brain showing dural enhancement.

The definitive treatment is epidural blood patch with approximately 20 mL of patient's blood at the site of leak, which relieves the headache. After blood patch, there has been no recurrence; very few cases had repeated episodes of orthostatic headache.

As there is increase in availability of MRI, spontaneous intracranial hypotension can be detected easily. It can be treated easily, preventing long-term morbidity as well as preventing the inappropriate usage of analgesics.

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Covishield Protects Against Double Mutant Strain, Says CCMB Director

Preliminary results from a study have revealed that Covishield protects against the B.1.617 variant of coronavirus, also called the double mutant strain, stated Rakesh Mishra, Director of the Centre for Cellular and Molecular Biology (CCMB).

He mentioned that the study was conducted by the CCMB, an institute of the Council for Scientific and Industrial Research (CSIR). Mishra tweeted that early results using *in vitro* neutralization assay demonstrated that both convalescent sera and Covishield-vaccinated sera protected against the B.1.617 variant.

The B.1.617 variant carries mutations from two different virus variants - E484Q and L452R. There has been apprehension among experts that the new variant could increase infection rates and easily evade immune response… (*HT – PTI*)

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Ethylene Dibromide Poisoning with Acute Myocarditis: A Rare Association

MAHESH DAVE*, ANIRUDDHA BURLI†, RAMIT SINGH PALA†, SAHIL KHARBANDA‡, MANASVIN SAREEN‡

ABSTRACT

Ethylene dibromide (EDB) is a commercially available fumigant used as a pesticide. Its toxicity may develop from poisoning after ingestion. It principally affects liver and kidneys causing centrilobular necrosis and tubular injury, respectively. We report a case of suicidal ingestion of EDB in a 29-year-old male. The patient presented with predominant gastrointestinal symptoms and hypotension. Upon further investigation, the patient had electrocardiograph changes and evidence of myocarditis. Prompt symptomatic treatment resulted in favorable outcome and patient was discharged. Hence, myocarditis, though rare, is yet a significant presentation of EDB poisoning.

Keywords: Poisoning, ethylene dibromide, myocarditis

Ethylene dibromide (EDB) or dibromoethane, also known as bromo fume, is a volatile, non-inflammable, colorless liquid with a sweet chloroform like odor. It is used as a solvent for resins, gums and waxes. The other uses of this chemical are as lead scavengers in gasoline as well as pesticide for grains, fruits and vegetables.

EDB is very toxic for human beings and is absorbed through skin, inhalation and ingestion and can cause acute toxicity. It is commercially available in the form of 3 mL or 5 mL ampoule easily in India and many other countries. The toxic dose varies from 5 to 10 mL (1-2 ampoules) causing severe liver and renal damage.

Acute toxic effects commonly observed after ingestion of EDB may be pain abdomen, nausea, vomiting, giddiness, headache, drowsiness and severe toxic effects may be in the form of liver and kidney involvement, subsequently causing hepatorenal failure and death.

Acute myocarditis is a very rare presentation reported following acute EDB poisoning and not documented in literature worldwide. Hence, we report this case of EDB poisoning presenting with acute myocarditis without hepatic or renal involvement, which is the rarest association.

CASE REPORT

A 29-year-old male was admitted in emergency medical ward with history of EDB pesticide ingestion 4 hours prior to admission. He consumed 2 ampoules (3 mL each) mixed with approximately 100 mL of water with suicidal intent. He had history of nausea, vomiting, pain abdomen, headache and giddiness at the time of admission. Past history revealed no existing comorbidities including any form of psychiatric illness.

His general physical examination was unremarkable. Vitals examination at the time of admission revealed pulse of 112 bpm, regular, normal volume. Blood pressure was 90/60 mmHg. Rest vital signs were within normal limit. Systemic examination revealed no significant abnormality.

In view of EDB poisoning and our past experiences, the patient was investigated for complete blood count (Hemoglobin - 11.3 g%, total leukocyte count [TLC] - 6,470 cells/mm^3, platelets - 1.25 lakh/mm^3), renal function test (blood urea - 29.9 mg/dL, serum creatinine - 0.93 mg/dL), liver function test (serum bilirubin - 0.4 mg/dL, serum glutamic oxaloacetic transaminase [SGOT] - 14 IU, serum glutamic pyruvic transaminase [SGPT] - 23 IU, alkaline phosphatase [ALP] - 72 IU),

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serum electrolytes and urine examination at the time of admission and the values were found within normal limits.

His arterial blood gas (ABG) analysis done at the time of admission showed pH - 7.31, partial pressure of oxygen (PaO_2) - 92 mmHg, partial pressure of carbon dioxide ($PaCO_2$) - 38 mmHg, serum bicarbonate (HCO_3) - 19 mmol/L and arterial oxygen saturation (SaO_2) - 96.4%, suggestive of metabolic acidosis. Subsequent ABGs were found normal.

Patient was put on routine management protocol of poisoning which included gastric lavage, use of activated charcoal and milk of magnesia along with fluid management. But even after fluid challenge, his blood pressure was persistently low and hence, he was investigated with electrocardiogram (ECG) and X-ray chest.

X-ray chest showed no cardiopulmonary abnormality.

His first ECG done 2 hours post-hospitalization showed heart rate 102/min with prolonged PR interval (0.22 s) with ST-segment elevation (concave upwards) with associated T inversions in leads V1 to V4 which was suggestive of acute myocarditis (Fig. 1).

In view of acute myocarditis, further confirmation was done with help of cardiac biomarkers, which included creatinine phosphokinase-MB (CPK-MB) and serum troponin T levels, which were found significantly elevated. CPK-MB was 74 U/L (Normal 0-25) and Trop T was 0.12 (Normal 0-0.01).

Patient was followed up regularly for 5 days with serial ECG and cardiac biomarkers.

Day 2 ECG showed heart rate 96/min with persistent ST-segment elevation in V1 to V4 with T inversions in V1 to V6 and normal PR interval (Fig. 2).

Day 3 ECG showed heart rate 52/min with ST-segment depression in II, III and aVF; ST-segment elevation in V1 and V2 with symmetrical T inversions in V1 to V6 (Fig. 3).

Day 4 ECG showed heart rate 42/min with ST-segment elevation in V1 and V2 (less than previous ECG) with normal T waves and PR interval (Fig. 4).

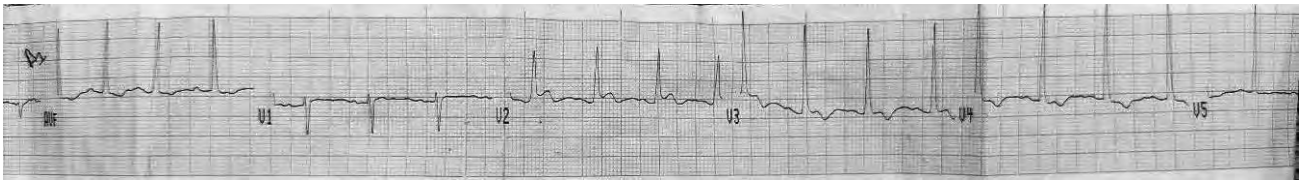

Figure 1. Day 1 - heart rate 102/min. PR interval (0.22 s). ST-segment elevation (concave upwards) with T inversions in leads V1 to V4.

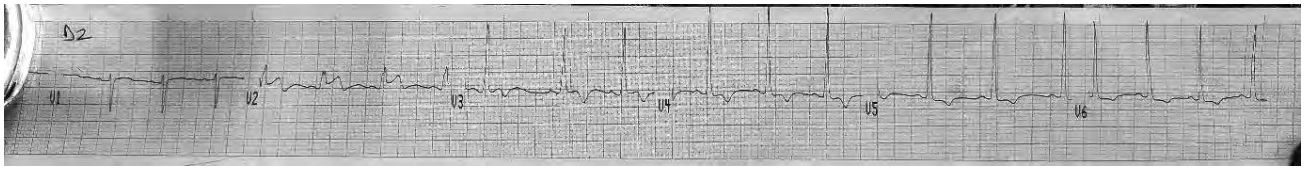

Figure 2. Day 2 - heart rate 96/min. ST-segment elevation in V1 to V4. T inversions in V1 to V6.

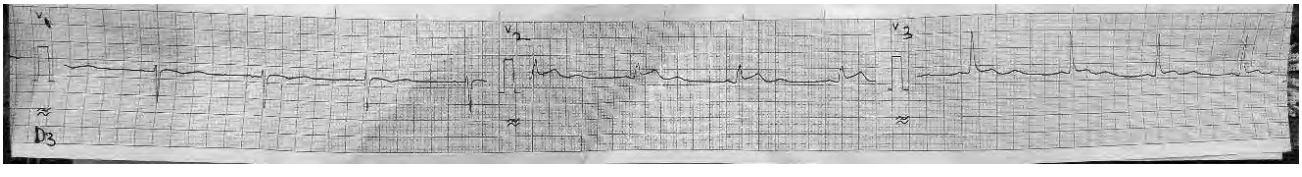

Figure 3. Day 3 - heart rate 52/min. ST-segment depression in II, III and aVF. ST-segment elevation in V1 and V2 with symmetrical T inversions in V1 to V6.

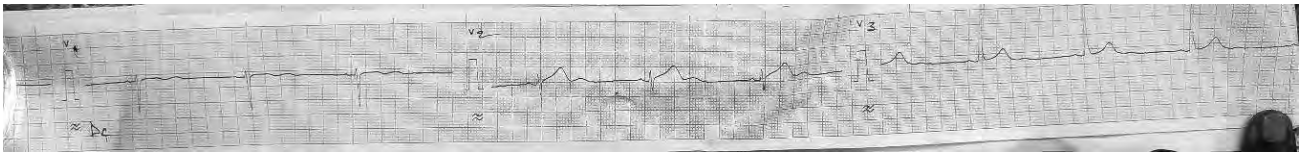

Figure 4. Day 4 - heart rate 42/min. ST-segment elevation in V1 and V2.

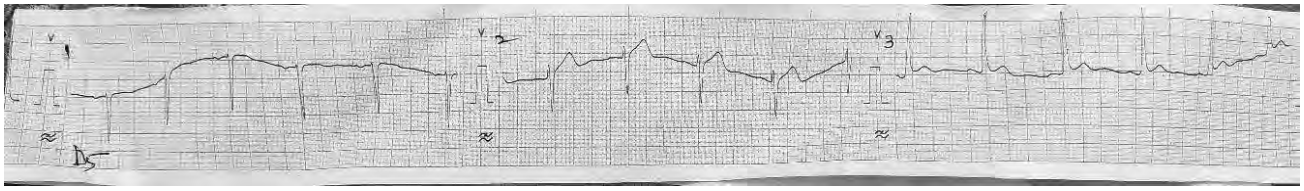

Figure 5. Day 5 - heart rate 84/min. ST-segment elevation in V1 and V2.

Day 5 ECG showed heart rate 84/min with ST-segment elevation in V1 and V2 (less than previous ECG) with normal T waves and PR interval (Fig. 5).

Serial CPK-MB and Trop T returned to normal after remaining persistently high for 4 days.

Further, 2-dimensional cardiac echocardiography revealed no significant abnormality with left ventricular ejection fraction (LVEF) of 60-65%, except for minimal pulmonary regurgitation.

Patient was managed by giving IV magnesium sulfate, IV hydrocortisone, carnitine, IV fluids, vitamin C and E. His blood pressure started improving 12 hours after treatment and was discharged after 5 days with advice for relative bed rest, vitamin C and E and carnitine therapy and follow-up at medical OPD.

DISCUSSION

Ethylene dibromide is a halogenated hydrocarbon which is colorless and available in Indian market as pure form in 3 mL and 5 mL ampoules, commonly used as grain preservative. It is well-absorbed from skin, respiratory and gastrointestinal tracts, metabolized in liver and excreted through kidney via urine as bromide conjugates of glutathione and L-acetyl cysteine. EDB is metabolized by two pathways.

A conjugated pathway catalyzed by glutathione S-transferase and oxidative pathway catalyzed by cytochrome P-450. The exact mechanism of acute EDB toxicity is yet not well-understood. Lipid peroxidation and liberation of free radicals damage membrane structure, resulting in acute liver injury (fulminating hepatitis, hepatic necrosis) and acute tubular necrosis of kidneys, leading to acute hepatorenal failure and death.

EDB poisoning is very uncommonly reported in literature. A very few autopsy reports in EDB poisoning available in literature suggest centrilobular necrosis, Kupffer cell damage, acute tubular necrosis, pulmonary edema and muscle necrosis as major findings.

Cardiac involvement in acute EDB poisoning is yet not reported in any case worldwide. In our patient, cardiac involvement was observed 3-4 hours after poisoning. The etiology of cardiac involvement is not known but probably is due to free radical-induced membrane peroxidation.

In this view, patient was treated with membrane stabilizing agent (magnesium sulfate), free radical scavengers (vitamin C and E, carnitine) and we were able to normalize the ECG changes and cardiac biomarkers on the 5th day.

CONCLUSION

In Southern Rajasthan, EDB is a common pesticide used for grain preservation and a common poisoning agent after organophosphate and celphos. The incidence of death in these cases is very high and maximum deaths are due to late hepatorenal failure. Cardiac involvement is rarely seen in EDB poisoning but careful evaluation is essential as it occurred in our case. Early detection of cardiac involvement and prompt treatment may save the life of the patients.

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Indian Journal of Clinical Practice, Vol. 31, No. 12, May 2021

Information Technology and Healthcare Education: Scope and Opportunities

SANCHIT TIWARI*, PK KAR†, BV MURLIMANJU‡, AMIT AGRAWAL#

Patient administration, laboratories and accounts handle large volumes of numeric data and the revolution in the field of information and technology (IT) has made the clinical activities involving calculations much easier. There is emergence of computer-aided history-taking and diagnosis. In a simplified language, it can be said that we need computers for data entry, data processing and for data storage where the data can be retrieved as and when necessary (for patient management or for research purpose). The basic unit what we all are aware is a computer hardware which in simplest terms is collection of various physical parts and includes monitor, keyboard, mouse, hard disk drive, motherboard, video card and many others components, largely determined by the needs of the users. Now the word processing and database management systems have penetrated the working clinician and health services management. Information technology in medical education and healthcare is a broad concept that encompasses procedures, tools and techniques which can be used to improve healthcare delivery and can facilitate health education. This concept includes complex technological models, software packages, hardware equipments and is supported by innovative technologies. Schwartz[1] predicted that by the year 2000, the computer-aided diagnosis will have instrumental role in medicine. This will further extend the physician's intelligence.[2] Health information technology will decrease delayed, missed and incorrect diagnoses in the clinical practice.[3] With the help of IT, human being became more productive and efficient with the information. Computer application has improved human tasks and activities. The convergence of information and communication technologies were the next steps and this has led the booming of networking, both within and between the organizations.[4]

The data sharing concepts and integrated information systems were evolved in the 90's. Hospital information systems took rich data like sounds, images, movies inside the hospital. The health records in the medical records department became completely digital, including the acquisition, storage and transmission of the data. The internet usage became essential, which enabled moving of data and information quickly and cost-effectively.[4] With the rapid rate of development and proliferation of information, we can expect more sophisticated use of computers, like voice and handwriting recognition in the future. The health professionals should take it as a challenge to implement techniques like tele-surgery and integrated electronic health records for the benefit of their patients. The sophisticated undergraduate and postgraduate web-based training has to be done as well.[4] Inadequate facilities and delayed diagnosis are causing higher mortality in a majority of cases in peripheral areas. High-quality history taking and physical examination is very much essential; however, time pressure and memory pose a major problem. In the 1960s, history-taking through computer-based patient interviewing was performed.[5,6] It was reported that the technology can be used as a complement rather than replacement to the physician-acquired history.[7] The electronically available patient information enables efficient review of patient information and recognition. Graphical representation of numerical data could be performed.[8] The display of patient data in graphs and tables have decreased the review times. They are also effective in answering the various clinical questions.[9] The diagnostic checklists comprising of 'don't miss' or 'commonly missed diagnoses' can be given to the doctors for common presenting symptoms and sign

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for cross verification.[3,10] This can be best performed with computer-based differential diagnosis listing.[3] Diagnostic protocols can be ingrained into various electronic tools.[3]

Various modules have been developed and promoted for healthcare delivery and for facilitating healthcare education, training and research. These include e-Hospital,[11] e-Office,[12] e-Library[13] and many other electronic health record management systems. **e-Hospital**[11] is promoted by National Informatics Centre (NIC) and is a health information management system, which can be deployed in cloud and can be managed across the hospitals. This helps to maintain treatment cycles related to outpatient and inpatient services and integrates clinical, administrative and billing-/insurance-related activities. The available modules include patient registration facility, emergency registration, clinics, billing and accounts, PACS Interface, pharmacy management, electronic medical records (EMR), telemedicine suite, to name a few. **e-Office** is a simplified, responsive module which is also developed by NIC and helps to maintain efficient, effective and transparent transactions and processes while ensuring data security and data integrity. The aim of **e-Library** is to provide paperless, uninterrupted and comprehensive access to online resources, e-journals, electronic documents and many other virtual resources.

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Pfizer, Moderna COVID-19 Vaccines do not Seem to Pose Serious Risk During Pregnancy

The Pfizer/BioNTech and Moderna COVID-19 vaccines do not seem to extend a serious risk during pregnancy, suggests a new study published in the *New England Journal of Medicine*.

The study, in addition to the existing evidence suggesting that mRNA vaccines are effective in pregnant and lactating women, indicates that the benefits of the vaccines outweigh the risks.

Investigators looked at a group within the CDC's V-safe system and obtained data on pregnancy outcomes and complications. The registry included 3,958 pregnant women, out of a total of 35,691, who had been administered an mRNA vaccine. There were 827 completed pregnancies, of which 115 (13.9%) experienced a pregnancy loss, and 712 (86.1%) resulted in a live birth. Preterm births were noted in 9.4% of the study participants and about 3.2% of these births were small for gestational age. No neonatal deaths were noted. In all, 221 pregnancy-related adverse events were reported to the CDC's VAERS registry; 46 of these were miscarriages. The proportions of adverse pregnancy and neonatal outcomes in vaccinated participants having a completed pregnancy appeared to be similar to those reported in studies among pregnant women carried out prior to the pandemic… (*CNN*)

Role of Atmospheric Pressure as a Trigger for Subarachnoid Hemorrhage

EZEQUIEL GARCÍA-BALLESTAS*, LUIS RAFAEL MOSCOTE-SALAZAR†, AMIT AGRAWAL‡

Studies suggest that there is a link between temperature decline from the highest of the previous day (TDP) to the lowest of the event day with the incidence of subarachnoid hemorrhage (SAH).[1] The impact of weather conditions, particularly the atmospheric pressure, on the occurrence of cerebral hemorrhage is well described in the literature. Several studies have reported a potential correlation between environmental factors and SAH onset, while certain others have not found a significant association, resulting in controversy due to different assessment of meteorological factors, patient selection, target geographical area and study design.[2-8] The atmospheric pressure is related to the temperature variation and atmospheric pressure determines nature of temperature fluctuation, magnitude of change and persistence duration. However, using prefecture-wide survey data amassing all patients with SAH in the defined area, has minimized referral and selection biases and proved the correlation of TDP with the incidence of spontaneous SAH. The triggering effect of TDP was prominent in younger women patients <65 years old. Interestingly, variations in barometric pressure are reported to be associated with the development of intracerebral hemorrhages, including SAH. It is possible that the effect depends on the change of magnitude of the barometric pressure, and secondary manifesting, as temperatures changes in preceding days and onset of new-onset SAH ictus. This aspect has been evaluated by various authors.[5,8-10]

Previous studies from the Netherlands, Japan and Northern France revealed significant associations between low daily temperatures and SAH.[2,3,11] Conversely, such an association was not found to be significant in studies from Germany and the US.[4,6] Although the study has many concerns (a small sample size; flack of atmospheric pressure trend over SAH ictus and limited information about exposure to cold, usage of protective clothing and living room modifications),[7] to add further, investigating environmental factors not only will help to know the impact of atmospheric pressure as a risk factor to trigger SAH but also shall help in deciding how the environment around these patients needs to be managed in critical care settings. The biggest challenge for the researcher would be to identify whether it is low pressure,[12] or high atmospheric pressure,[5] which is more important. Additionally, it will help to guide how the patients with diagnosed, yet unruptured, aneurysms can be managed and what kind of day-to-day activities in what weather conditions they can participate in.

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COVID-19 Continues to Interrupt Essential Health Services in 90% of Countries

The second round of a WHO pulse survey suggests that more than 1 year since the COVID-19 pandemic began, considerable disruptions still prevail, with nearly 90% of countries still reporting one or more interruptions to essential health services. There appears to be no consequential change worldwide since the first survey was conducted in the summer of last year.

However, within countries, the extent of disruptions has generally shown a decrease. In 2020, countries reported that, on average, around half of the essential health services were interrupted, but in the first 3 months of 2021, progress was reported, with only over a third of services now being interrupted. This survey addresses 63 core health services across delivery platforms and health areas. It was sent to 216 countries and territories across the six WHO regions and 135 responses were returned from senior ministry of health officials from January through March 2021… (*WHO*)

Cadila Healthcare Starts Producing Its Potential COVID-19 Vaccine

Cadila Healthcare has started production of its potential COVID-19 vaccine and is expected to seek EUA for the same in May or June, reported the company's managing director. The company aims to make up to 240 million doses in a year. Government officials have stated that they are waiting for the company to seek approval for ZyCoV-D. Sharvil Patel said that the goal was to produce 10 million doses a month starting from June, taking the annual capacity to 120 million. The rest of the production will come from third-party producers. This vaccine is a DNA plasmid product. A small part of the virus's genetic code is injected to stimulate the recipient's immune response. The vaccine is currently designed to be given as a three-dose regimen; however, the company is also carrying out trials on a two-dose regimen… (*NDTV – Reuters*)

CDC Recommends Pregnant People Receive a COVID-19 Vaccine

The CDC recommends that pregnant people should get a COVID-19 vaccine, stated Director Dr Rochelle Walensky.

Dr Walensky's comment comes after a new study observed no safety concerns in a large group of pregnant people who were administered the vaccine during the third trimester, and no safety concerns for their babies.

Dr Walensky encouraged people to talk to their doctors or primary care providers to ascertain the best for them and for their baby. Preliminary findings from CDC scientists published in the *New England Journal of Medicine* determined that the Pfizer and Moderna mRNA COVID-19 vaccines do not seem to present any serious risk during pregnancy… (*CNN*)

Indian Journal of Clinical Practice, Vol. 31, No. 12, May 2021

Lipodystrophy at Unusual Site Due to Unusual Cause

BV NAGABHUSHANA RAO

CASE PRESENTATION

A 58-year-old female patient consulted us for her diabetes control. She was a known diabetic for the last 18 years and had been on insulin injection the last 10 years. She was on 30 units of Human Mixtard before breakfast and 25 units before dinner. In addition, she was also taking teneligliptin 20 mg and metformin 500 mg sustained release before lunch. Her blood sugars were erratic. She was frequently hyperglycemic and even a small increase in insulin dose landed her in hypoglycemia.

Physical examination did not reveal significant abnormality except for a soft tissue swelling on the ventral aspect of her left forearm (Fig. 1). The swelling was 6 × 8 cm in size mobile and had no erythema or tenderness. Laboratory investigations were within normal limits and glycated hemoglobin (HbA1c) was 8%.

We discussed further with her regarding the methodology of storing, loading, measuring and injecting insulin. We found that she was always injecting insulin on the ventral aspect of her left forearm. She lived alone in a place where medical facilities were scarce. She was afraid to take insulin on the abdomen as she thought she might go deeper and hurt her intestines. She could find none in her village who could inject insulin. Due to financial constraint and nonavailability, she would not changing the needles frequently.

As she had been injecting insulin subcutaneously at the same site, she developed lipohypertrophy (LH) over her left forearm. Absorption of insulin at the site of LH is erratic, predisposing her to fluctuations in blood sugar. She was given a live demonstration of administration of insulin over various sites in her body and she developed confidence to inject insulin in her abdominal skin. She stopped injecting to her left forearm and the swelling regressed gradually.

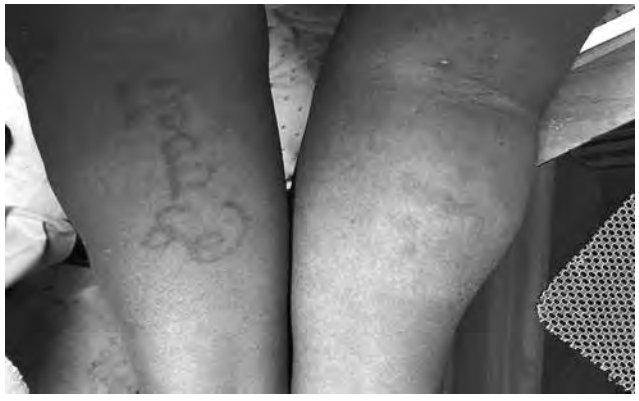

Figure 1. Soft tissue swelling on the ventral aspect of left forearm.

DISCUSSION

Lipohypertrophy (LH) and lipoatrophy (LA) are frequent problems in clinical practice in patients on subcutaneous insulin. LH is a lump under the skin caused by an accumulation of fat at the site of many subcutaneous injections of insulin. As high as 69.8% of patients with type 1 diabetes in India were found to have LH at one time or another during their lifetime, illustrating the frequency of this problem.[1] A systematic review and meta analysis reveal that 38% of the people who take insulin had LH.[2] The incidence of LH has come down drastically with the discovery and utilization of newer insulins, which are less antigenic.

LH can delay the absorption of insulin and jeopardize diabetes control. There were reports in literature where poor absorption of insulin through LH was the culprit of inducing diabetic ketoacidosis.[3]

In contrast, it was reported that erratic absorption may precipitate hypoglycemia. Recurrent hypoglycemia due

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to held up insulin in LH lesion had been reported.[4] In a study of LH in type 1 diabetes, it was found that injection at the same site recurrently is a major factor inducing LH rather than the size of the needle or its reuse.[5] It is very interesting to learn that organized LH interventions with clinical, biological and economical parameters could help to regress LH early and prevent new lesions.[6] Though clinical examination is essential to diagnose LH, an ultrasound examination may give an early clue, especially in those who are markedly obese.[7]

CONCLUSIONS

It is important to educate the patient the need of rotating the site of insulin injection. Healthcare workers should check the injection sites frequently.

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WHO Launches Effort to Eliminate Malaria in 25 More Countries by 2025

WHO congratulates the increasing number of countries that are approaching, and attaining, zero cases of malaria. The agency launched a new initiative that aims to stop the disease transmission in 25 more countries by the year 2025.

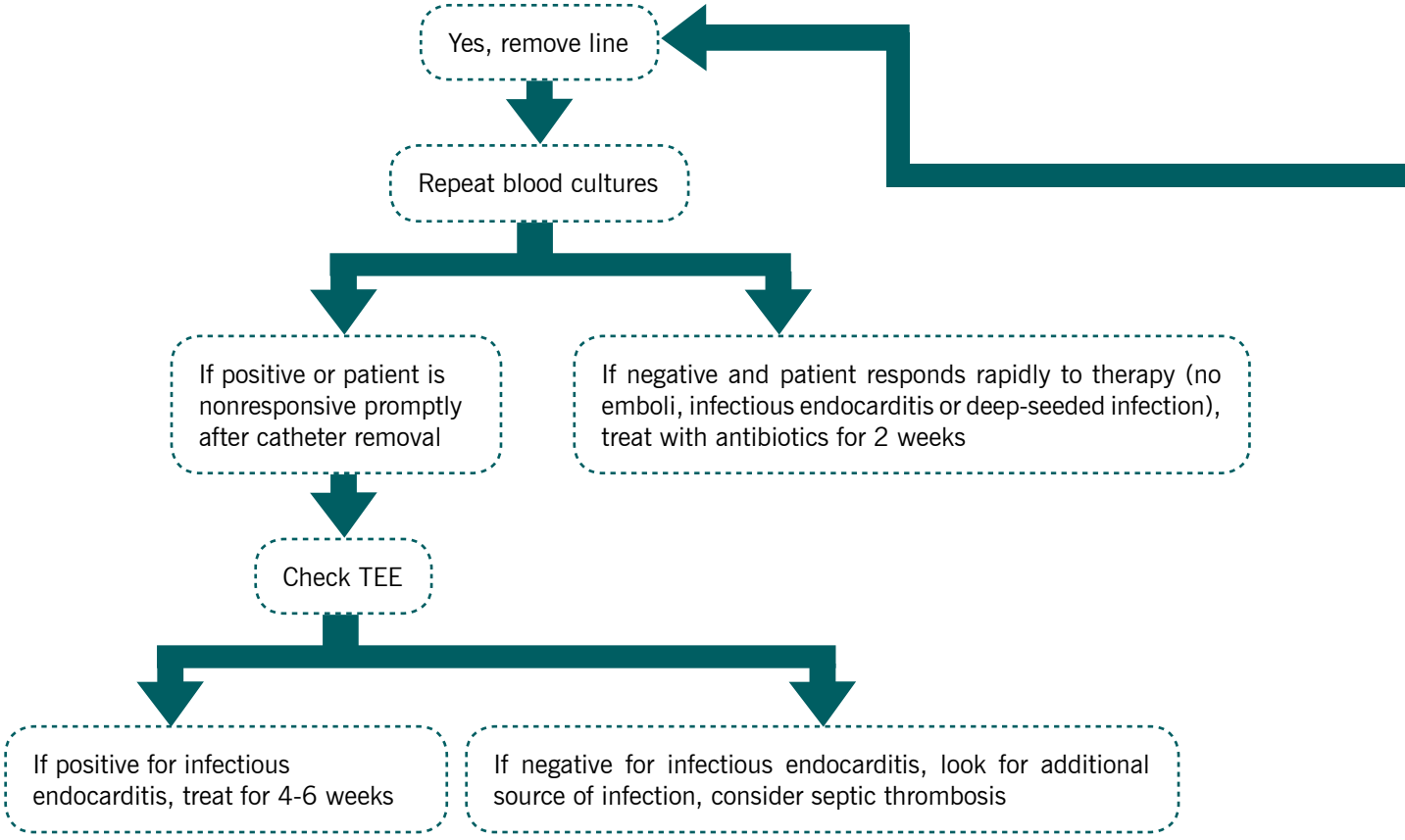
Among the 87 countries with malaria, 46 reported less than 10,000 cases of the disease in 2019 compared to 26 countries in 2000. By the end of last year, 24 countries had reported that they had interrupted malaria transmission for a period of 3 years or more. Eleven of these were certified malaria-free by WHO. The emergence of COVID-19 posed a serious challenge to malaria responses across the globe. The WHO has urged countries to continue maintaining essential health services, including for malaria, and make sure that communities and health workers are protected from COVID-19 transmission… (*WHO*)

Covaxin has 100% Efficacy Against Severe COVID-19 Disease: Phase 3 Interim Analysis

Bharat Biotech has announced second interim results from Phase 3 trials. The company and Indian Council of Medical Research (ICMR) stated that Covaxin showed 78% vaccine efficacy against COVID-19 disease and 100% efficacy against severe disease with an effect on reduction in hospitalizations. The efficacy against asymptomatic COVID-19 infection was 70%, pointing to diminished transmission in recipients of the vaccine.

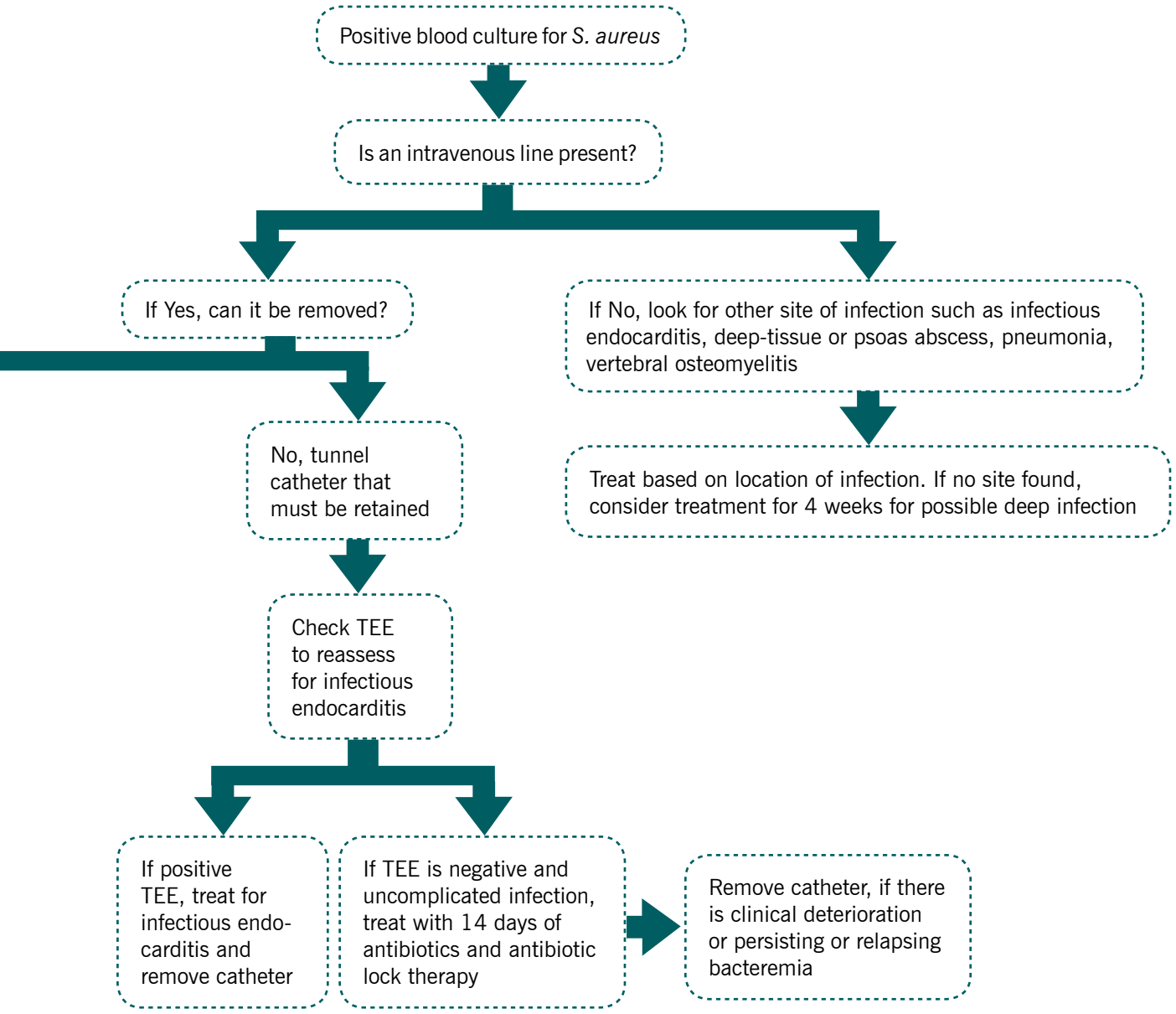
The Phase 3 study had recruited 25,800 participants aged 18 to 98 years, including 10% above the age of 60, and the analysis was conducted 14 days after the second dose. The company revealed that the safety and efficacy results from the final analysis will be available in the month of June, and the final report will be submitted to a peer-reviewed publication… (*ET Healthworld*)

Management of *Staphylococcus aureus* Bacteremia



TEE: Transesophageal echocardiography.

Adapted from Bamberger DM. Management of *Staphylococcus aureus* infections. Am Fam Physician. 2005;72(12):2474-81.


Positive blood culture for *S. aureus*
Is an intravenous line present?
If Yes, can it be removed?
If No, look for other site of infection such as infectious endocarditis, deep-tissue or psoas abscess, pneumonia, vertebral osteomyelitis
No, tunnel catheter that must be retained
Treat based on location of infection. If no site found, consider treatment for 4 weeks for possible deep infection
Check TEE to reassess for infectious endocarditis
If positive TEE, treat for infectious endo-carditis and remove catheter
If TEE is negative and uncomplicated infection, treat with 14 days of antibiotics and antibiotic lock therapy
Remove catheter, if there is clinical deterioration or persisting or relapsing bacteremia

Indian Journal of Clinical Practice, Vol. 31, No. 12, May 2021

An MBBS Doctor Admits a Patient Under Him and a Specialist Visits the Patient 1 or 2 Times. But, the Patient does not Change the File Name or Transfers the Case. Is This Correct or Incorrect?

KK AGGARWAL

Yes, the treatment can be carried on by the MBBS doctor, even if the specialist visits the patient 1 or 2 times. Further, as per the provisions of **Regulation 3.6 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002,** it is the duty of the physician to prepare a case summary of the patient while referring the patient to the specialist and then the specialist should communicate his opinion in writing to the attending physician. The relevant provisions of **Regulation 3.6 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002** are reproduced hereunder:

"Chapter 3: Duties of Physician in Consultation

3.6 Patients referred to specialists: *When a patient is referred to a specialist by the attending physician, a case summary of the patient should be given to the specialist, who should communicate his opinion in writing to the attending physician."*

Further, there are certain responsibilities of the physician towards each other which are enumerated in **Chapter 4 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002,** which are reproduced hereunder:

"Chapter 4: Responsibilities of Physicians to Each Other

4.1 Dependence of physicians on each other: *A physician should consider it as a pleasure and privilege to render gratuitous service to all physicians and their immediate family dependants.*

4.2 Conduct in consultation: *In consultations, no insincerity, rivalry or envy should be indulged in. All due respect should be observed towards the physician in-charge of the case and no statement or remark be made, which would impair the confidence reposed in him. For this purpose no discussion should be carried on in the presence of the patient or his representatives.*

4.3 Consultant not to take charge of the case: *When a physician has been called for consultation, the Consultant should normally not take charge of the case, especially on the solicitation of the patient or friends. The Consultant shall not criticize the referring physician. He/she shall discuss the diagnosis treatment plan with the referring physician.*

4.4 Appointment of substitute: *Whenever a physician requests another physician to attend his patients during his temporary absence from his practice, professional courtesy requires the acceptance of such appointment only when he has the capacity to discharge the additional responsibility along with his/her other duties. The physician acting under such an appointment should give the utmost consideration to the interests and reputation of the absent physician and all such patients should be restored to the care of the latter upon his/her return.*

4.5 Visiting another Physician's case: *When it becomes the duty of a physician occupying an official position to see and report upon an illness or injury, he should communicate to the physician in attendance so as to give him an option of being present. The medical officer/physician occupying an official position should avoid remarks upon the diagnosis or the treatment that has been adopted."*

President, HCFI

Indian Journal of Clinical Practice, Vol. 31, No. 12, May 2021

Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Minutes of Virtual Meeting of CMAAO NMAs on "Will Surge in Cases in India Affect the Neighboring Countries?"

10th April, 2021 (Saturday, 9.30 am-10.30 am)

Participants - Member NMAs: Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer, CMAAO; Dr Angelique Coetzee, President-South African Medical Association; Dr Marthanda Pillai, India, Member-World Medical Council; Dr Marie Uzawa Urabe, Japan Medical Association; Dr Md Jamaluddin Chowdhury, Bangladesh Medical Association; Dr Qaiser Sajjad, Secretary General-Pakistan Medical Association; Dr Akhtar Hussain, South African Medical Association; Dr Tashi Tenzin, Bhutan Medical Association

Invitees: Dr Russell D'Souza, Australia UNESCO Chair in Bioethics; Dr S Sharma, Editor-IJCP Group

Key points from the discussion

- India has crossed the first peak and is experiencing the second wave, which is larger than the first wave. A significantly high number of persons are testing positive for coronavirus disease 2019 (COVID-19) even after full vaccination.
- India has high vaccination rate (more than 3 million vaccines per day) and very high infection rate (more than 8%). India is recording around 1,50,000 new cases every day (as on the date of meeting).
- Israel has controlled infection rate by intensifying vaccination, while in Michigan, the infection rate is still rising despite more than 30% vaccination rate.
- Vaccine failure is inevitable; AstraZeneca vaccine has 70% efficacy, so has 30% failure rate; Pfizer vaccine has 5% failure rate.
- We do not know if the post-vaccine COVID is due to a new strain or is it the wild virus infection.
- The AstraZeneca-Oxford vaccine is effective against the UK variant of the coronavirus; hence, these could be cases of re-infection with the Brazil or South Africa strain, against whom the AstraZeneca vaccine is ineffective.
- More than 100 doctors at four different hospitals have tested positive after taking the vaccine. Majority are mild infections. Could these be a result of a super-spreading event precipitated by the vaccine? We do not know.
- A large number of patients are presenting with classical symptoms of COVID but negative reverse transcription polymerase chain reaction (RT-PCR); but this could be due to the redefining of Ct cut-off threshold from 40 to 35 or E-gene target failure. In children, the viral load is low, hence may be false negative.
- It is unlikely that the vaccine is causing disease enhancement.
- Could inadequate antibodies (non/partially neutralizing) be the answer? Systemic inflammation is seen without pulmonary involvement. No COVID pneumonia in most patients.
- The question arises if vaccine should be given to post-COVID patients.
- Mutations occur with high virus transmission and high infection rate.
- In India, although a large number of people are vaccinated, the percentage of people vaccinated is not very high. The herd immunity is not yet achieved. In the state of Punjab, 80% cases are of UK variant. We do not know if the double mutant identified in India causes super-spreading events.
- COVID precautions are still very important after the vaccine. This message needs to be re-emphasized.
- It remains to be seen if the surge in cases in India will affect the neighboring countries.
- South Africa is using the Johnson & Johnson (J&J) vaccine. So far, 3,00,000 doctors and healthcare workers have been immunized. People have been informed that the immunity starts only after 28 days of the vaccine, so there is still a risk of getting COVID-19.
- These clusters of infection show that a person can still spread the infection even after the vaccine. If no antibodies were developed after taking the vaccine,

one can become a super-spreader. Two doses may not be adequate. The genetic variant needs to be studied. Genomic testing is very important.

- Anecdotal cases cannot be dismissed and need to be considered seriously.
- Clotting is a real "preventable" event. If after the fourth day of the vaccine, there is more than 30% fall in platelets and rise in D-dimer, immediately start anticoagulant (rivaroxaban).
- In Hong Kong, community cases are zero to single digit.

Minutes of Virtual Meeting of CMAAO NMAs on "Anecdotal Examples of Various Post-Vaccine Side Effects"

3rd April, 2021 (Saturday 9.30 am-10.30 am)

Participants - Member NMAs: Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer, CMAAO; Dr Angelique Coetzee, President-South African Medical Association; Dr Ravi Naidu, Malaysia Immediate Past President-CMAAO; Dr Marthanda Pillai, India, Member-World Medical Council; Prof Ashraf Nizami, President-Pakistan Medical Association; Dr Marie Uzawa Urabe, Japan Medical Association; Dr Md Jamaluddin Chowdhury, Bangladesh Medical Association; Dr Qaiser Sajjad, Secretary General-Pakistan Medical Association; Dr Akhtar Husain, South African Medical Association; Dr Prakash Budhakoty, Nepal Medical Association; Dr Tashi Tenzin, Bhutan Medical Association

Invitees: Dr Russell D'Souza, Australia UNESCO Chair in Bioethics; Dr S Sharma, Editor-IJCP Group

Key points from the discussion

- CMAAO Mantra: "In susceptible high-risk (pro-inflammatory and/or pro-coagulative) individuals, reactogenic vaccines can trigger transient thrombo-inflammation lasting first few (up to 4) days.
- Norway was first to report, in mid-January, 33 deaths short time after COVID vaccine (Pfizer-BioNTech mRNA vaccine). All of them were elderly (≥75 years) and frail individuals. UK's Medicines and Healthcare Products Regulatory Agency reported 227 deaths shortly after Pfizer vaccine and 275 deaths after AstraZeneca vaccine, through February 28. The Paul Ehrlich Institute in Germany reported deaths of 7 elderly people shortly after receiving the Pfizer vaccine. The US, which has three vaccines (Pfizer + Moderna + J&J), reported 1,637 deaths till March 8. All deaths were in comorbid patients, either evident or silent.
- Deaths will occur after a vaccine; trends should be analyzed.
- Twelve European countries and Thailand temporarily put their vaccine campaign with AstraZeneca vaccine on hold and later stated that the benefits were more than the risks. Every patient must be evaluated and decision should be taken on a case-to-case basis.
- Austria was the first country to report coagulation disorders (venous thromboembolism).
- Thirty-nine deaths out of 71 deaths reported in India (till 13th March) were related to cardiovascular disease.
- Three patterns have been observed: Venous thrombosis presenting as pulmonary embolism, arterial thrombosis presenting as sudden cardiac event and frail people, who die suddenly after the vaccine.
- COVID-19 is an acute manageable immunogenic thrombogenic inflammatory contagious novel viral disease causing a pandemic.
- The COVID-19 vaccine is an acute thrombo-inflammatory nonreplicative noncontagious viral protein. Like the natural infection, vaccines too may cause inflammation, thrombosis and immune reactions. However, unlike the vaccine, the natural viral protein will not cause allergy (anaphylaxis). The vaccine will cause allergic reactions.
- The natural virus is unpredictable and is longer lasting, while the vaccine is predictable and the effect lasts for short time (up to 4 days).
- Whole virus killed virus is used in Sinopharm vaccine and Covaxin. The S-gene has been used is Moderna and Pfizer vaccines. AstraZeneca and Sputnik vaccine have converted S-gene into DNA.
- AstraZeneca vaccine is a viral vector vaccine and has used chimp adenovirus, which enters the cell, but does not replicate. The Sputnik vaccine has used two adenovirus vectors (5 and 26), while the J&J vaccine has used adenovirus 26.
- The AstraZeneca vaccine is showing more reactogenicity versus other vaccines as double reactions are occurring in the body. The adenovirus also provokes the immune system by switching off the cell's alarm response.
- Anaphylaxis occurs within 15-30 minutes of the vaccine.

- Allergy is caused by a protein (PEG or polysorbate 80). Serious allergic reactions occur one in a million. Their incidence is very low in India.
- Non-IgE–mediated (complement-mediated) reactions may occur after 6 hours: angioneurotic edema, rash, urticaria; not fatal and can be prevented by montelukast + levocetirizine.
- Local injection site BCG like reactions (type 4 reaction) may occur between 2nd and 4th day, which usually fade after the 6th day. Such reactions may occur even remotely. No scar develops.
- Delayed local injection-site reactions to vaccine may occur, though they are uncommon (T-cell–mediated reactions) (*NEJM*).
- Other reactions observed include aphthous ulcers, petechial rash, ear eczema, painful lymphadenitis (axillary), episcleritis, recurrent urticaria, seizures, neurological pain, tremors, spinal pain, transient ischemic attack, transient blurring of vision. All recovered.
- Delayed allergic reactions, unrelated to type 4 hypersensitivity reactions, may occur.
- The virus can precipitate underlying inflammation: rheumatoid arthritis, adult chickenpox and herpes zoster.
- A case of death due to rupture of abdominal aortic aneurysm 10 days after receiving a COVID-19 vaccine has been reported in Thailand.
- Post-vaccine loss of smell and taste in a person who developed loss of smell and taste post-COVID also.
- Sympathetic overactivity can manifest as accelerated hypertension and transient atrial fibrillation.
- Transient hyperglycemia after the vaccine has been reported.
- Vaccine-induced thrombocytopenia with superficial clots has been reported; purpuric rash; conditions that cause thrombocytopenia include disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, heparin-induced thrombocytopenia. Such patients need rivaroxaban and not heparin. Therefore, check platelets after the 4th day. If platelets start decreasing after Day 4, immediately start rivaroxaban.
- A case of posterior tibial artery thrombosis after the vaccine has been reported.
- Post-COVID, post-vaccine systemic inflammation with normal pulmonary function (no pneumonia on high-resolution computed tomography [HRCT] chest) may occur manifesting as rising C-reactive protein (CRP) and high fever.
- Inflammation can be prevented: Prevent Th17 response by preloading with vitamin D; if routine inflammation with raised CRP, preload with colchicine; if very high low-density lipoprotein (LDL), preload with statin; if cardiac manifestations, preload with doxycycline; in high risk patients, preload with aspirin.
- In Bangladesh, the number of cases and deaths are a cause of concern.
- The UK variant will become the predominant wild virus strain globally.
- The reinfection (clinical) rate is 4.5% in India. In the West, it is less than 1%.
- Thirty percent vaccine failure with AstraZeneca/Covishield has been reported; 40% with Sinopharm vaccine and 5% with Pfizer/Moderna vaccines.
- If corona infection occurs within 14 days of the vaccine, it is considered as primary infection with similar mortality. If the infection occurs after 14 days of the vaccine, it is considered as breakthrough infection; no mortality has been reported.
- In Hong Kong, 14 deaths have been reported after receiving the vaccine. These deaths have been described as incidental unrelated to the vaccine, but could be triggered by the vaccine. All deaths were related to thromboembolic events (strokes, heart attacks).
- Bhutan had 2 deaths after 4-5 days of Covishield vaccine; one 44-year-old due to alcohol withdrawal causing seizure and sustained severe bleeding in brain; the other one above 80-year-old man with severe bronchial asthma. But these were not declared as due to vaccine.
- South Africa is administering the single dose J&J vaccine. More than 2,00,000 healthcare workers have received the vaccine so far, although vaccination is continuing at a slower pace. Eighteen side effects have been reported; there has been one case of anaphylactic shock, which resolved. Now persons older than 65 years with comorbidities are being enrolled for the vaccine after 1-2 weeks. Spread of the infection after the Easter holiday is anticipated.
- Pakistan is using the Sinopharm vaccine; the country has procured Sputnik vaccine, but is used by the private sector. Vaccination is slow. Pakistan also has the single dose Cansino vaccine. No complications have been reported.

- Singapore has administered 1.3 million vaccinations; 3,75,000 have received two doses.

FDA Authorizes Moderna to Add More Vaccine Doses into Vials

The US Food and Drug Administration (FDA) has authorized Moderna to add more vaccine doses into its COVID-19 vaccine vials, with the range now being between 11 and 15 doses that can be extracted. The FDA cleared new vials from Moderna that can contain up to 15 doses. The agency further stated that the presently used 10-dose vials can safely extract up to 11 doses. The move may further increase vaccine supply in US in the weeks to come and could also hasten Moderna's delivery timeline, as per *The New York Times*. The company intends to deliver 200 million doses by the end of May and 300 million by the end of July. (*WebMD*)

Three COVID-19 Phenotypes of Patients Who Present to Emergency Room

Investigators have described three COVID-19 phenotypes of patients who present to the ER in an article published online in *PLoS One*.

- Researchers looked into the electronic health records from 14 hospitals in the midwestern United States and from 60 primary care clinics in Minnesota. Data were obtained for 7,538 patients with confirmed COVID-19 from March 7 through August 25, 2020. Of these, about 14% (1,022) required hospitalization and were included in the study. Data were obtained on comorbidities, medications, lab results, clinic visits, hospital admission information and patient demographics.
- Most patients (n = 613 or 60%) in the study presented to emergency rooms with "phenotype II".
- Patients presenting with phenotype II less frequently had a history of hepatic disease compared to those with phenotype I or III. They had more moderate disease and nearly 10% mortality.
- A total of 236 patients (23%) had "phenotype I", or the "adverse phenotype". This was tied to the worst outcomes. These patients appeared to have the most hematologic, renal and cardiac comorbidities ($p < 0.001$). These patients were more likely to be non-White (38.8% vs. 45.6% vs. 60.7%, respectively, $p = 0.002$) and non-English speakers (47.9% vs. 39.2% vs. 23.7%, respectively, $p < 0.001$).
- Phenotype I patients were older than patients in phenotypes II and III (67.2 [52.9, 79.0] years vs. 60.9 [45.9, 75.4] years and 58.6 [34.8, 71.3] years, respectively, $p < 0.001$).
- "Phenotype III", or the favorable phenotype, formed the smallest group, with 173 patients (16.9%); they had the best outcomes. Those in phenotype III had the highest rate of respiratory comorbidities ($p = 0.002$) despite lowest complication and mortality rates. They had higher odds of having had a history of smoking, alcohol abuse and neutropenia.
- Most patients with chronic lung diseases were on inhalers and this finding might suggest that inhalers are more protective.
- Phenotype III patients had a 10% greater risk of hospital readmission compared to the other two phenotypes.
- Phenotype III patients were also more often female compared to patients with phenotype I or II (57.6% vs. 41.6% and 53.4%, respectively, $p = 0.002$).
- Phenotypes I and II were associated with 7.3-fold and 2.57-fold increases, respectively, in hazard of death compared with phenotype III. (*Medscape*)

Weak Antibody Response Following First Dose of mRNA COVID-19 Vaccine in Kidney Transplant Recipients

- The burden of immunosuppression may induce a weak antibody response in kidney transplant recipients following first dose of an mRNA vaccine, noted a study published in *Kidney International*.
- International recommendations on COVID-19 vaccine distribution prioritize immunocompromised patients, including kidney transplant recipients. However, the guidance was issued without inclusion of this population in vaccine clinical trials.
- In the study, 242 kidney transplant recipients who had received the first dose of the Moderna vaccine from January 21 through January 28, 2021, were included. None of them had a history of COVID-19 diagnosis and tested negative for anti-SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) antibodies on the day they were given the first dose of vaccine. Twenty-eight days after the first dose, the antibody response against the spike protein was evaluated, with titers >50 arbitrary units per mL (AU/mL) considered as a positive serology.
- One kidney transplant recipient developed mild symptomatic COVID-19, seven days after the first dose and 26 (10.7%) kidney transplant recipients had a positive serology at 28 days after the dose.

- The median immunoglobulin (Ig)G titer was 224 AU/mL (interquartile range 76-496 AU/mL) in seropositive kidney transplant recipients, whereas the median IgG titer in the seronegative patients was <6.8 AU/mL.
- Seroconverted patients had longer time from transplantation (median, 15.4 vs. 5.8 years; $p < 0.001$), had lesser odds of having received induction treatment ($p < 0.001$), were less likely to have received steroids (34.6% vs. 61.9%, $p = 0.01$) and had lower level of serum creatinine (median, 104 vs. 120 μmol/L; $p = 0.05$).
- This finding appears to be different from the immunocompetent individuals, who seroconverted after the first injection.
- The study emphasizes on the need to not delay the second vaccine dose in immunocompromised patients.
- Close surveillance must be considered to discuss the opportunity of a third dose in less responsive patients. (*DG Alerts*)

Vaccine in Young People

The University of Oxford has halted the administration of COVID-19 vaccine that they have developed with AstraZeneca, in a small UK study to test it in children and teenagers, until more information is available about rare blood clot issues in adults who have received it.

The pediatric trial being done by Oxford was started in mid-February to test the vaccine in over 200 individuals aged 6 to 17 years. No safety issues have been observed in the trial itself. However, concerns about rare clotting events in adults have prompted regulatory reviews in the UK and Europe to look into any potential link with the vaccine.

This halt comes as a setback for the Oxford-AstraZeneca vaccine, which has been questioned about its efficacy and potential side effects even as millions of doses have been administered following safety issues in over 70 countries.

The European Medicines Agency (EMA) has again stated that the AstraZeneca COVID-19 vaccine is safe and effective and the benefits in protecting against COVID-19 outweigh any possible risk. However, it says that a link between rare cases of thrombosis with thrombocytopenia and the vaccine cannot be ruled out.

The EMA announcement emphasizing the safety of the vaccine came at a press conference which, confusingly, took place at the same time when a UK press conference was held at which it was recommended that the AstraZeneca vaccine should not be used in those below 30 years of age if an alternative vaccine was available.

Speaking at the EMA press conference on April 7, Emer Cooke, Executive Director at the EMA, stated that their review suggested that the AstraZeneca vaccine was not associated with any increased risk of overall thromboembolic events or blood clots, but a small number of very rare but serious clotting disorders have been noted, which led to a more focused review.

The EMA advises that patients should seek medical care if they develop any of the following symptoms: shortness of breath; chest pain; swelling in leg; persistent abdominal pain; neurological symptoms, including severe and persistent headaches or blurred vision; or tiny blood spots under the skin other than the site of injection. There have been some very rare cases of unusual events of thrombosis and thrombocytopenia and bleeding.

In some cases, tiny clots develop in several blood vessels during the initial 7-14 days following vaccination. This is termed as DIC. In some other cases, clots have developed in blood vessels that drain blood from the brain (cerebral venous sinus thrombosis [CVST]). These conditions are tied to low platelet count.

At the EMA press conference, Sabine Straus, MD, Chair of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), stressed that as of April 6, seven cases of DIC and 18 cases of CVST had been reported from among the 20 million people who had received the AstraZeneca vaccine.

Of the CVST cases, 7 were reported from Germany, 3 from Italy, 2 from Norway, 1 from Spain, 3 from the UK and 2 from India.

Meanwhile, at the UK press conference, it was reported that there had been 79 reports of blood clotting cases with low platelets from the UK following the use of the AstraZeneca vaccine; 44 of these were categorized as CVST with thrombocytopenia.

Anthony Harnden, deputy chair of the UK's Joint Committee on Vaccination and Immunization (JCVI), said that if someone has received a first dose of the AstraZeneca vaccine, they should be given the second dose. He further stated that they have not seen any case of thrombosis with thrombocytopenia after the second dose thus far, but agreed that they haven't administered as many second doses yet. He recommend against mixing vaccines at present.

(*The Washington Post; Medscape*)

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News and Views

Link Between AstraZeneca COVID-19 Vaccine, Rare Blood Clots Plausible, Says WHO Committee

The World Health Organization (WHO) Global Advisory Committee on Vaccine Safety's (GACVS) coronavirus disease 2019 (COVID-19) subcommittee has looked into the reports of rare cases of blood clots with low platelet counts after vaccination with the AstraZeneca jab.

During a meeting held on April 7, 2021, the subcommittee reviewed the information from the European Medicines Agency (EMA) as well as from the UK's Medicines and other Health products Regulatory Agency (MHRA), and other Member States. The subcommittee noted that on the basis of latest information, a causal link between the vaccine and blood clots with low platelet counts seems plausible but is not confirmed. It stated that specialized studies are required to completely understand the relationship between the vaccine and possible risk factors. Though concerning, the events are very rare, with low numbers reported among around 200 million vaccinations with the AstraZeneca vaccine worldwide… (*WHO*)

COVID-19 Surge in India Hitting Children Hard

The second wave of COVID-19 is impacting younger individuals and children, unlike the first wave when the elderly and those with comorbidities were most vulnerable.

In Maharashtra, 60,684 children were infected from March 1 through April 4. Among these, 9,882 were below 5 years of age. In Chhattisgarh, 5,940 children were infected, with 922 of them being under five. In Karnataka, 7,327 children had contracted the infection and 871 among these were below 5 years of age. The corresponding numbers in Uttar Pradesh were 3,004 and 471. Delhi recorded 2,733 infections among children, with 441 of them being less than 5 years old.

Public health experts suggest that weaker immunity in children and a lack of COVID-appropriate behavior are to be blamed… (*NDTV*)

Patients Allergic to COVID-19 Vaccine Given Second Dose with Graded Dosing

A graded dosing protocol enabled 2 patients with hypersensitivity reactions to the first dose of Moderna COVID-19 vaccine to safely receive the second vaccine doses, stated researchers.

One of the patients had an immediate hypersensitivity reaction and was managed on site while the other required emergency department transport. Both the individuals were given divided second doses, reported researchers in *Annals of Internal Medicine*.

Three to four weeks following the second dose, both patients had immunoglobulin G (IgG) antibodies against the spike protein, thus indicating that vaccination was effective with the graded dosing protocol as well. One of them had no reaction to the second dose while the other one developed some nonserious allergic symptoms… (*Medpage Today*)

India to Review Vaccines Following Blood Clot Warning

A panel of experts is looking into any cases of blood clotting in India, even mild cases, occurring as a side effect of the two COVID-19 vaccines being administered in the country, reported Mint.

Currently AstraZeneca COVID-19 vaccine, manufactured by the Serum Institute, branded as Covishield and Bharat Biotech's COVAXIN are being administered in the country. The review is being done following European drug regulator's statement of a possible link between AstraZeneca's vaccine and rare blood clotting events in adults who had been administered the shot. However, the regulator added that the vaccine's benefits still outweighed the risks. (*Reuters*)

UK Offers Alternative to Oxford-AstraZeneca Vaccine for Those Below 30

People below 30 years of age in the UK will be offered an alternative COVID-19 vaccine to the AstraZeneca shot on account of evidence linking it to rare blood clots.

The recommendation comes after the UK drugs regulator found in a review that by the end of March, 79 individuals had developed rare blood clots following vaccination. Nineteen of them had died. The MHRA's review revealed that 79 cases and 19 deaths occurred after 20 million administered doses of the vaccine, translating to a risk of about four in a million of developing a blood clot, and one in a million of death. About two-thirds of the cases were in women, and the people who died were 18 to 79 years of age, with three of them below 30… (*BBC*)

Johnson & Johnson to Start Vaccine Trial in India

Johnson & Johnson has informed Indian regulators that it soon intends to start clinical trials of its single-dose COVID-19 vaccine in the country.

The company sent a letter to India's Central Drugs Standard Control Organisation (CDSCO) stating that it would soon apply for permission to carry out clinical bridging trials in India, according to a report.

The report comes at a time when many vaccination centers in India are tackling a shortage of vaccine supplies and the country fights a second wave of COVID-19 infections. While the country presently has two vaccines in use, one developed by Oxford University and AstraZeneca and the other from Bharat Biotech, other vaccine candidates are undergoing trials in the country, including a vaccine developed by Cadila Healthcare Ltd… (*ET Healthworld – Reuters*)

Study Identifies Common Lingering Symptoms After Mild COVID-19

According to a new study, loss of smell, loss of taste, dyspnea and fatigue appear to be the most common symptoms reported by healthcare professionals in Sweden 8 months after mild COVID-19 illness.

About 1 in 10 HCWs experience one or more moderate-to-severe symptoms that have a negative impact on their quality of life, revealed the study. The Research Letter published online in *JAMA* noted that there was no increased risk for long-term symptoms following asymptomatic infection. For the study, researchers compared symptom reporting of 323 hospital employees who had mild COVID-19 at least 8 months earlier with 1,072 employees who did not have COVID-19. About 26% of the study participants who had COVID-19 previously had at least one moderate-to-severe symptom lasting for over 2 months, compared to 9% in the control group… (*Medscape*)

Risk of Contracting COVID-19 from Surfaces Low: CDC

The US Centers for Disease Control and Prevention (CDC) has updated its guidelines on cleaning and disinfecting household surfaces and stated that the risk of contracting coronavirus by touching a contaminated surface or object is low.

According to the agency, the chance of contracting the virus from surfaces is less than 1-in-10,000. The latest update could possibly end routine deep cleaning of hotel rooms, offices, schools, restaurants and public transport for preventing the spread of COVID-19. The agency said that though it is possible to contract the infection through surface contact, research suggests that the risk is low as surface transmission is not the main route of spread of SARS-CoV-2… (*The Indian Express*)

Vaccinating Adults Seems to Protect Children Around Them

Latest data from Israel suggests that vaccinating adults against COVID-19 also tends to protect unvaccinated people living around them.

Around a third of Maccabi Healthcare Services' (MHS) 1.95 million members, all aged above 16 years, had received at least one vaccine dose by January 30. Looking at outcomes in 223 communities, researchers noted that as the number of vaccinated adults increased, infection rates among unvaccinated MHS members in the same community declined, especially among children. The researchers concluded that the vaccine-associated protection of unvaccinated individuals appears promising, but further studies are needed to better understand whether and how it might have a role in herd immunity… (*HT – Reuters*)

Vaginal Gel Promising in Preventing Common STIs

An investigational vaginal gel was found to significantly decrease urogenital chlamydia and gonorrhea in women at high risk for infection, in comparison with placebo, in a randomized trial published in the *American Journal of Obstetrics and Gynecology*.

EVO100, an investigational antimicrobial, bioadhesive vaginal gel, contains L-lactic acid, citric acid and potassium bitartrate. Investigators assessed the efficacy and safety of this gel in the AMPREVENCE study in the prevention of chlamydia and gonorrhea. EVO100 led to a significant reduction in sexually transmitted infection (STI) incidence for both types of STIs. *Chlamydia trachomatis* infection rate among EVO100 users was 4.8% compared to 9.7% in placebo users. In the *Neisseria gonorrhoeae*-analysis–eligible women, infection rates were 0.7%, compared to 3.2% in the placebo group… (*Medscape*)

Benefits of Continuing HIV Services Outweigh Risk of COVID Transmission

UNAIDS and WHO have backed mathematical modeling to determine the benefits of continuing to provide human immunodeficiency virus (HIV) services compared to the harm of additional COVID-19 transmission. According to the analysis, continuing HIV services would prevent 19 to 146 acquired

immune deficiency syndrome (AIDS)-related deaths per 10,000 individuals over a 50-year time period, while the added COVID-19-related deaths on account of exposures related to HIV services would be around 0.002-0.15/10,000.

The analysis thus suggests that the benefits of continuing HIV services during the COVID-19 pandemic outweigh the risk of additional COVID-19-related deaths.

The analysis evaluated disruptions to four vital HIV services - voluntary medical male circumcision, HIV diagnostic testing, viral load testing and programs to prevent mother-to-child transmission of HIV. The analysis compared COVID-19 deaths in 2020 and 2021 among health workers and clients on account of continuing with the HIV services with averted AIDS-related deaths now and over the next 50 years due to continuation of services… (*WHO*)

WHO and Partners Urge to Halt Sale of Wild Mammals at Food Markets

The WHO and its partners have urged countries to halt the sales of live wild mammals in food markets, also called "wet markets", in order to prevent new deadly diseases, such as COVID-19.

The interim guidance was published recently which aims to decrease public health risks associated with these transactions considering that most emerging infectious diseases have their origins in wildlife. The temporary guidelines, issued by WHO, with the World Organization for Animal Health (OIE) and the UN Environment Programme (UNEP), stated that animals, in particular wild animals, account for over 70% of all emerging infectious diseases in humans, several of which are caused by novel viruses. Wild mammals sold in markets pose risk since it cannot be checked if they carry dangerous viruses… (*UN*)

WHO Global Compact to Expedite Action to Tackle Diabetes

The WHO has launched a new Global Diabetes Compact that aims to boost efforts towards prevention of diabetes and making treatment available for all those who need it.

The Compact was launched at the Global Diabetes Summit, co-hosted by WHO and the Government of Canada, and supported by the University of Toronto. Among the most urgent priorities is to improve access to diabetes diagnostic tools and medicines, especially insulin, in low- and middle-income countries. The Compact also focuses on catalyzing progress by setting global coverage targets. A "global price tag" will appraise the costs and benefits of meeting new targets for diabetes care across the globe. The Compact will also encourage governments to fulfill the commitments they made to include diabetes prevention and treatment into primary healthcare and universal health coverage packages… (*WHO*)

Brazil's P1 Variant Mutating, may become More Dangerous, Says Study

Brazil's P1 coronavirus variant is mutating in ways which could possibly make it able to evade antibodies even better, suggest scientists.

Research into the variants circulating in Brazil has revealed mutations in the spike region of the virus. Scientists stated that these changes could make the virus more resistant to vaccines, which target the spike protein. This will have grave implications. According to Felipe Naveca, one of the study authors, this appears to be another escape mechanism that the virus is creating to evade the response of antibodies. Naveca added that the changes look similar to the mutations noted in the more aggressive South African variant, against which certain vaccines have been shown to have diminished efficacy… (*Reuters*)

EU Commission not to Renew AstraZeneca and Johnson & Johnson Vaccine Contracts at Expiry

The EU Commission has made a decision not to renew COVID-19 vaccine contracts in the coming year with AstraZeneca and J&J, reported Italian daily La Stampa, citing an Italian health ministry source. It stated that the European Commission, in agreement with the leaders of several EU countries, decided that it would not renew the contracts with the companies that produce viral vector vaccines, valid for the current year, at expiry. It added that the focus would be on COVID-19 vaccines using messenger RNA technology, such as Pfizer and Moderna vaccines. An EU Commission spokesman said that all options were being kept open in order to be prepared for the next stages of the pandemic… (*ET Healthworld – Reuters*)

Shortage of Innovative Antibiotics Across the Globe Fuels Drug-resistance

The world continues to fail to develop the much needed antibacterial drugs despite increasing awareness about the threat of antibiotic resistance, stated a report by the WHO. The WHO has noted that none of the 43 antibiotics that are under clinical development at

present sufficiently attend to the issue of drug resistance in the world's most dangerous bacteria. According to Dr Hanan Balkhy, WHO Assistant Director General on antimicrobial resistance (AMR), the continuous failure to develop, manufacture and distribute potent new antibiotics is strengthening the impact of AMR and puts our potential to successfully treat bacterial infections in jeopardy. Almost all the new antibiotics that have been introduced into the market over the recent decades are variations of drug classes that had been discovered by 1980s… (*WHO*)

Haffkine Institute to Produce Covaxin

The Central government has allowed Maharashtra government to produce Bharat Biotech's Covaxin at the Haffkine Institute in Mumbai, Maharashtra.

The State government had sought the Central government's approval in getting Haffkine have a deal with Bharat Biotech to produce Covaxin under some arrangement. The state Chief Minister's office in a press note issued stated that Ren Swarup, Secretary of the Government of India, heading the Dept. of Biotechnology (DBT) in the Ministry of Science and Technology, has granted permission to the state to produce the vaccine for 1 year. Chief Secretary Sitaram Kunte has been asked by the Chief Minister to appoint an official so that Haffkine could follow the appropriate process and start production of the vaccine with immediate effect… (*ET Healthworld*)

Rare Blood Clot Risk Higher from COVID-19 Than Vaccine: Study

A University of Oxford study published recently has revealed that the risk of rare blood clots following the COVID-19 infection is nearly 100-fold higher than normal, and several-fold higher than it is following vaccination or following influenza.

According to the research, the rare blood clotting, called cerebral venous thrombosis (CVT), was more commonly seen after COVID-19 infection, than in any of the comparison groups, with 30% of these cases observed in those below 30 years of age. In comparison with the COVID-19 vaccines being administered at present, this risk is 8-10 times higher, and compared to the baseline, nearly 100 times higher reported the study. The study authors thus concluded that COVID-19 heightens the risk of CVT to a considerable extent. Additionally, the COVID-19 risk is higher than that seen with the current vaccines… (*NDTV – PTI*)

Blocking Middle Airline Seats could Decrease COVID-19 Spread: CDC

As Americans have started traveling and airlines have started filling their planes to capacity, the CDC suggests that blocking the middle seats on commercial airliners could potentially decrease COVID-19 transmission by 23-57%.

Investigators assessed laboratory models of single-aisle and double-aisle aircraft with aerosol dispersion used as a surrogate for coronavirus. The risk reduction was found to be 23% for a single passenger sitting in the same row and two seats away from an infected person, rather than in an adjacent seat. Additionally, there was a 57% risk reduction when the middle seat was left vacant in a three-row section that had a combination of infected and non-infected passengers. The findings are reported in the CDC's *Morbidity and Mortality Weekly Report*… (*Medscape*)

FDA Revokes Emergency Use Authorization for Bamlanivimab

The US FDA has dismissed the EUA that allowed the use of investigational monoclonal antibody therapy bamlanivimab, when administered alone, for the treatment of mild-to-moderate COVID-19 in adults and some pediatric patients.

On the basis of evaluation of emerging scientific data, particularly the sustained increase in SARS-CoV-2 variants resistant to bamlanivimab alone, leading to a heightened risk for failure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) treatment, the agency has concluded that the known and potential benefits of bamlanivimab, given alone, do not appear to outweigh the known and potential risks for its authorized use. According to the FDA, the criteria for issuance of an authorization are no longer fulfilled and the agency has thus revoked the EUA… (*FDA*)

Scientists at Johnson & Johnson Counter Idea That COVID-19 Vaccine's Design Tied to Clots

Johnson & Johnson scientists have countered an affirmation in a medical journal that the design of their vaccine against COVID-19, which is similar to AstraZeneca's, may explain why both the vaccines have been tied to very rare brain blood clots in some of the individuals who have received the vaccines.

While the US FDA is examining this design used in both the vaccines to ascertain if it accounts for the risk, J&J scientists, in a letter in the *New England Journal of Medicine*, opposed a case report published by Kate Lynn-

Muir and colleagues at the University of Nebraska, alleging that the rare blood clots could be associated with adenoviral vector vaccines… (*Reuters*)

Blood Type not a Risk Factor for COVID-19 in US

According to a new study, blood type does not appear to affect susceptibility to COVID-19 in the United States.

Investigators looked at data on around 1,08,000 people from Utah, Idaho and Nevada tested for COVID-19, whose blood type was mentioned in their medical records. None of the blood types, be it A, B, AB or O, was tied to their risk of getting infected, need for hospital admission or intensive care, reported the study published in *JAMA Network Open*. Smaller studies from China, Italy and Spain have shown a link between type A blood and higher COVID-19 risks and type O blood and lower risks. A large study from Denmark also linked blood type to COVID-19 severity.

However, studies from New York and Boston, like the new study, did not detect any such associations. According to study coauthor Dr Jeffrey Anderson of the Intermountain Healthcare Heart Institute in Salt Lake City, the effects of blood type may differ across populations… (*Reuters*)

More Exercise Tied to Lower Chance of Severe COVID-19

Individuals who exercised regularly and then tested positive for COVID-19 had lesser odds of experiencing more severe COVID-19 outcomes, reported a new study.

Even those who could not exercise 150 minutes or more in a week still had significant benefits in comparison with people who reported exercising 10 minutes or less. In comparison with the most active people in the study, those exercising 150 minutes or more a week, patients with COVID-19 who were consistently inactive had a 226% greater likelihood of being hospitalized, 173% greater odds of an intensive care unit (ICU) admission and 149% greater odds of death. The findings were published online in the *British Journal of Sports Medicine*… (*Medscape*)

PTSD Tied to Ischemic Heart Disease

A study that employed data from Veterans Health Administration (VHA) electronic medical records has suggested that there appears to be a significant association between post-traumatic stress disorder (PTSD) among female veterans and an elevated risk for incident ischemic heart disease (IHD). The heightened risk for IHD was found to be the highest among women below 40 with PTSD, and among racial and ethnic minorities.

Among the 9,940 women who had incident IHD during follow-up, 5,559 did not have PTSD while 4,381 had PTSD. PTSD was shown to be significantly tied to an increased risk for IHD. Over a median follow-up of 4.9 years, female veterans with PTSD appeared to have a 44% higher rate of developing incident IHD compared to those without PTSD (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.38-1.50). The findings are published online in *JAMA Cardiology*… (*Medscape*)

AstraZeneca Vaccine Against South African Variant could be Ready by End-2021

A modified version of the AstraZeneca COVID-19 vaccine adapted to fight a coronavirus variant first identified in South Africa could be ready by the end of this year, stated an AstraZeneca official in Austria in an interview.

AstraZeneca's Austria country manager, Sarah Walters, told a newspaper that evidence suggesting that the current AstraZeneca vaccine was less effective against the more contagious variant first detected in South Africa were too small to reach any final conclusions. Walters added that AstraZeneca and Oxford University are working on modifications to the vaccine for the South African variant and the vaccine is expected to be ready by the end of 2021… (*NDTV – Reuters*)

Israel Revokes Public Mask Mandate, Opens Schools

Israel has revoked a public mask mandate and has fully reopened its education system as it continues to ease coronavirus restrictions following the mass vaccination drive in the country. All primary and secondary school grades went back to classrooms on April 18. Health officials also lifted a requirement to wear a mask in public spaces which was in place since 1 year. However, masks are still required indoors and in large gatherings.

The country has rapidly vaccinated a vast majority of its population against COVID-19. Most of the coronavirus restrictions have been lifted in the country now and it also announced that it would be reopening the country to vaccinated foreign tourists beginning in May… (*The Hindu – AP*)

■■■■

Indian Journal of Clinical Practice, Vol. 31, No. 12, May 2021

Spiritual Prescription: The Role of Prayer in Healing

KK AGGARWAL

Religious beliefs may have a powerful influence on the health of our patients, and we need to know about them. A large and growing number of studies have shown a direct relationship between religious involvement and positive health outcomes, including mortality, physical illnesses, mental illness, health-related quality of life and coping with illness.

Studies also suggest that addressing the spiritual needs of patients may facilitate recovery from illness. A large number of the nearly 350 studies of physical health and 850 studies of mental health that made use of religious and spiritual variables noted that religious involvement and spirituality have a link with better health outcomes.

Although the relationship between religious involvement and spirituality with health outcomes seems valid, it is difficult to establish causality. The benefits of religious and spiritual involvement are likely conveyed through complex psychosocial, behavioral and biological processes that are incompletely understood. All physicians should take a spiritual history of their patients, which could help discern their spiritual needs during treatment.

According to Dr Harold Keonig of Duke University Medical Center, in majority of cases, the doctor should not attempt to address complex spiritual needs of patients. When the patient is reluctant to talk with clergy and prefers to discuss spiritual matters with a trusted physician, taking a little extra time to listen and be supportive is usually all that is required.

Providing support for religious beliefs and practices that do not conflict with medical care may be appropriate, but when beliefs conflict with medical care, it is important not to criticize the belief, but rather to listen, gather information, enter into the patient's world view and maintain open lines of communication, perhaps enlisting the help of the patient's clergy.

Recently a study published in the journal *Mayo Clinic Proceedings* confirmed the importance of religion and spirituality for many patients undergoing medical treatment. The single-center, randomized, double-blind trial was conducted at the Mayo Clinic in Rochester, Minn. from July 4, 1997 to October 21, 1999 and involved 799 male and female coronary care patients aged 18 years or older. Earlier too, a number of published studies have already assessed the effects of spiritual factors on healthcare outcomes: 75% report a positive effect; 17% report no effect and 7% report a negative effect.

In the study, the patients were randomized into the intercessory prayer group and the control group. Intercessory prayer was administered at least once a week for 26 weeks by five intercessors per patient. After 26 weeks, a medical setback (such as death, cardiac arrest, re-hospitalization, coronary revascularization or an emergency department visit for cardiovascular disease) occurred in 25.6% of the prayer group and 29.3% of the control group. Among high-risk patients, such a setback occurred in 31% of the prayer group and 33% of the control group. Among low-risk patients, the difference between the groups was 17% for the prayer group and 24% for the control group.

Though the results were in favor of prayer yet the study had some limitations, which might have influenced the low positive results. It did not measure the 'power of God', nor was the prayer offered for patients by loved ones, relatives and friends. The researchers said most patients have a spiritual life and regard their spiritual health and physical health as equally important. People may have greater spiritual needs during illness and are looking to have those needs met.

Prayer works on the principle that in the relaxed state, the mind becomes suggestive. The inner healing starts when the intent reaches the inner consciousness or a state of stillness. Prayer is different from meditation. In prayer, one is talking to the GOD and in meditation, GOD is talking to you. Meditation is much stronger than prayer as it bypasses the mind and deals with the spirit or the consciousness. In prayer, the mind is in an active working phase. Meditation is the phase of restful alertness.

It all works at the level of autonomic nervous system. The parasympathetic state of mind is the healing state. Both prayer and the meditation take one from sympathetic to the parasympathetic state.

Group Editor-in-Chief, IJCP Group

The Old Man and the Rose

During the mid-1950s when I was a kid, my dad worked in a furniture shop at Spadina and Queen in Downtown Toronto. Sometimes, I got to go to the shop with him and I made a bit of pocket change running to the restaurant and getting coffee for everybody. I would pass the rest of the day away just hanging around the store, not doing much of anything and not paying much attention to all the hustle and bustle of people and things that were all around me.

One day, as my dad and I were driving to the shop, I looked out the passenger window of the car and I saw an old man standing at the street corner. For some reason, our eyes met and held for about 20 seconds as we went by the corner. There was nothing fearful about this man but it was a significant encounter for me. Up to that point in my life, I had given no thought to anyone I saw on the street, in stores or anywhere else. My life was my family and my friends on the block and that was it. I had no interest in anyone beyond that circle.

But, I was intrigued by that old man. For the first time, I had an empathy and an interest in what that person was all about. What kind of life had he lived? Where had he been in his time? How had he come to this corner just at the moment I was going by?

Over the years, I had long forgotten about this old man, but he came to mind for me recently and I remembered those 20 seconds or so that I looked into the eyes of a stranger and wondered what he was all about.

It seems we are all so busy these days. There are so many details, so many calls to make and so many things to look after that we barely have time for sincere and genuine interest in others.

We are inundated by warnings from great thinkers in our society encouraging us to 'stop and smell the roses'. But I'm afraid it has taken me decades to really appreciate the wisdom of these words.

If I ever have the opportunity to speak to a young person today, I do my best to convey this message. But unfortunately, young people are too busy to heed good advice. Much like I was so many years ago. Youth indeed is so often wasted on the young.

If I had the chance, I would tell young people to stop what they are doing and look around. I would tell them to try as hard as they could to fully understand what is right in their line of sight, what is in the range of their hearing at the moment, what is in their immediate reach and grasp.

I would like so much to tell people, especially young people, that if you are thoughtless and indifferent to others on your road in life, then you are missing life itself. Do not be intrusive or tactless, for heaven's sake, but take a moment and ask someone, how did you come here or how did you get into this business?

No matter what that person tells you, their answer will make you richer. You can grow emotionally, you can excel as a person and you can be wealthy by every measure if you just appreciate the gifts that people and life all around you are ready to give right at this moment just by their simple presence.

We should appreciate that great symphonies were written from only seven simple notes that God gave the entire universe. We should know that great works of art are measured by the emotions they evoke, not just how they look next to the plant stand.

We should never forget that heartache cannot be cured, but can be eased by someone willing to give genuine sympathy. The true greatness of joy can only be known when it is shared with others.

Recently, I attended a trade show at the convention centre in downtown Toronto. During the lunch break, I went to a book sale along the trendy Queen West area. I was thinking about returning to the show or carrying on my walk when I realized I was standing at the corner of Spadina and Queen. At that moment a car went by and I caught the eye of a young boy looking at me from the passenger window. We looked at each other for about 20 seconds before the car disappeared around the corner. I wondered if that boy was thinking about what sort of person I was.

And I realized that I was now an old man. Like the man I saw so many years ago. I wondered if 50 years had just simply flashed by or whether that boy and I had just simply changed places in the span of 20 seconds.

Before I returned to the trade show, I stopped at a florist. I bought a rose and put it in the lapel of my jacket. For some reason, I felt it was the most important thing I would do for the rest of the day.

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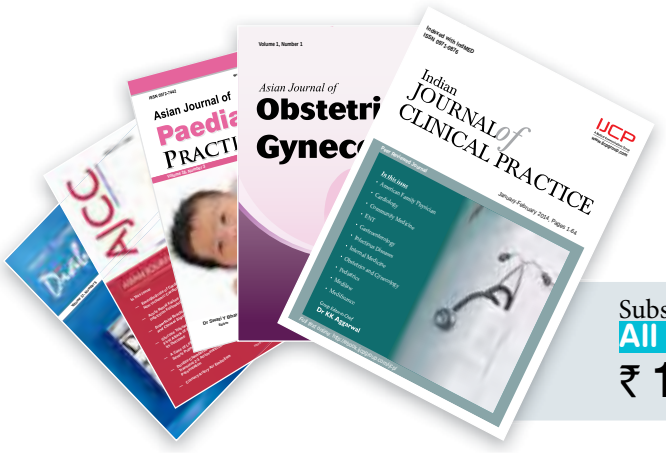

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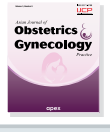
Asian Journal of Obs & Gynae Practice 	4	1,500/- ☐	NA
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Lighter Side of Medicine

HUMOR

TRAFFIC COURT

A New York man was forced to take a day off from work to appear for a minor traffic summon. He grew increasingly restless as he waited hour after endless hour for his case to be heard. When his name was called late in the afternoon, he stood before the judge, only to hear that court would be adjourned for the next day and he would have to return the next day. "What for?" he snapped at the judge.

His honor, equally irked by a tedious day and sharp query roared, "Twenty dollars contempt of court. That's why!" Then, noticing the man checking his wallet, the judge relented. "That's all right. You don't have to pay now." The young man replied, "I'm just seeing if I have enough for two more words."

WHOEVER TELLS THE BIGGEST LIE

Two boys were arguing when the teacher entered the room. The teacher says, "Why are you arguing?"

One boy answers, "We found a 10 dollar bill and decided to give it to whoever tells the biggest lie."

"You should be ashamed of yourselves," said the teacher, "When I was your age, I didn't even know what a lie was."

The boys gave the 10 dollars to the teacher.

MY GRADES

A high school student came home one night rather depressed.

"What's the matter, Son?" asked his mother.

"Aw, gee," said the boy, "It's my grades. They're all wet."

"What do you mean 'all wet?'"

"You know," he replied, "…below C-level."

MASTERPIECE

One day a girl came home crying to her mom. The mom asked what was wrong.

The girl responded, "I'm not a creation, God made men first! I'm nothing!"

Then the mom said, "Oh baby that's not true, God may have made men first, but there's always a rough draft before the masterpiece."

SMART KID

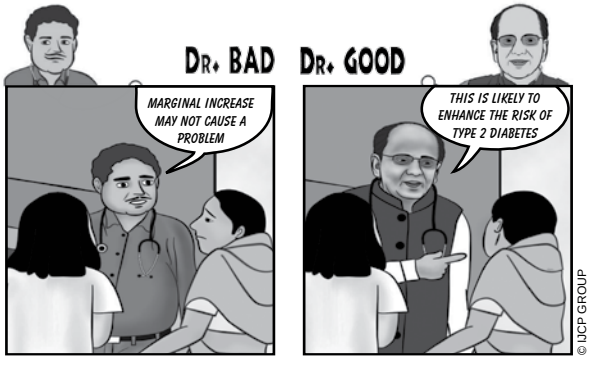
So little Johnnie comes home with his report card for 5th grade, and shows it to his mother. His mom reads the report card and gets more and more upset as she sees his grades. "Johnnie, you have 5 "F's" and a "D" in Math! Wait until your Father sees this!"

So Johnnie's dad comes home from his job at the lab, looks the report card over thoughtfully. Johnnie's Mom says, "Well, aren't you going to say SOMETHING to him??"

Johnnie's dad pulls him aside, and says, "Son, I think you are putting too much time and effort on your Math."

Dr. Good and Dr. Bad

SITUATION: A 41-year-old obese female was asked to get her lipid profile tested, the findings of which showed high levels of TC, TG and TC/HDL-C ratio.



LESSON: The researchers have shown that the risk of diabetes increases with high serum levels of TC, TG, TC/HDL-C and TG/HDL-C ratios. The risk also correlates with interactions between high TC and TG levels and TC/HDL-C and TG/HDL-C ratios and age and BMI.

Diabetes Res Clin Pract. 2017;135:150-7.

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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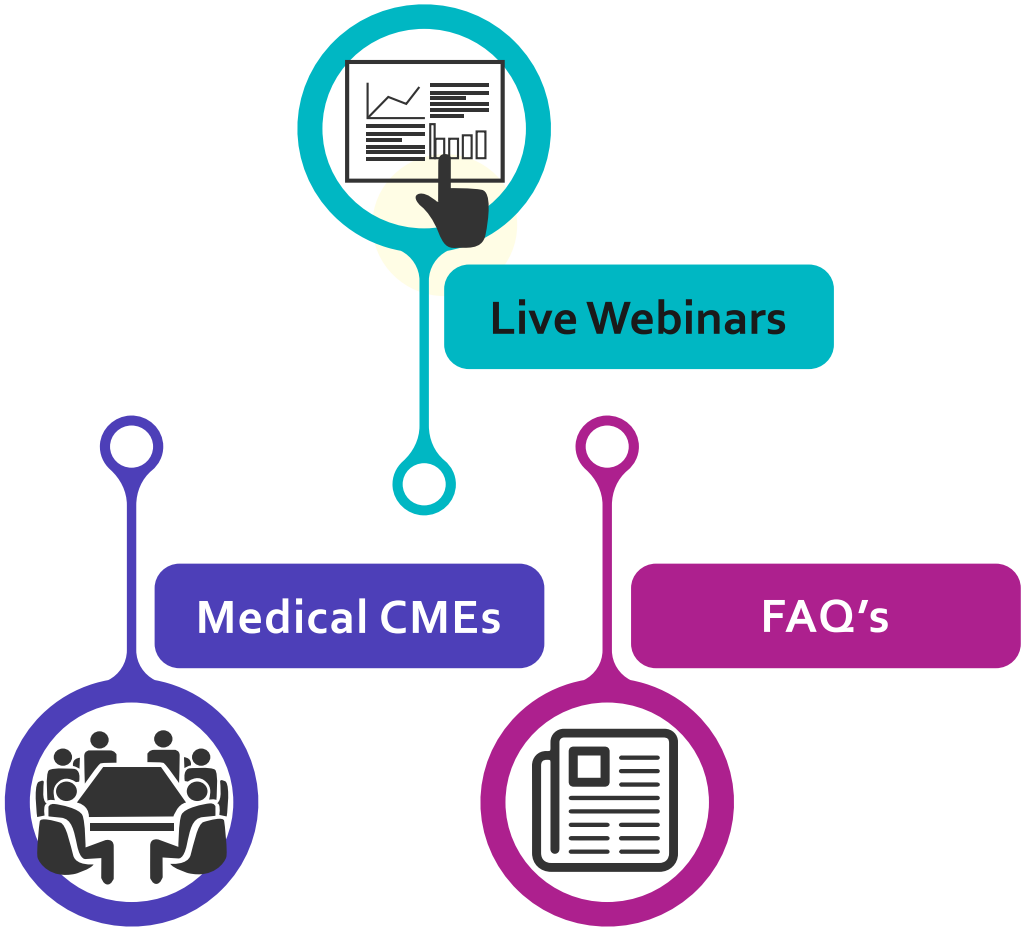

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