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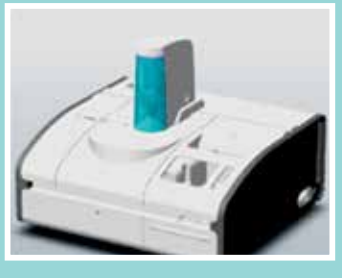

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Indian Journal of Clinical Practice, Vol. 31, No. 1, June 2020

Dr KK Aggarwal
President, CMAAO and HCFI
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Mortality Reduction in CMAAO Countries – Drug Protocol for Treating Doctors

CMAAO GUIDELINES

- Evidence of fever, hyperimmune inflammatory response (high erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] or ferritin): Tab Hydroxychloroquine (HCQ) 400 mg 1 tab twice on first day, 400 mg 1 tab once a day based on acute phase reactants response.
- Tab Doxycycline (DOXY) 200 mg first day and 100 mg from Day 2 to 7 or Azithromycin 500 mg daily for 5 days (antibiotic with antiviral response).
- Anti-parasitic Tab Ivermectin 12 mg 1 tablet once only (by all family).
- If severe hypoxia or pneumonia with very high D-dimer and Ferritin give IL-6 pathway inhibitors (Actemra 400 mg 50K) IV: 8 mg/kg as a single dose (*NIH 2020b; NIH 2020e*).
- In high risk cases in first 3 days of onset: Favipiravir or Fabiflu 1600 mg twice daily on Day 1, followed by 600 mg twice daily for a total duration of 7-14 days (*Cai 2020; NIH 2020a*).
- Inj Clexane 0.6 mL o.d. or b.i.d. in all above age 58, heart patients, hypertension, diabetes, heart failure, asthma, chronic obstructive pulmonary disease (COPD), post cancer, on oxygen, sudden drop of oxygen on rest or exertion.
- Prednisolone 1 mg/kg stat if sudden development of hypoxia on exertion or rest (3-7 days).
- Inj Remdesivir 200 mg Day 1 and 100 mg Day 2-5 at the development of oxygen requirement.
- Sleep prone on your abdomen.
- Prone oxygen by oxygen concentrator, minimum rate to get 92-96% oxygen levels.
- Vitamin D Cap D-Rise 2000 IU once a day for 3 months.
- Elemental Zinc 75 mg daily.
- Vitamin C 500 mg twice daily for 3 days and then 500 mg daily.
- Tab Ranitidine 150 mg twice daily till the duration of illness.
- Tab Meftal 200 mg or Naprosyn 500 mg or Indomethacin 25 mg or Nice 100.
- SpO_2 and pulse monitoring regularly, especially Day 4-7 three times daily.
- Inform your local authorities, if COVID positive.
- Inform if temperature >103°F or lasts >14 days or breathlessness, SpO_2 falls by >4 after 6 minutes walking, persistent chest pain.
- Sudden loss of smell and taste is not a serious sign, may persist for some time, may come and go, may come before fever.
- Conjunctivitis may occur in one eye and is not a serious sign.

- Rash may occur on any part of body (more in women) and is not a serious sign.
- Pus cells may be present in urine, indicate cystitis and not secondary infection (total leukocyte count [TLC] will remain low).
- Monocytes presence indicates high viral response.
- High CRP >100 means very high inflammatory response.
- Loose motions (70% women) means super spreader and often a mild sign. May come and go. Take ORS.
- Whole family may get COVID or COVID like illness, all may have different symptoms, at least one will get loose motions.
- All should do betadine (povidone-iodine) gargles twice daily and povidone-iodine nasal wash.
- Get complete blood count with ESR, CRP, lactate dehydrogenase on Day 1 and Day 5 onwards every third day.
- If lymphocyte count is low (<1,000): LOPIMUNE twice a day for 2 weeks (Ritonavir and Lopinavir).
- Review with reports at hcfimedicalreports@gmail.com
- 9th day onwards you have nonreplicative virus and cannot pass on the infection to others.
- Reverse transcription polymerase chain reaction (RT-PCR) test may remain positive for up to 48 days.
- Those who are 65 plus or have underlying diabetes or heart disease should wear three-layered fabric mask.

■■■■

Adherence to BP Meds Linked to Reduced Mortality Risk in the Elderly

Good adherence to antihypertensive treatment is tied to a significant reduction in mortality risk among the elderly, even for the frailest, suggests new research.

Investigators noted that among individuals with good clinical status, high adherence to antihypertensive treatment was associated with a 44% reduction in all-cause mortality, compared with very low adherence. Adherence was also found to be linked with reduced risk for cardiovascular mortality. The findings were published online in *Hypertension*… (*Medscape*)

Glucose Monitor System Cuts Hospitalizations for DKA

Ketoacidosis rates were greatly reduced with initiation of a continuous glucose monitor, reports a French study presented at the American Diabetes Association (ADA) virtual meeting.

Among people who started on the FreeStyle Libre system, annual rates of diabetic ketoacidosis (DKA) decreased by 52% and 47% for those with type 1 diabetes and type 2 diabetes, respectively, reported researchers. Not including diabetic comas, incidence of hospitalization for ketoacidosis events came down from 5.46 per 100 patients to 2.59 per 100… (*Medpage Today*)

FDA Approves First Treatment for Adult Onset Still's Disease

The US Food and Drug Administration (FDA) has granted approval for canakinumab injection for the treatment of Active Still's disease, including Adult-Onset Still's Disease (AOSD).

The drug was previously approved for Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older. It blocks the effects of interleukin-1 and suppresses inflammation in patients with this autoinflammatory disorder… (*FDA*)

Indian Journal of Clinical Practice, Vol. 31, No. 1, June 2020

Disposal of Unused Medicines: A Study Based on Experiences with Indian Patients

RASHMI ZALPURI*, VISHAL KAMRA†, JK SHARMA‡, LAXMI RAWAT#

ABSTRACT

There is a lack of awareness among the patients regarding the disposal methodologies for the unused medications, resulting in the pollution of environment and severe diseases among the human beings. Therefore, this is an area of concern in the current scenario. A study was conducted in this regard at Mahavir Hospital, Rohini, Delhi. A total of 80 patients were interviewed over a period of 5 months (April to August 2017). The most common diseases reported among these patients were hypertension and diabetes. Review of the interviews revealed that there are mainly three types of disposal methods, which are being adopted by the patients in general. The most common method adopted by the patients is throwing unused medicines away with household garbage (approx. 75%). Returning the unused medicines to the pharmacy or doctor (approx. 20%) is the second most adopted method and the third conventional method used by these patients is the burning of the unused medicines along with the nearby garbage. These patients were asked for such reasons of disposal and the answer by most of them was found to be the scarcity of time and they also said that they do not bother about vicinity. There is a clear need to create public awareness about issues on safe medicine disposal and medication take back programs.

Keywords: Unused medicine, proper disposal, patient opinion, practice

There are cases where patients do not use all the medications that are provided to them due to various reasons: to avoid unpleasant side effects, symptoms have been alleviated, compliance issues, drug-dosage changes, intolerance to the unwanted effects or medications coming closer to their expiration dates. Expired and unused medicines are usually managed in a number of ways. Expired medications should never be kept in home or given to friends and family because it might increase the risk of accidental ingestion or fatal outcomes. It has been reported by the World Health Organization (1999) that expired medicines are not suitable for drug donations. Other methods which are being undertaken for disposal of medications are by rinsing them down a sink, flushing through the toilet or simply throwing them in the trash.

Another appropriate method is to return the unused medicines to the pharmacy. It has been seen that only few pharmacists will take expired and unused medications back for proper disposal; however, the majority will not. There are a number of problems associated with the disposal of medicines which eventually result in hazardous environmental effects and economic burden. Studies indicate that the presence of large number of pharmaceuticals and their products in water has been a major concern.

Trace amounts of medications have been found in groundwater, surface bodies of water and also in treated drinking water. The major effect of environmental contamination by medicines is the development of antibiotic resistance, population exposure to mutagenic and irritant anticancer drugs and the possibility of falling fertility by endocrine disrupting compounds.

A large number of studies also showed that even trace amounts of these compounds had a detrimental effect on the environment by affecting the aspects of biological activities. Along with the compounds, their concentration is also a matter of concern, which is responsible for unwanted effects and genital abnormalities in fish. Usually, the concentration is negligible; however,

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long-term exposure to such chemicals can prove to be hazardous. It has been shown that these chemicals also affect human cells in laboratories. It is important to know that these unused medicines include analgesics, antibiotics and other agents that act on central nervous system.

The most common way for medications to enter into water system is through excretion via urine and feces. Therefore, proper disposal of expired and unused medicines represents an easy way to prevent these pharmaceuticals from entering into water supplies. In various households, it is a common scenario to find the unused portions of the medicines on the shelves, even after their need has been ended. In India, particularly, the extent of problem in the home and public disposal practices is largely unknown. Therefore, this study was conducted to grab the opinion and practice towards disposal of unused and expired medicines among the patients involved with Outpatient and Inpatient departments.

METHODOLOGY

An interview was conducted during the period from April to August 2017. A total of 80 patients from OPD participated in this study. Verbal consent was taken from the hospital committee. Few participants were identified and appointment was fixed to conduct an interview in the premises of the hospital. The questions consisted of general introduction and type of diseases and demographic characters. They were asked about the opinion or in general practice towards disposal of unused medications: Do you know about proper disposal of unused medication?; How do you dispose your unused or expired medication?; Do you know how the environment gets affected with the improper disposal of medication?; Do you know the unused medicines can be returned to the pharmacist?; How do you manage unused medication disposal or do you want to educate yourself about unused medication?

The time duration for interview was approximately 20-30 minutes. The data was analyzed manually due to small sample size.

RESULTS AND DISCUSSION

A total of 80 patients participated in the study with 70% male participants (Fig. 1). The common diseases reported among the participants were hypertension (32), diabetes (17), stomach infection (10), congestion due to cough and cold (7), breathing problem (6), depression (5) and heart problem (3) (Fig. 2).

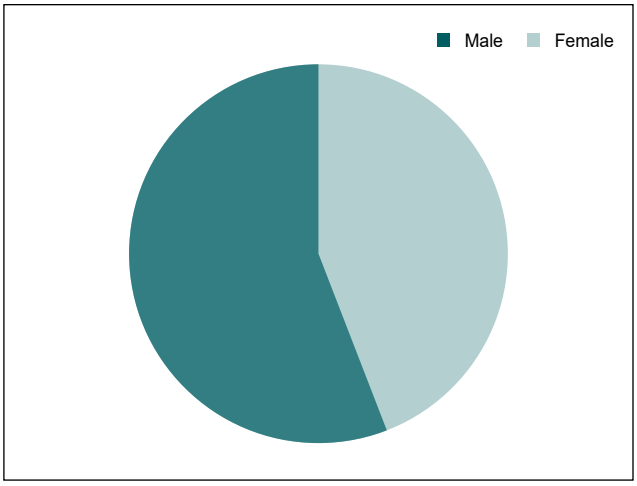

Figure 1. Gender variation in the study.

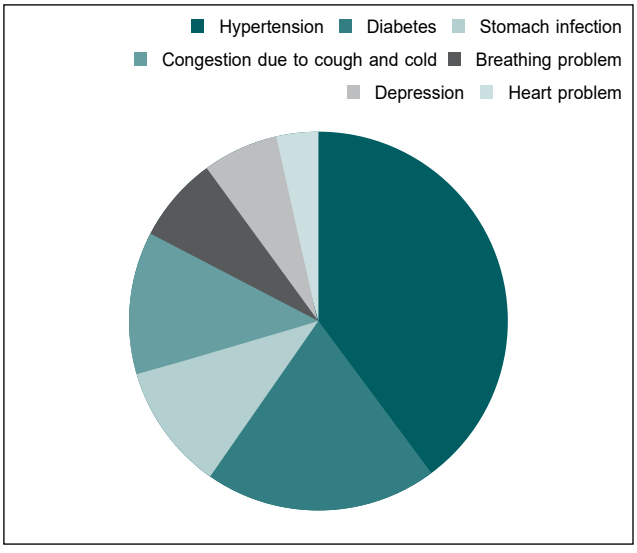

Figure 2. Types of diseases found during the study period.

Opinion Towards Unused Medication Disposal Among Participants

There were three methods practiced by the participants - the maximum participants threw unused medication away with household garbage (approx. 75%). Returning the unused medicine to pharmacy (20%) was the second most adopted method and the third conventional method used by the patients was the burning of the unused medicine (3%) along with the nearby garbage and approximately 2% did not bother about disposal (Fig. 3).

Opinion Towards Knowledge About the Effect of Improper Disposal of Unused Medication

Nearly 65% participants agreed that they did not know the effect of improper disposal of unused medication

IJCP SUTRA: "Doctors are aware of what medications to take and this use of non-prescription drugs should be regulated through appropriate measures."

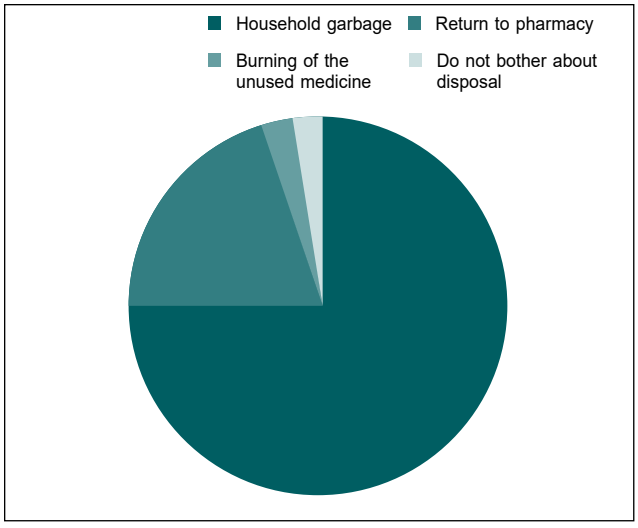

Figure 3. Methods of disposal practiced by patients.

as they believed that herbal tonics and energy drinks or vitamins did not adversely affect the environment, because they are used to heal the patient without any harm. About 30% of them mentioned that they know the bad effect of improper disposal of medication on the environment, water and human beings.

The study revealed that the maximum number of participants did not know about the bad effect improper disposal of unused medications. The most common method to dispose unused medications among the patients is to throw them into trash. As per the respondents, the pharmacist/physician did not educate them about the proper disposal of unused medications.

These patients were asked for such reasons of disposal and the answer by most of them was found to be the scarcity of time and they also said that they do not bother about vicinity.

CONCLUSION

The study clearly indicates that there is a clear need to create public awareness about issues of safe medicine disposal and medication take back programs.

A visit to the pharmacy can provide opportunities for patient education. There should be proper informational pamphlets distributed with medications regarding their disposal.

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Dapagliflozin Slows T2D Onset in Heart Failure Patients

Treatment of patients with heart failure but without diabetes with dapagliflozin led to a reduction in the relative incidence of new-onset diabetes over a median follow-up of 18 months in a prespecified analysis from the DAPA-HF trial that included 2,605 heart failure patients without diabetes at baseline.

During the follow-up period, 7.1% of patients in the placebo arm developed type 2 diabetes, compared to 4.9% of those receiving dapagliflozin, representing a 2.2% absolute difference and a 32% relative risk reduction that was statistically significant. The findings were presented at the virtual annual scientific sessions of the American Diabetes Association… (*Medscape*)

Face Mask Type Matters When Sterilizing, Says Study

When sterilizing face masks, the type of face mask and the method of sterilization affect filtration efficiency, suggests new research. The greatest reduction in filtration efficiency post sterilization was found in surgical face masks.

Using plasma vapor hydrogen peroxide (H_2O_2) sterilization, filtration efficiency of N95 and KN95 masks was maintained at >95%; however, for surgical face masks, it was reduced to <95%. When sterilized with chlorine dioxide (ClO_2), filtration efficiency was maintained at >95% for N95 masks. For KN95 and surgical face masks; however, it was reduced to <80%. The findings were published online June 15 in *JAMA Network Open*… (*Medscape*)

Herd Immunity Building, Says ICMR

Several studies have suggested that people are slowly building immunity towards the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.

A sero-surveillance study conducted by the Indian Council of Medical Research (ICMR) has recently shown that 7 of 1,000 people surveyed had been infected in the past, and had developed IgG (immunoglobulin G) antibodies, suggesting improved immunity… (*ET Healthworld – TNN*)

Comorbidities Increase COVID-19 Deaths by Factor of 12

Coronavirus disease 2019 (COVID-19) patients with an underlying condition appear to be 6 times as likely to be hospitalized and 12 times as likely to die, in comparison with those without such condition, reports the Centers for Disease Control and Prevention (CDC).

Among those with underlying conditions such as cardiovascular disease or diabetes, 45.4% of patients with COVID-19 were hospitalized compared to 7.6% of patients without an underlying condition. Furthermore, 19.5% of COVID-19 patients with underlying conditions died, compared to 1.6% of those with no underlying condition. The findings were published in the *Morbidity and Mortality Weekly Report*… (*Medscape*)

Indian Journal of Clinical Practice, Vol. 31, No. 1, June 2020

Correlation of Hematological Parameters with Right-sided Pleural Effusion in Pediatric Dengue Cases: A Cross-sectional Study

HARISH GV*, RAJASHEKAR REDDY TUPALLI†

ABSTRACT

Background: Capillary leak in dengue presents as ascites, pleural effusion and pericardial effusion. Among the cases of dengue admitted to our hospital in past 2 years, we have observed that right side pleural effusion was more common than left side or bilateral effusion. **Objectives:** 1) To study about hematological parameters and radiological findings in cases of dengue in pediatric age group. 2) To correlate hematological parameters with radiological findings of right-sided pleural effusion. **Study design:** Cross-sectional study. **Participants:** This study was conducted at our tertiary care teaching hospital Prathima Institute of Medical Sciences (PIMS), Karimnagar in Telangana. A total of 138 cases were included in the study and their hematological parameters were correlated with the radiological findings of pleural effusion. **Investigations:** Investigations included complete hemogram on the day of admission, on the day of diagnosis of pleural effusion and at discharge. Radiological investigations included chest X-ray, ultrasonogram of abdomen and chest. **Results:** Out of 138 cases, 71 (51%) had pleural effusion, of which, 46 cases (64.78%) had bilateral effusions with right side more often affected than left. Twenty-one (29.57%) cases had only right-sided pleural effusion. The mean platelet count and hematocrit were 67,640/μL and 31.8%, respectively on the day of pleural effusion. **Conclusion:** In cases of dengue with thrombocytopenia Grade 4 (20,000-50,000/μL), pleural effusion is more common on the right side detected by radiological investigation on Day 4 of illness.

Keywords: Dengue, radiological findings, right side pleural effusion, thrombocytopenia

Dengue fever is a tropical viral disease caused by the dengue virus transmitted by *Aedes aegypti* mosquito. Dengue virus is an arbovirus with single-stranded RNA belonging to genus Flavivirus; it has four serotypes - DENV-1, 2, 3 and 4. A fifth serotype, DENV-5, has been reported in Malaysia but the exact characterization of the virus has not been done.[1]

In 2017, a total of 1,88,401 cases were reported in India and Telangana recorded 5,369 cases during that period.[2] First infection with dengue virus leads to dengue fever and second infection with different serotype leads to dengue with warning signs and severe dengue due to increased capillary permeability, causing fluid losses in third spaces, intravascular fluid depletion and shock. The immune complex of antibody and virus affects the macrophages leading to antibody-dependent enhancement and release of cytokines, cascading capillary leak.[3] Research seems to point towards disturbance in the endothelial glycocalyx layer in dengue leading to capillary leaks and bleeding manifestations.[4] Pleural effusion usually develops during the critical phase on Day 4-6 of illness.[5] Radiological investigations like chest X-ray, ultrasonogram (USG) and computed tomography (CT) scan have been used in diagnosing pleural effusion.[6-8]

The current study was conducted at tertiary care teaching hospital, Prathima Institute of Medical Sciences, Karimnagar in Telangana, as we have observed in past 2 years that the incidence of right side pleural effusion was more common than left side or bilateral effusion, and hence we have correlated hematological parameters with the radiological finding of right-sided pleural effusion.

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METHODS

This was a cross-sectional study conducted during the period July 2018 to November 2018, in children admitted in pediatric ward and ICU at our hospital diagnosed as dengue. All children had complete hemogram and dengue serology done at admission. Cases having capillary leak with third space losses, respiratory distress and clinically diagnosed cases of pleural effusion were subjected to chest X-ray and/or USG. In these cases, complete hemogram was repeated on the day of radiological diagnosis of pleural effusion.

Children with existing congenital cardiac disorders, underlying pulmonary diseases and renal disorders were excluded from the study. A total of 138 cases were included in the study. All the data was entered into Microsoft Excel Sheet and it was analyzed using Statistical Package for Social Sciences (SPSS), Version 21.

RESULTS

Of the 138 cases in the study, 76 (55.07%) were male and 62 (44.92%) were female. Twenty (14.49%) cases were aged less than 1 year, 27 (19.5%) cases were between 1 year and 5 years, 49 (35.50%) cases were between 6 and 10 years, 33 (23.91%) cases were between 11 and 15 years and 9 (6.52%) cases were between 15 and 18 years (Fig. 1).

Thirty-one (22.4%) cases were diagnosed as probable dengue, 88 (63.7%) cases were diagnosed as dengue with warning signs and 19 (13.7%) cases were severe dengue.

A total of 71 (51%) cases developed pleural effusion. Of these, 46 (64.78%) cases had bilateral pleural effusion with right side more often affected than left (including both USG and chest X-ray), 21 (29.57%) cases had only right side pleural effusion (USG and chest X-ray), 3 (4.2%) cases had pleural effusion on left side (USG and chest X-ray) and 1 (1.4%) case had bilateral equal pleural effusion (Fig. 2).

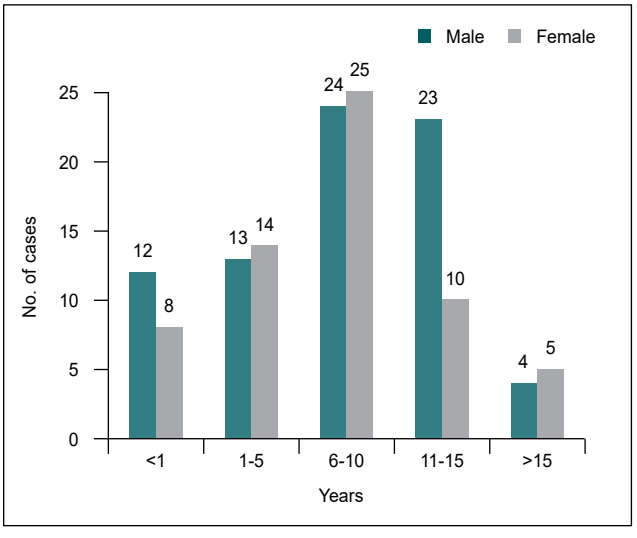

Figure 1. Age and sex distribution of cases in the study.

The mean day at which pleural effusion developed was 4th day of illness.

The mean platelet count on the day of admission was 76,460/μL. The mean platelet count on the day of radiological diagnosis of pleural effusion was 67,640/μL. The mean platelet count at discharge was 1,24.360/μL (Table 1).

The mean hematocrit at admission was 32.41%. The mean hematocrit on the day of pleural effusion was 31.8%. The mean hematocrit at discharge was 30.68% (Table 1).

The mean platelet count and hematocrit in bilateral pleural effusion cases were 85,000/μL and 24.90%, respectively (Table 2).

The mean platelet count and hematocrit in cases with bilateral pleural effusion with right > left side were 51,670/μL and 31.51%, respectively (Table 2).

The mean platelet count and hematocrit in right side pleural effusion cases were 62,800/μL and 34.03%, respectively (Table 2).

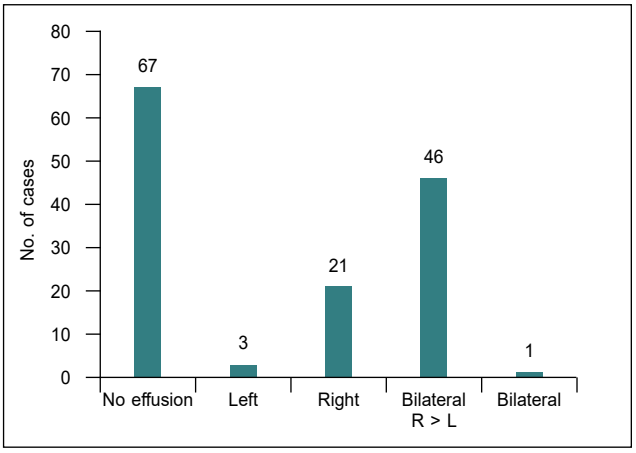

Figure 2. Case distribution according to site of pleural effusion.

Table 1. Mean Platelet and Hematocrit of All Cases

Day	Admission	Day of pleural effusion	Discharge
Mean platelet ($x10^3$/μL)	76.46	67.64	124.36
Mean hematocrit (%)	32.41	31.8	30.68

The mean platelet and hematocrit in cases with left side pleural effusion were 62,330/μL and 28.50%, respectively (Table 2).

Among 138 cases, 119 (86.2%) cases were NS1 positive, of which 62 (52.1%) cases had pleural effusion, with 43 cases having bilateral pleural effusion with right > left side, 17 cases had right side pleural effusion and only 2 cases had effusion on left side.

In our study, we graded thrombocytopenia on the day of detection of pleural effusion into 5 grades - Grade 1 included cases with platelet count >1.5 lakh/μL, Grade 2 included cases with platelet count between 1 lakh and 1.5 lakh/μL, Grade 3 with platelet count between 50,000 and 1 lakh/μL, Grade 4 with platelet count 20,000-50,000/μL and Grade 5 with platelet count <20,000/μL.

Among these, pleural effusions were more common with platelet counts between 20,000-50,000/μL, i.e., in Grade 4 with 33 (46.47%) cases, followed by Grade 3 with 25 cases (35.2%), Grade 2 and Grade 5 included 5 (7%) cases and Grade 1 had 3 (4.2%) cases among cases with pleural effusion (Table 3).

Table 2. Mean Platelet and Hematocrit for the Pleural Effusion Cases

Pleural effusion site	Mean platelet ($x10^3$/μL)	Mean hematocrit (%)
Bilateral	85	24.90
Bilateral R > L	51.67	31.51
Right side	62.8	34.03
Left side	62.33	28.50
No effusion	80.08	31.55

Table 3. Pleural Effusion Site vs. Thrombocytopenia Grading

Pleural effusion (total)	Bilateral	Bilateral R > L	Right	Left
Platelet >1.5 lakh/μL (3)	0	2	1	0
Platelet 1-1.5 lakh/μL (5)	0	3	1	1
Platelet 50 k-1 lakh/μL (25)	1	14	10	0
Platelet 20 k-50 k/μL (33)	0	23	8	2
Platelet <20 k/μL (5)	0	4	1	0
Total	**1**	**46**	**21**	**3**

Right-sided pleural effusion had higher incidence in Grade 4 thrombocytopenia, i.e., with platelet count between 20,000 and 50,000/μL, followed by in Grade 3, i.e., 50,000-1 lakh/μL.

DISCUSSION

Dengue is an arboviral disease caused by dengue virus categorized under Flavivirus, and includes five serotypes. Although the serotypes are antigenically similar, they are different enough to elicit cross protection only for few months after infection with any one of them. Infection confers lifelong immunity for that serotype. The vector for virus is female *Aedes aegypti* mosquito, which becomes infective after an extrinsic incubation period between 5 and 33 days at 25°C, and between 2 and 15 days at 30°C. Dengue begins abruptly after an intrinsic incubation period of 3-10 days.[9] The host immune response plays an important role in the pathogenesis of dengue fever. Many pathogenic mechanisms have been proposed, like immune complex-mediated mechanism; T-cell–mediated antibodies cross-reacting with vascular endothelium, enhancing antibodies, complement and its products, cytokines and chemokines. The most accepted theory stays the virus strains enhancing the antibodies and memory T-cells in secondary infection causing release of cytokines which act on the vascular endothelium, platelets and various other organs causing vasculopathy, coagulopathy and shock.[3]

The course of illness in dengue is in three phases - the febrile phase, the critical phase and the recovery (convalescent) phase. The cases are defined and classified into three groups based on the severity of the clinical manifestations as probable dengue, dengue with warning signs and severe dengue.[10] In our study of 138 cases, 22.4% were cases of probable dengue, 63.7% were dengue with warning signs and 13.7% were severe dengue. In a similar study conducted by Kabilan et al,[11] in a tertiary care hospital in South India, among 143 cases, 65% had dengue fever, 11.2% had dengue hemorrhagic fever and 23.8% had dengue shock syndrome. In our study which extended over a period of 5 months, there were 138 cases with 20 (14.4%) cases being infants, 27 (19.5%) cases aged 1-5 years and 82 (59.4%) cases aged 6-15 years. This is comparable with the study by Kabilan et al,[11] which extended over 3 months and had total of 143 cases, 29 (20%) being infants, 41 (28.7%) being between 1 year and 5 years and 51% being 6-15 years. In both the studies, the incidence of dengue was more in the age group 6-15 years.

Capillary leakage occurs usually between 3rd and 7th day of illness and patients present with hemoconcentration, pleural effusion and ascites during which the patient may be afebrile. The anti-NS1 antibodies act as autoantibodies that cross-react with the endothelium and the platelets, which triggers the intracellular signaling causing changes in capillary permeability, disturbing the integrity of the glycocalyx layer of endothelial cells. In our study, 64.78% cases had bilateral pleural effusion with right side more than left, 29.57% had isolated right side pleural effusion, while only 4.2% cases had isolated left side pleural effusion. Previously, many studies had mentioned pleural effusion as one of the manifestations of dengue. In a study conducted by Venkata Sai et al,[7] right side pleural effusion had more incidence (71.87%) than left side pleural effusion (21.87%) and the effusion was detected between 5th and 7th day, while the mean day of detection of pleural effusion in our study was 4th day. Similarly, in a study conducted by Santhosh et al,[12] bilateral (26%) and right side (22.9%) pleural effusion had higher incidence when compared to the left side effusion (1 patient).

In a study conducted by Shabbir et al,[13] left side pleural effusion was more common with left side effusion noted in 50% cases, right side effusion in 40% cases and bilateral in 10% cases.

Thrombocytopenia occurs due to the destruction of platelets by the autoantibodies, disseminated intravascular coagulation (DIC), bone marrow suppression during early phase of disease and peripheral sequestration of platelets. In our study, we have correlated thrombocytopenia with pleural effusion, and we have observed that the mean platelet count in cases of bilateral pleural effusion right > left side was less when compared to other sites of pleural effusion. In the study conducted by Santhosh et al,[12] pleural effusion was correlated with platelet count, and they found that effusion was more common with platelet count <40,000/μL. In our study, 46.47% of the cases with pleural effusion had platelet count between 20,000 and 50,000/μL, i.e., Grade 4 thrombocytopenia.

CONCLUSION

In cases of dengue with thrombocytopenia Grade 4 (20,000-50,000/μL), pleural effusion is more common on the right side detected by radiological investigation on Day 4 of illness.

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Prevalence of Thyroid Dysfunction in Pregnancy

RUCHIKA GARG*, PRABHAT AGRAWAL†, VISHY AGRAWAL‡, URVASHI*, SAROJ SINGH#

ABSTRACT

There are a few reports of prevalence of hypothyroidism during pregnancy from India with prevalence rates ranging from 4.8% to 11%. Subclinical thyroid dysfunction has adverse outcome on the mother and fetus such as miscarriage, preterm delivery, pre-eclampsia, eclampsia and placental abruption and can also impair the neurocognitive development of the fetus. We conducted a cross-sectional study to find out the prevalence of thyroid disorder in pregnancy in North India. The study was conducted in the antenatal OPD of the Dept. of Obstetrics and Gynecology and Dept. of Medicine, SN Medical College, Agra and antenatal clinic of District Hospital, Agra from July to December 2017. Overall, 1,020 women with uncomplicated intrauterine singleton pregnancy were included. Thyroid-stimulating hormone (TSH), free T4 (fT4) and free T3 (fT3) were measured by high sensitive radioimmunoassay. Out of 1,020 pregnant women, 109 were found as having thyroid disorders. The prevalence of thyroid disorder among women in the age groups 20-25 years, 26-30 years and 31-35 years was 8.7%, 1.8% and 0.19%, respectively. The prevalence of subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism was 6.67%, 1.27%, 1.86% and 0.88%, respectively. The mean TSH level among women with subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism was 3.50, 7.92, 0.05 and 0.014 mIU/L, respectively. The prevalence of thyroid disorder in the first, second and third trimester was 68.80%, 23.85% and 7.33%, respectively. This study has shown high prevalence of thyroid dysfunction, especially subclinical and overt hypothyroidism, in India.

Keywords: Thyroid disorder, pregnancy, subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, overt hyperthyroidism

Pregnancy is a state in which the combination of events modifies the function of thyroid. There is a change in the level of thyroxine-binding globulin (TBG), total T3 and T4 and thyroid-stimulating hormone (TSH) during normal pregnancy.[1]

The prevalence of hypothyroidism in pregnancy is around 2.5% according to the Western literature and prevalence of hyperthyroidism in pregnancy is 0.1-0.4%.[2,3] There are a few reports of prevalence of hypothyroidism during pregnancy from India with prevalence rates ranging from 4.8% to 11%.[4,5] During pregnancy, the thyroid gland may increase in size by 10% in iodine-sufficient countries and to a greater extent in iodine-deficient countries. Production of thyroid hormones and iodine requirement are increased by approximately 50% during pregnancy. In addition, pregnancy is a stressful condition for the thyroid gland, resulting in hypothyroidism in women with limited thyroid reserve or iodine deficiency.

Data from published studies have underscored the association between miscarriage and preterm delivery in women with normal thyroid function who test positive for thyroid peroxidase (TPO) antibodies.[6] The prevalence of Grave's disease is around 0.1-0.4% and that of thyroid autoimmunity (TAI) is around 5-10%.

Studies have shown that the subclinical thyroid dysfunction has adverse outcome on the mother and fetus such as miscarriage, preterm delivery, pre-eclampsia, eclampsia and placental abruption. It may also impair the neurocognitive development of the fetus.[7]

That's why we conducted this study to find the prevalence of thyroid disorder in pregnancy in North India.

MATERIAL AND METHODS

It is a cross-sectional study conducted in the antenatal OPD of the Dept. of Obstetrics and Gynecology and Dept. of Medicine, SN Medical College, Agra and

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antenatal clinic of District Hospital, Agra from July 2017 to December 2017.

We included 1,020 women with uncomplicated intrauterine singleton pregnancy. We excluded women who had history of thyroid disease or intake of thyroid drugs, multifetal gestation, known chronic disorders (diabetes and hypertension) or patients with bad obstetrics history due to some other cause. After enrolling the patients, a written informed consent was taken, and detailed history and examination was done.

Blood samples were collected after obtaining the consent and were sent for thyroid hormone profile testing.

TSH, free T4 (fT4), free T3 (fT3) were measured by high sensitive radioimmunoassay.

Subclinical hypothyroidism means increase in TSH with normal fT3 and fT4. Overt hypothyroidism means increase in TSH with decrease in fT3 and fT4.

Subclinical hyperthyroidism was defined as serum TSH concentration below the lower limit of reference range with fT3 and fT4 concentration within normal range.

Overt hyperthyroidism was defined as serum TSH concentration below the lower limit of reference range with increase in fT3 and fT4 concentration. Reference ranges of antithyroid antibodies were:

- Thyroid peroxidase antibody (TPOAb) <35 IU/mL
- Thyroglobulin antibody (TgAb) <20 IU/mL.

American Thyroid Association (2007) recommends cut-off values for TSH as:

- First trimester <2.5 mIU/L
- Second and third trimester <3 mIU/L
- Lower limit of normal TSH 0.04 mIU/L.

RESULTS

In the present study, a total of 1,020 pregnant women were screened and 109 females were found as having thyroid disorders.

Table 1 shows that the prevalence of thyroid disorder among women in the age groups 20-25 years, 26-30 years and 31-35 years was 8.7%, 1.8% and 0.19%, respectively. Table 2 shows that the prevalence of subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism was 6.67%, 1.27%, 1.86% and 0.88%, respectively.

Table 3 shows that out of 1,020 women; 109 were found as having thyroid disorder and the prevalence of thyroid disorder in the study was 10.68%.

Table 4 shows that the mean TSH level among women with subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism was 3.50, 7.92, 0.05 and 0.014 mIU/L, respectively. Table 5 shows that the prevalence of thyroid disorder in the first, second and third trimester was 68.80%, 23.85% and 7.33%, respectively.

Table 1. Distribution of Patients According to Age Groups

Age Group	No. of patients with thyroid dysfunction	Percentage (%)
20-25	89	8.7
26-30	19	1.8
31-35	02	0.19

Table 2. Distribution of Patients According to Different Types of Thyroid Disorders

Type of disorder	No. of cases	Percentage (%)
Subclinical hypothyroidism	68	6.67
Overt hypothyroidism	13	1.27
Subclinical hyperthyroidism	19	1.86
Overt hyperthyroidism	09	0.88
Total	**109**	**10.68**

Table 3. Prevalence of Thyroid Disorders

Sample	No. of cases with thyroid disorder	Percentage (%)
1,020	109	10.68%

Table 4. Mean TSH levels in Different Types of Thyroid Disorders

Types	No. of cases	Mean TSH level
Subclinical hypothyroidism	68	3.50
Overt hypothyroidism	13	7.92
Subclinical hyperthyroidism	19	0.05
Overt hyperthyroidism	09	0.014

Table 5. Distribution of Patients with Thyroid Disorders According to Trimesters

Trimesters	No. of patients (%)
First trimester	75 (68.80)
Second trimester	26 (23.85)
Third trimester	08 (7.33)

DISCUSSION

The main aim of the study was to know the prevalence of thyroid disorders in pregnancy. The prevalence of thyroid disorders in our study was 10.68% and it was consistent with the study by Sahu et al[5] in which the prevalence of thyroid disorders was 12.7%. It was also comparable to the study conducted by Wang et al[8] (10.2%), Taghavi et al[9] (14.6%) and Ajmani et al[10] in which the prevalence of thyroid disorder was 13.25%.

In the study conducted by Thanuja et al,[11] the prevalence of thyroid disorder was less (about 5%) and in the study conducted by Rajput et al,[12] the prevalence of the thyroid disorder was high (26.5%).

The prevalence of subclinical hypothyroidism in our study was 6.67% and it was consistent with the study by Sahu et al in which it was 6.47%. Prevalence of subclinical hypothyroidism in pregnancy according to the study conducted by Thanuja et al in Mangalore was less (0.7%), while it was 2.3% according to the study conducted by Casey et al.[13] It was high in the study conducted by Dhanwal et al (13.5%),[14] Murty et al (16.11%),[15] and Singh et al (18%).[16]

The prevalence of overt hypothyroidism in the study was 1.27% and it was comparable to the studies conducted by Taghavi et al, Bandela et al[17] and by Ajmani et al in which the prevalence was 2.4%, 2.87% and 3%, respectively.

Prevalence of overt hypothyroidism in pregnancy in the studies conducted by Wang et al (0.3%) and Dhanwal et al (0.7%) was less compared to the present study. In this study, the prevalence of thyroid disorder in first, second and third trimester was 68.80%, 23.85% and 7.33%, respectively and this is in accordance with the study by Rao and Patibandla.[18]

In India, the most common cause of hypothyroidism in pregnancy is iodine deficiency. Hashimoto thyroiditis is the most common cause of hypothyroidism in iodine-sufficient areas. Presence of goitrogens[19] in diet, micronutrient deficiency such as selenium and iron deficiency may cause hypothyroidism and goiter.[20] Poverty, insufficient iodine supplementation and fluorinated water may be the cause of thyroid disorder among pregnant women. Serum TSH and fT4 are the best screen and diagnose hypothyroidism during pregnancy. The prevalence of overt or subclinical hypothyroidism depends on the upper TSH cut-off level used. There is strong evidence that the reference range for serum TSH is lower throughout the pregnancy compared with the nonpregnant state. The lowest serum TSH levels are observed during the first trimester of pregnancy and are apparently related to human chorionic gonadotropin (hCG) stimulation of the thyroid gland as serum hCG levels are highest early in gestation.

CONCLUSION

Thyroid disease is prevalent in women of childbearing age group and for this reason it is common in pregnancy and puerperium. Women with thyroid disorder, both overt and subclinical, are at increased risks of pregnancy-related complications, such as spontaneous abortion, pre-eclampsia, preterm labor and abruption placentae and fetal complications such as low birth weight babies, preterm delivery, intrauterine growth retardation and stillbirth.

At present, there are no recommendations available for detection or screening of thyroid dysfunction among Indian pregnant women. Recent consensus guidelines recommend testing only in cases of high-risk women having personal history of thyroid or other autoimmune disorders or with a family history of thyroid disorders.

This study has shown the high prevalence of thyroid dysfunction, especially subclinical and overt hypothyroidism, in India and thus emphasizes the need to include thyroid function test in the routine screening in the antenatal clinic and the patients to be potentially aware of associated maternal and fetal complications.

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More Data to Suggest Proning Helps COVID-19 Patients

Oxygenation was seen to improve in hospitalized patients with COVID-19 with severe hypoxemic respiratory failure when placed in the prone position, reported a small study in New York City.

An hour after initiation, oxyhemoglobin saturation increased by a median 7 percentage points (95% confidence interval [CI] 4.6-9.4; range 1-34) from baseline in awake, spontaneously breathing patients with at least one awake session of the prone position, reported researchers in *JAMA Internal Medicine*… (*Medpage Today*)

Brief Intervention Linked with Lower Repeat Suicide Attempt

For patients who had attempted or were considering suicide, brief encounters with healthcare providers appeared to decrease the risk of subsequent suicide attempts and improved access to follow-up care, suggested a meta-analysis of 14 trials.

A pooled analysis of 4,270 suicidal patients revealed that those who underwent brief interventions, comprising of a single in-person encounter, were noted to have a significantly lower risk of attempting suicide again in the subsequent 2-12 months in comparison to those who did not undergo such intervention, reported researchers in *JAMA Psychiatry*… (*Medpage Today*)

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Monitoring of Airborne Fungi in a Hospital Unit

SHASHI CHOPRA*, GOMTY MAHAJAN†, YADWINDER SINGH‡

ABSTRACT

Background: Nosocomial infections are caused mainly by airborne pathogens found in healthcare facilities and their surroundings. Fungi are ubiquitous in environment and are considered critical pathogens of hospital-associated infections. **Objective:** The aim of this study was to evaluate the concentrations of fungal species in the air of a tertiary care hospital. **Methods:** The air samples were collected by open plate technique once after 3 months from indoor and outdoor area of different wards and operation theaters over different periods of the year. In total, 160 air samples were cultured into Sabouraud dextrose agar and Blood agar plates and incubated at 25°C for 7-10 days. Fungal species were identified by macroscopic and microscopic features. The number of airborne fungi was presented in colony-forming unit per cubic meter (CFU/m^3). **Results:** Four hundred sixty-nine colonies were isolated in a year. The highest fungal CFU was isolated from female surgery ward and least from operation theaters. The most isolated fungi were *Aspergillus* spp. (29.42%), followed by *Curvularia* spp. (15.77%), *Alternaria* spp. (14.28%), *Scedosporium apiospermum* (10.23%), *Penicillium* spp. (8.95%), *Cladophialophora* spp. (7.46%), *Paecilomyces* spp. (6.82%). The yeast spp. isolated from indoor and outdoor samples were 7.09% and 4.77%, respectively. **Conclusions:** Different fungal species may have different pathogenicities and body resistance is the key against fungal infections. Therefore, the need of the hour is to monitor the indoor air to prevent nosocomial infections.

Keywords: Airborne fungal spores, *Aspergillus*, indoor air, nosocomial infections

Physical, chemical and biological agents of the indoor and outdoor environment can affect public health.[1] Indoor air quality in hospitals is a concern because it contains a wide range of infectious airborne microorganisms that may cause hospital infections.[2,3] Immunocompromised patients are more prone to nosocomial infections, due to reduction in their defensive ability—whether due to cancer, hemolymphoproliferative diseases or human immunodeficiency virus (HIV) infection,[4-7] medical therapy or organ transplantation. Bioaerosols in the hospital air are one of the potential sources of infection.[8] Fungi and bacteria are the major types of bioaerosols present in hospital environments.[9,10] Fungal pollutants in indoor environment depend on many factors such as: temperature, moisture, ventilation and organic matter present in building materials. Also, outdoor fungal spores may be transmitted through visitors, patients and air conditioning.[10] Airborne micro-fungi in indoor hospital environments are mainly formed by filamentous fungi that belong to the *Aspergillus* species (spp.), Mucorales (*Rhizopus* spp.), *Fusarium* spp., *Cladosporium* spp., *Paecilomyces* spp., *Scedosporium* spp., *Penicillium* spp., *Scopulariopsis* spp., *Pseudallescheria boydii*, *Sporothrix* spp. and *Acremonium* spp.[8,11,12] Yeast isolates have also been found that belong to the genus of *Candida, Trichosporon, Rhodotorula, Saccharomyces* and *Cryptococcus*.[11,13-15] The evaluation of density and diversity of bioaerosols in the hospital can be a good indicator of the cleanliness of these environments.[3]

The aim of this study was to assess the fungal aerosols in indoor and outdoor environment of hospital, which will be helpful in future to reduce fungal hospital-acquired infection (HAI) rates in immune compromised patients.

MATERIAL AND METHODS

A prospective surveillance study was conducted in the Dept. of Microbiology of a teaching hospital for a period of 1 year (April 2018 to March 2019) to evaluate the airborne fungal contamination in the hospital by Settled Plate method. Prior to the study, clearance from hospital ethical committee was taken. Both indoor and outdoor samples were collected from Surgery, Medicine, Obstetrics and Gynecology wards,

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Labor room, Intensive care unit and Operation theaters over different periods of the year. Outdoor samples were collected as control for comparison of indoor microbial loads.

The air samples were collected by open plate method (passive sampling method).[16] The two standard petri dishes containing culture media of Sabouraud dextrose agar (SDA) with chloramphenicol and Blood agar (BA) were put at a height of 100-150 cm above the ground level during sampling for 20 minutes[17] to collect fungal particles. This procedure was repeated at an interval of 3 months. On the whole 160 (BA [80] and SDA [80]) plates were used for indoor and outdoor samples over 1 year period.

After exposure, the plates were placed in BOD incubators at 25°C for 7-10 days and monitored daily. The fungal colonies were identified on the basis of macroscopic and microscopic morphology. Macroscopically, the surface, texture and pigment production by fungi were noted. The presence of specific reproductive structures, presence/absence of conidia and their size, shape and structure of conidia, septation in mycelium were noted microscopically by seeing the lactophenol cotton blue wet mount preparation. Data was statically analyzed.

RESULTS

In this study, total 469 fungal colonies were isolated in a year. Out of these, 155 (33%) colonies were isolated from indoor samples and 314 (67%) from outdoor samples. The highest fungal colony-forming unit (CFU) were isolated from female surgery ward (Table 1) and least from operation theaters. The most isolated fungi were *Aspergillus* spp. (29.42%), followed by *Curvularia* spp. (15.77%), *Alternaria* spp. (14.28%), *Scedosporium apiospermum* (10.23%), *Penicillium* spp. (8.95%), *Cladophialophora* spp. (7.46%), *Paecilomyces* spp. (6.82%) (Table 2). The dominant fungi isolated from surgery and medicine wards were *Penicillium, Aspergillius* spp. and *S. apiospermum*. The yeast spp. isolated from indoor and outdoor samples were 7.09% and 4.77%, respectively. The mean of different fungal genera isolated from indoor and outdoor plates were 1.93 and 3.9 fungus/plate, respectively.

Table 1. Concentration of Fungal Population in Indoor and Outdoor Air of Different Wards and Operation Theaters in the Hospital

Sample place	CFU	Mean	Standard deviation
Wards (Indoor)			
Surgery (Male)	24	3	1.5
Surgery (Female)	28	3.5	1.4
OBG	22	2.7	1.66
Medicine (Male)	25	3.12	1.72
Medicine (Female)	22	2.7	1.66
Wards (Outdoor)			
Surgery (Male)	48	6	2.5
Surgery (Female)	40	5	1.06
OBG	42	5.25	3.23
Medicine (Male)	45	5.06	1.48
Medicine (Female)	53	6.62	2.38
Labor room (Indoor)	7	0.87	0.53
Labor room (Outdoor)	13	1.62	0.91
ICU (Indoor)	15	1.87	0.33
ICU (Outdoor)	55	6.8	1.45
NICU (Indoor)	7	0.87	0.53
NICU (Outdoor)	10	1.25	0.7
Operation theater (OT)			
Main OT (Indoor)	3	0.37	0.5
Main OT (Outdoor)	7	0.87	0.53
Gyne OT (Indoor)	2	0.25	0.34
Gyne OT (Outdoor)	1	0.12	0.34

DISCUSSION

In the present study, the concentration and distribution of fungi in the indoor air and outdoor air were monitored over 1 year. The distribution of fungi was quite different between indoor and outdoor environment. Pattern of indoor and outdoor isolates was similar. Fungi loads in indoor air were less than that of the outdoor air. Whenever outdoor microbial loads increased, there was a corresponding increase in microbial loads of indoor air. This indicates that indoor microflora is influenced by outdoor environmental conditions. Problems of indoor air quality are recognized as important risk factors for human health and were documented previously also by different workers.[18-20] Indoor air is important also because populations spend a substantial fraction of time within buildings. Microbial pollution involves hundreds of species of bacteria and fungi that grow indoors when sufficient moisture is available. Exposure to microbial contaminants is clinically associated with respiratory symptoms, allergies, asthma and immunological reactions.[21] The amount of fungi after entering from the outdoor environment tends to increase in the presence of favorable conditions in the indoor environment and can cause health problems in both immunodeficient as well as healthy people.[22] Airborne fungal spores are very important agents in nosocomial infection and respiratory diseases and their effect on human health

Table 2. Percentage of Different Fungi Isolated from Indoor and Outdoor Environment of Wards and Operation Theaters

Fungus	Indoor fungi isolated (%)	Outdoor fungi isolated (%)	Mean (%)
Aspergillus niger	23 (14.83)	42 (13.37)	32.5 (13.85)
Aspergillus flavus	13 (8.38)	28 (8.9)	20.5 (8.74)
Aspergillus fumigatus	08 (5.16)	24 (7.64)	16 (6.82)
Curvularia spp.	27 (17.41)	47 (14.96)	37 (15.77)
Alternaria spp.	24 (15.48)	43 (13.69)	33.5 (14.28)
Scedosporium apiospermum	15 (9.67)	33 (10.5)	24 (10.23)
Penicillium spp.	14 (9.03)	28 (8.91)	21 (8.95)
Cladophialophora spp.	10 (6.45)	25 (7.96)	17.5 (7.46)
Paecilomyces spp.	08 (5.16)	24 (7.64)	16 (6.82)
Rhizopus spp.	2 (1.3)	05 (1.59)	3.5 (1.49)
Yeast spp.	11 (7.09)	15 (4.77)	13 (5.54)
Total colonies isolated	**155**	**314**	**-**

is linked with their genera, species and concentrations in air.[16,17] Many studies have shown the relationship between HAI and the existence of microorganisms in hospital environments, including in the air of wards.[2,23]

In the present study, 33% fungal colonies were isolated from indoor air samples, whereas other workers reported much higher rates of 62.03% and 69.11 CFU/m^3.[23,24] No significant seasonal variation was seen in the distribution of the fungi with regards to the average spore counts. In this study, among filamentous fungi, *Aspergillus* spp. were the most dominant fungal isolates followed by *Curvularia* spp. and *Alternaria* spp. *Aspergillus* spp. was found in high numbers in indoor air samples. *Aspergillus* spp. that can grow indoors include *Aspergillus fumigatus* and *Aspergillus flavus* and can cause nosocomial infections,[25] allergic bronchopulmonary aspergillosis and sinusitis. Aspergillosis can occur in immunocompromised hosts or as a secondary infection, following inhalation of fungal spores or the toxins produced by them. Symptoms include persistent cold, watery eyes, prolonged muscle cramps and joint pain, etc. Chronic asthmatics may progress to have their bronchial passages colonized by either *A. fumigatus*, *Bipolaris hawaiiensis* or *Wangiella dermatitidis*.[19] Constant allergic response maintains the fungal colonization.[19] *Aspergillus* species can cause invasive Aspergillosis and produce mycotoxins which are known to be carcinogens. Although there are no strict numerical guidelines for determining the level of fungal contamination in hospital air, the national guidelines of the United Kingdom for prevention of nosocomial aspergillosis for interpretation of the fungal spore burden state that the fungal spores in air should be ≤5 conidia/m^3 in the absence of air filtration.[26] Other fungal spores also have the ability to cause allergies as well as other respiratory diseases and hypersensitivity reactions not only in immune suppressed patients but also in healthy individuals.

Hence, more attention should be given to safeguard indoor environments; otherwise the growth of pathogenic microorganisms can cause toxigenic health hazards.[27] The present study showed that *Curvularia* spp. and *Alternaria* spp. were also predominant fungi isolated from indoor. Other workers also reported *Aspergillus*, *Penicillium* and *Alternaria* as the most frequently isolated fungal genera in indoor.[16,28] It seems that different geographic locations can influence the dominant fungal agents. *Curvularia* spp. is responsible for nosocomial dialysis-related peritonitis and post-surgical endocarditis, whereas *Alternaria* spp. can cause deep infections in the immunocompromised patients.[29] Our results showed that almost all of the wards were polluted by various fungi.

CONCLUSION

Different fungal species may have different pathogenicities and body resistance is the key against fungal infection. Therefore, it needs in-depth investigation of aerosol fungal pathogenicity and body immunity to determine harms of fungal aerosols in people.

Regular surveillance and stringent measures including air disinfection system, ventilation systems, using the high-efficiency particulate air (HEPA) filters for high-risk wards, closing the windows, control entry and exit doors, control or totally eliminate flowers taken by the patients' visitors are necessary to reduce mold spores.

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Thyroid Abnormality: A Hospital-based Retrospective Study

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ABSTRACT

Introduction: Endocrine disorders are common among Indian population, out of which, thyroid disorders represent an important subset of these endocrine disorders. **Aims and objectives:** To study the prevalence of thyroid abnormality in outpatients. **Material and methods:** The study was conducted on outpatient basis and analyzed the holistic medical reports of a sample of 200 outpatients to study the prevalence of thyroid abnormality. **Results:** Thyroid abnormality was found in 10% of persons in Darbhanga Medical College and Hospital (DMCH) as compared to Indian prospective (~20%). **Conclusion:** The fractional prevalence of thyroid disorders, observed at the DMCH, is lower than national average.

Keywords: Hypothyroidism, hyperthyroidism, TSH, T3, T4

Thyroid abnormality is a generic term used to refer to a set of disorders pertaining to functioning of the thyroid gland and levels of thyroid secretions in the body.

Projections from various studies on thyroid disease estimate that about 42 million people in India suffer from thyroid diseases.[1]

Thyroid disorders can range from a small, harmless goiter (enlarged gland) that needs no treatment, to, life-threatening cancer.

The most common thyroid problems involve abnormal production of thyroid hormones. Hypothyroidism and hyperthyroidism refer to sub-requisite and surplus activity of the thyroid gland, respectively. Both of these varieties have several unique, nuanced subtypes, attributed to various causatives. Additionally, cancer of the thyroid gland is quite rare and occurs in about 5% of thyroid nodules.[2]

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Hyperthyroidism is a physiological phenomenon characterized by the excessive production of thyroid hormone, owing to overactivity of the thyroid gland.[3] Typical symptoms albeit subject to interpersonal variation, mainly comprise of one or many of: sleep irregularities, an irritable demeanor, general fatigue, muscle weakness, tachycardia, diarrhea, thyroid-gland enlargement, heat intolerance, trembling of hands, and loss of weight. Graves' disease is causative in about 50-80% of the cases in the United States of America. Other causes include multinodular goiter, thyroid inflammation, toxic adenoma, consumption of excessive iodine and surplus intake or administration of the synthetic thyroid hormone. A significantly less prevalent cause is pituitary adenoma. The diagnosis may be suspected based on signs and symptoms and then confirmed with blood tests, which typically depict a low thyroid-stimulating hormone (TSH) and raised triiodothyronine (T3) or thyroxine (T4). Measuring radioiodine uptake by the thyroid, performing a thyroid scan and thyroid-stimulating immunoglobulin (TSI) antibody-analyses may help ascertain the cause.[4]

There are three main treatment options: radioiodine therapy, i.e., oral ingestion of iodine-131 isotope, anti-thyroid medications and/or β-blockers, and thyroid surgery.[4] Surgical intervention is only appropriate in drastic cases, typically with hyper-enlargement or cancer-risk emergencies.

The ailment is fairly commonplace, estimated to be affecting roughly 1 in a 100 people. Its observed

frequency is 2-10 times greater in females than in males.[4] Onset is commonly between 20 and 50 years of age.[5] Broadly hyperthyroidism is more common in persons with age over 60 years.[4]

Hypothyroidism (underactive thyroid) is a condition in which the thyroid gland doesn't produce enough of certain crucial hormones. Hypothyroidism may not cause noticeable symptoms in the early stages. Over time, untreated hypothyroidism can cause a number of health problems, such as obesity, joint pain, infertility and heart disease.

Hypothyroidism encompasses a broad clinical spectrum that may range from an overt state of myxedema, end-organ effects and multiorgan failure to an asymptomatic or subclinical state that presents with normal levels of T4 and T3 and mildly elevated levels of serum thyrotropin.[6-10] The prevalence of hypothyroidism in the developed world is about 4-5%.[11,12] The prevalence of subclinical hypothyroidism in the developed world is about 4-15%.[11,13]

Thyroid diseases are different from other diseases in terms of their ease of diagnosis, accessibility of medical treatment, and the relative visibility that even a small swelling of the thyroid offers to the treating physician. Early diagnosis and treatment remain the cornerstone of management.

MATERIAL AND METHODS

The study was conducted upon a sample of 200 outpatients coming to hospital from July 2018 to August 2018. The patients were >10 years of age. The TSH level was checked for all the patients.

RESULTS

Out of 200 patients included, 180 had no abnormality of the thyroid gland (Table 1 and Fig. 1). Figure 2 shows a comparison of prevalence of thyroid disorder in our study with that of control Indian data.[14]

CONCLUSION

The fractional prevalence of thyroid disorders, observed at Darbhanga Medical College and Hospital (DMCH), is lower than the estimated national average. Fractional prevalence of thyroid disorder in the population was 10% but that of another Indian data was about 20%.[14] Thyroid diseases are, arguably, among the commonest endocrine disorders worldwide. India too is no exception. Thyroid diseases are different from other diseases in terms of their ease of diagnosis, accessibility of medical

Table 1. TSH Levels of Study Population

Normal TSH	180 (90%)
Hypothyroidism (TSH >10)	14 (7%)
Hypothyroidism (TSH <10)	4 (2%)
Hyperthyroidism	2 (1%)

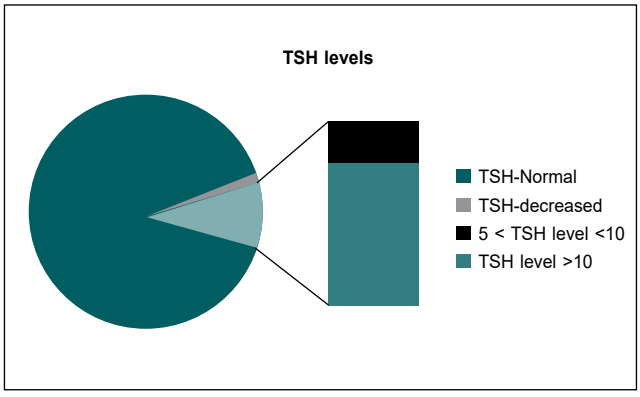

Figure 1. TSH levels of study population.

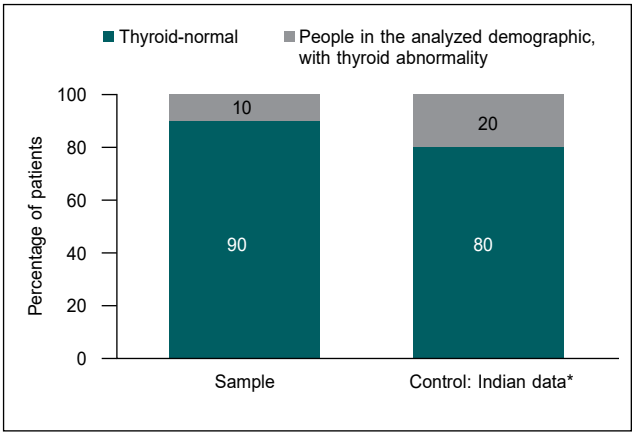

Figure 2. Comparison of prevalence of thyroid disorder in our study with that of control Indian data.

*Approximate value.

treatment and the relative visibility that even a small swelling of the thyroid offers to the treating physician. Early diagnosis and treatment remain the cornerstone of management.

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■■■■

Update on COVID-19

A study published in *The Lancet Infectious Diseases* showed that the predominant pattern of lung lesions in patients with COVID-19 patients was diffuse alveolar damage.

Luca Carsana, at Papa Giovanni XXIII Hospital, Bergamo, Italy, and colleagues assessed lung tissue samples from 38 patients who died from COVID-19 in two hospitals in northern Italy from February 29, 2020 to March 24, 2020.

Investigators obtained a median of 7 tissue blocks from each lung, selecting the most representative areas as seen at macroscopic examination. In an attempt to better characterize the inflammatory infiltrate, immunohistochemical staining was done on the most representative areas of randomly selected cases for inflammatory infiltrate and cellular components, including staining with antibodies against CD68, CD3, CD45, CD61, TTF1, p40 and Ki-67.

Lungs of all patients were heavy, congested and edematous, with patchy involvement. Histological examination revealed features of exudative and early or intermediate proliferative phases of diffuse alveolar damage, which included capillary congestion and necrosis of pneumocytes in all cases, hyaline membranes in 33 cases, interstitial and intra-alveolar edema in 37 cases, type 2 pneumocyte hyperplasia in all cases, squamous metaplasia with atypia in 21 cases and platelet-fibrin thrombi in 33 cases.

Hyaline membrane formation and pneumocyte atypical hyperplasia are common. It is important to note that the presence of platelet-fibrin thrombi in small arterial vessels is consistent with coagulopathy, which is common in patients with COVID-19 and should be among the key targets of therapy.

The patients had a mean age of 69 years and most (87%) were male. Time spent in the intensive care unit or intermediate medical ward varied between 1 day and 23 days. At the time of hospitalization, all patients had clinical and radiological features of interstitial pneumonia. Of the 26 patients with available D-dimer results, all had high levels (>10 × the upper reference limit). Mean time from symptom onset to death was 16 days.

(Source: The Lancet Infectious Diseases)

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Hypertension in Pregnancy: A Bumpy Ride for the Two Nascent Lives

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ABSTRACT

A huge proportion of pregnancies are convoluted by medical disorders. With greater advances in pediatric care and artificial fertility, the numbers of women who attempt a pregnancy bracketed by serious complications have exponentially increased. High blood pressure during pregnancy has been found to be associated with deterioration of maternal and fetal well-being. Pregnancy associated with hypertension is linked with numerous life-threatening complications. This article provides an overview of already existing as well as fresh onset of hypertension during pregnancy and the role of magnesium in pre-eclampsia.

Keywords: Pre-eclampsia, hypertension, pregnancy, gestational hypertension

THE ENDANGERED STORY OF PREGNANCY

Every passing year welcomes more than 125 million new babies to this world, not all of them swirl through a smooth journey to their existence. A huge proportion of pregnancies are convoluted by medical disorders. With greater advances in pediatric care and artificial fertility, the numbers of women who attempt a pregnancy bracketed by serious complications have exponentially increased. The medical issues that impede the physiological adaptations that occur normally during pregnancy increase the number of conception with poorer outcomes. On other instances, a pregnancy that supervenes an already lingering medical condition can potentiate it to dangerous levels.

THE BURDENED ADAPTATIONS OF PREGNANCY

Pregnancy witnesses a precipitous rise in the cardiac output by as much as 40%, most of which is pertaining to the increase in the stroke volume and partially due to the increased pacing of the heart. The third trimester increases the heart rate by more than 10 beats beyond the baseline. The systemic vascular resistance, which is an important function responsible for the generation of blood pressure (BP), falls during the second trimester and this decline is linked with a fall in the BP. A BP of 140/90 mmHg is considered abnormally high during pregnancy and has been found to be associated with deterioration of maternal and fetal well-being as much as that it has been linked to an increased perinatal morbidity and mortality.

MEASUREMENTS: DO IT THE RIGHT WAY

The measurement of BP in pregnant women is in concert with the guidelines laid down by the American College of Cardiology/American Heart Association and the Canadian Hypertension Education Program. BP should be measured in sitting posture, with back supported, uncrossed feet lying flat on the ground and arms extended, using a properly sized cuff (length and width of which should be 80% and 40% of the arm circumference, respectively). The cuff should be deflated at the rate of 3 mmHg/sec and the column should be read to the nearest of 2 mmHg. A palpatory systolic pressure should be measured prior to the auscultatory measurement to avoid the phenomenon of auscultatory gap, which could lead to a recording of spuriously low BP. A lateral recumbent posture while measurement may result in a falsely low BP, hence should be avoided during pregnancy.

The confirmatory diagnosis of hypertension mandates at least 2 measurements taken at least 4 hours apart. Hypertension of pregnancy is a spectrum of

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ailments which may be caused by a pre-existing chronic hypertension or a newly sprouted gestational hypertension and pre-eclampsia.

RIDE ON AN ALREADY TIRED HORSE

Pregnancy that prevails over an already existing chronic hypertension, which is present even prior to 20 weeks of gestation, is found to be the culprit behind several incidences of intrauterine growth retardation and perinatal morbidity and mortality. These women are predisposed to the relatively more dangerous conditions like placental abruption and pre-eclampsia, which even further may precipitate into life-threatening eclampsia. The National Institute for Health and Care Excellence (NICE) guidelines published on June 25, 2019, like its previous editions of guiding principles, advocate and educate that a detailed evaluation of the modifiable causes of hypertension should be done prior to conception. The women who receive angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazide or thiazide-like diuretics for the management of chronic hypertension prior to pregnancy are informed that there is an amplified possibility of congenital abnormalities if they take these drugs during pregnancy. They are suggested to bring a halt to these drugs if they come to know about their conception, if at all possible, within 2 operational days of notification of pregnancy and they should be offered healthier alternatives. They are advised to shed some extra pounds by engaging in healthy exercise and diet. The extra salt and any puff of smoke should be shown the exit doorway. The goal of BP of 135/85 mmHg should be set for them and to achieve this, first of all, labetalol should be considered. If it fails to deliver, nifedipine should be tried, followed by methyldopa, if both of these fail. The guidelines advocate the use of aspirin 75-150 mg daily from 12th week onwards. Should hypertension get worse during pregnancy, baseline appraisal of renal function is obligatory to help in making a distinction between the effects of chronic hypertension from those of overlaying pre-eclampsia. There are no compelling statistics that suggest that the treatment of mild chronic hypertension prevents the perinatal outcomes from becoming untoward.

GESTATIONAL HYPERTENSION

The progression of elevated BP after 20 weeks of gestation or during the first 24 hours postpartum in the nonattendance of prior chronic hypertension or proteinuria is referred to as gestational hypertension. Milder gestational hypertension that does not evolve into the more malevolent forms of pre-eclampsia has not been allied with adverse pregnancy outcomes or a deleterious and protracted prognosis. There is no additional benefit rendered by offering a planned early birth before 37 weeks to women with either chronic hypertension or gestational hypertension when BP is <160/110 mmHg, with or without antihypertensive treatment, except when there are other co-existing medical indications. If at all a planned early birth is needed in pregnancy with hypertension, a course of antenatal corticosteroids and magnesium sulfate should be offered, if indicated, to manage preterm labor. If a woman has used methyldopa to treat chronic hypertension, gestational hypertension or pre-eclampsia, during pregnancy, it has to be stopped within 2 days after the birth and changed to a substitute antihypertensive treatment. In women with gestational hypertension, assessment should be conceded in a secondary care setting by a doctor who is trained in the management of hypertensive disorders of pregnancy. An obese, older women (>40 years) with gestational hypertension, who is nulliparous or one who is pregnant after an interval of more than 10 years or someone who carries a family history of pre-eclampsia or when she is bearing a multifetal pregnancy, necessitate an additional attention because these are naturally at a higher risk of developing pre-eclampsia. In women with gestational hypertension, who have already given birth, the treatment should be continued if they are still in the hypertensive range. The drug therapy should be titrated down if the BP has been pulled down to below 130/80 mmHg.

THE RENAL MESS

Customarily, pregnancy is characterized by an increase in glomerular filtration rate and creatinine clearance. This augmentation occurs from a rise in renal plasma flow and increased glomerular filtration pressures. Patients with core renal disease and hypertension may anticipate an aggravation of hypertension during pregnancy. If superimposed pre-eclampsia creeps in, the supplementary endothelial injury falls out in a capillary leak syndrome that may craft a management, which is extremely exigent. In general, patients with primary renal disease and hypertension profit from insistent management of BP. Preconception counseling is also indispensable for these patients so that precise risk consideration and medication changes can transpire prior to pregnancy. A pre-pregnancy serum creatinine level of <1.5 mg/dL is coupled with a constructive forecast. When renal disease worsens

during pregnancy, close alliance between the internist and the maternal-fetal medicine specialist is critical so that decisions concerning delivery can be weighed to balance the sequelae of prematurity for the newborn against long-standing sequelae for the mother with admiration for the future renal functions.

HAYWIRED END ORGANS: PRE-ECLAMPSIA

As many as 5-7% of all pregnant women develop pre-eclampsia, which has been defined as the fresh onset of hypertension (with a BP >140/90 mmHg) and proteinuria (this can either be a 24-hour urinary protein of >300 mg/24 h, or else a protein creatinine ratio ≥0.3) that has occurred after 20th week of gestation. The current revisions to the diagnostic criteria have excluded proteinuria from being an unconditional prerequisite for making the diagnosis of pre-eclampsia. Further, the terms mild and severe pre-eclampsia which were used earlier have been refuted and the disease has now been named as pre-eclampsia either accompanied with or without severe features. Fetal growth restriction is no longer a crucial decisive factor for pre-eclampsia with brutal features.

THE PUPPETS BEHIND THE SCENE

The fact is that the accurate pathophysiology of pre-eclampsia still remains unanswered conundrum, a few studies have elucidated the unwarranted excessive placental assembly of antagonists to both vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF-β). These antagonists to VEGF and TGF-β disorganize the finely orchestrated endothelial and renal glomerular function resulting in edema, hypertension and proteinuria. The histological renal picture of glomerular endotheliosis is established during pre-eclampsia. Glomerular endothelial cells are engorged and puffed up and these now attempt to encroach on the vascular lumen. Pre-eclampsia is coupled with fallacies of cerebral circulatory autoregulation, inviting an increased risk of stroke at mildly and moderately elevated BPs. The presence of newly established hypertension and proteinuria is said to be stern if it is accompanied by the end-organ damage. The markers of an end-organ damage may include a ruthless elevation of BP (>160/110 mmHg), substantiation of central nervous system (CNS) disarray (headaches, distorted vision, seizures or coma), renal dysfunction (represented by oliguria or a serum creatinine level >1.5 mg/dL), pulmonary edema, hepatocellular grievances (serum alanine aminotransferase levels jumping more than twofold the upper limit of normal), along with the hematological dysfunctions (with a platelet count <1,00,000/L or establishment of disseminated intravascular coagulation [DIC]). The HELLP syndrome, an acronym used for the Hemolysis, Elevated Liver enzymes and a Low Platelet count, is said to be a unique subtype of severe pre-eclampsia and is found to be a major cause of morbidity and mortality in this disease. The platelet dysfunction and coagulation disorders augment the menace of stroke even further.

NO NEED FOR HURRY

Pre-eclampsia settles down in a few weeks after the termination of pregnancy. For pregnant women with pre-eclampsia, a premeditated delivery prior to 37 weeks of gestation reduces the mothers' morbidity but opens up the fetus to a spectrum of risks of premature birth. The supervision of pre-eclampsia is a sturdy assignment because it requires the clinician to poise the health of the mother and fetus simultaneously. In all purposes, prior to term, women with pre-eclampsia without stern features may be managed conservatively with restricted physical activity, even though bed rest is not recommended, with a close eye on the monitoring of BP and renal function, and a watchful fetal scrutiny. For women with pre-eclampsia only with probable unfavorable outcomes, delivery is recommended, otherwise the patients are lined up for the expectant management in a tertiary hospital setting. Management on tenterhooks for pre-eclampsia with riskier features who are far from term, buys some remuneration for the fetus, but brings significant risks for the mother. Thresholds for considering planned early birth could include: 1) Inability to control BP despite using 3 or more antihypertensives in appropriate doses; 2) SPO_2 <90%; 3) Worsening liver function test (LFT), kidney function test (KFT), platelet count; 4) Neurological features, such as severe intractable headache, repeated visual scotoma or eclampsia; 5) Placental abruption; 6) Reversed end-diastolic flow in the umbilical artery Doppler velocimetry and 7) A non-reassuring cardiotocograph.

Postponing delivery further than 34 weeks gestation in this group of patients is not suggested. In pre-eclampsia without ruthless features, delivery at 37 weeks is recommended. The state-of-the-art treatment of pre-eclampsia is delivery of the fetus and placenta. For women with pre-eclampsia with severe features, aggressive management of BP >160/110 mmHg reduces the risk of cerebrovascular accidents. IV labetalol or hydralazine is most universally used to acutely manage severe hypertension in pre-eclampsia; labetalol is

related with smaller number of episodes of maternal hypotension. It has been advocated to not use volume expansion in women with severe pre-eclampsia unless hydralazine is used; it has been allowed to use up to 500 mL crystalloid fluid before or at the same time as the first dose of IV hydralazine is given in the antenatal period. In women with severe pre-eclampsia, limitation of fluids to 80 mL/hour, unless there are other ongoing fluid losses, has been suggested. Lofty arterial pressure should be abridged unhurriedly to avoid hypotension and a dwindled blood flow to the fetus.

MAGNIFICENT MAGNESIUM

Magnesium sulfate is the favored agent for the deterrence and management of eclamptic seizures. Outsized, randomized clinical trials have established the authority of magnesium sulfate over phenytoin and diazepam in plummeting the risk of seizure and, may be, the risk of maternal death. Magnesium may downsize the seizures by playing with *N*-methyl-ᴅ-aspartate (NMDA) receptors in the CNS. The widespread use of magnesium sulfate for seizure prophylaxis in pre-eclampsia devoid of severe features is no longer suggested by most experts. There is accord that magnesium sulfate should be used in all cases of pre-eclampsia with relentless features, or in cases of eclampsia. Women who have had pre-eclampsia emerge to be at an amplified jeopardy of cardiovascular and renal disease soon after in time.

With an ever increasing attempt of playing with already jeopardized pregnancies, the duty and considerations required by the physicians have gone higher right from psychotherapy prior to conception till the streamlining of management post-delivery. This has invited a deeper understanding of the physiology of pregnancy so that the maternal and fetal lives are appropriately cared for.

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Countries Failing to Prevent Violence Against Children

Nearly 1 billion children across the world are affected by physical, sexual or psychological violence every year, and suffer injuries, disabilities and death, as countries fail to follow strategies to protect them, suggests a new report published by the World Health Organization (WHO), UNICEF, UNESCO, the Special Representative of the United Nations Secretary-General on Violence against Children and the End Violence Partnership.

The report – *Global Status Report on Preventing Violence Against Children 2020* – is the first of its kind and underscores the need in all countries to escalate efforts to implement strategies to prevent and respond to violence against children… (*WHO*)

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Effectiveness of Steroids in Thrombocytopenia in Dengue Patients – A Review

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ABSTRACT

Dengue is a mosquito-borne viral disease. Dengue hemorrhagic fever (DHF) is a deadly complication of dengue fever (DF) characterized by increased vascular permeability and clotting problems. Dengue shock syndrome (DSS) is another complication of DF that is characterized by circulatory failure and rapid progress to critical state of shock. This article provides an insight into the contributory factors, pathogenesis, and management of dengue with special focus on the role of corticosteroids in the management of the viral illness.

Keywords: Dengue, dengue hemorrhagic fever, dengue shock syndrome, dengue vaccine, corticosteroids

Dengue is a mosquito-borne viral disease, which presents with symptoms of high fever (40^0C), accompanied by severe headache, retro-orbital, muscle and joint pain. Nausea, vomiting, swollen glands and rash are the other typical symptoms. Symptoms last for 2-7 days after the incubation period. In certain cases, complications arise due to plasma leakage, fluid accumulation, respiratory distress and severe bleeding or organ impairment leading to severe dengue.[1] Dengue virus (DENV) are arboviral pathogens belonging to the Flavivirus genus and Flaviviridae family, found mainly in the tropical and subtropical regions. The serotypes include DENV 1 to 4, which are antigenically different and have a single-stranded RNA. The virus transmission occurs via sylvatic, enzootic cycle between mosquitoes and nonhuman primate host, whereas the endemic cycle occurs between humans and mosquitoes.[2] The vector belongs to Aedes family. The primary vector is *Aedes aegypti* and the secondary vector is *Aedes albopictus*.[3,4]

Dengue hemorrhagic fever (DHF) is a deadly complication of dengue fever (DF) characterized by increased vascular permeability and clotting problems. Dengue shock syndrome (DSS) is another complication of DF that is characterized by circulatory failure and rapid progress to critical state of shock. It also presents with petechiae and ecchymoses.[5]

Since it is a viral infection, there is no specific treatment. Treatment of DF mainly involves rest and fluids. Certain observational studies suggest the use of corticosteroids as it seems to benefit in DSS or DHF, preventing the complications of DF. The evidence regarding the beneficial effect of corticosteroids in DF is inconclusive.[6]

HISTORY

The global distribution is about 390 million dengue infections per year, out of which 96 million manifest at any severity. In 2010, it was identified that Asia accounted for 70% of these infections.[7] Mid-1900s saw frequent epidemics of dengue in urban zones and the first outbreak happened in 1963 in Calcutta.[8] In 1943-1944, dengue virus was isolated for the first time and the first virologically proved epidemic of dengue fever occurred in 1963-1964 along the East Coast of India.[9]

VECTOR AND INCUBATION PERIOD

A. aegypti and *A. albopictus* are both the vectors in DENV transmission. The extrinsic incubation period (EIP) is temperature dependent and refers to the time period between viremic blood meal to mosquito becoming infectious. A set of observational studies have set EIP to be 8-12 days. A study conducted by Chan and Johansson identifies EIP to be 5-33 days at 25°C and

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2-15 days at 30°C.[10] The two significant periods for humans are intrinsic incubation period (IIP) and latent period. IIP basically refers to the onset of symptoms and the latter refers to the time period between infection and onset of infectiousness. According to the World Health Organization (WHO), IIP is about 4-10 days and the Center for Disease Control and Prevention (CDC) mentions it to be around 3-14 days. The Chan and Johansson study identifies it to be 3-10 days.[10]

CONTRIBUTING FACTORS

The increased incidence of dengue in India is due to the unplanned urbanization, changes in environmental factors, host-pathogen interactions and inadequate vector control and population immunologic factors.[8] The environmental factors mainly involve temperature and precipitation. Temperature influences the development rate, mortality and reproduction of mosquitoes, whereas the precipitation influences water habitat for larvae and pupae. Warm temperature and humidity increase the longevity of the adult mosquitoes. It shortens viral incubation period or EIP and facilitates faster viral replication leading to increased transmission.[8]

PATHOGENESIS

The pathogenesis of dengue is unclear, the following is considered as the mechanism involved in dengue infection.

The infection is preceded by the bite of an infected mosquito. This is followed by the dissemination of virus, leading to infection of multiple lymphoid and nonlymphoid tissues. The viremia ensues following the accumulation of virus in the bloodstream leading to the clinical symptoms and interferon expression. Viremia peaks after the onset of fever and then a plateau stage is attained, later gradually declining, depending upon the host immune system.[11] The three phases of dengue include febrile phase, critical phase (plasma leakage) and the recovery phase. DENV binds to the Fcγ receptors on mast cells resulting in cytokine, vascular endothelial growth factors, chymotrypsin production. This leads to endothelial activation and production of inflammatory lipid mediators that increase the vascular permeability and vascular leakage.[12] In the 1960s, Southeast Asia found children dying of a new form of severe dengue named dengue vascular permeability syndrome or DVPS. DVPS is a syndrome that occurs late in the course of an acute dengue illness consisting of thrombocytopenia, altered hemostasis, activated complement, elevated liver transaminase levels with hepatomegaly, vascular permeability and hypoalbuminemia.[13] This condition is identified with second heterotypic DENV infection or infants born to dengue-immune mother, characterized by abrupt onset of fever moving on to cold clammy extremities, slow venous filling, flushed face, restlessness, epigastric pain and petechiae.[14] New evidences point that nonstructural protein 1 (NS1) is a toll-receptor 4 agonist that stimulates primary human myeloid cells to produce cytokines similar to severe dengue disease.[14]

DHF, according to WHO is classified into I, II, III and IV grades, where I and II are mild cases with no shock and III and IV are more severe accompanied by shock. Hemorrhagic manifestation, thrombocytopenia and increased vascular permeability are other signs in DHF, apart from the symptoms seen in DF. Prolonged shock leading to blood being cut-off from gastrointestinal (GI) tract resulting in anoxia, cell death, GI bleed and vasculogenic cytokines are responsible for the hemorrhagic nature of DHF. DENV tropism, activation of complement system, virus virulence, organ pathology, cells of immune system, transient autoimmunity, host genetic factors, antibody-dependent enhancement, cross-reactive T-cell responses, all contribute to DHF.[15]

The defining feature of severe dengue is increased capillary permeability causing plasma leakage, leading to intravascular volume depletion. If the condition is left untreated, it could lead to shock and death.[16]

THROMBOCYTOPENIA AND DENGUE

Thrombocytopenia is one of the most significant clinical manifestations of severe dengue, which can progress to either DHF or DSS. Platelet count decreases due to increased destruction of platelets in peripheral blood or decreased production in bone marrow. The major mechanism of platelet destruction is linked to the activation of complement factor C3 followed by binding of the C5b-9 complex to the platelet surface, which leads to increased platelet destruction.[17]

PREVENTIVE STRATEGIES

Vector control is aimed at the elimination of breeding sites such as water filled man-made containers, improved storage of water and maintenance of environment hygiene.[16] The use of insecticide and larvicide may be effective for a short period of time, but it poses a threat of developing insecticide resistance.[18]

Genetic manipulation of the *A. aegypti* can be a successful tool for pest control. An intracellular bacterium

Wolbachia has been considered as it provides an advantage of invading the population by cytoplasmic incompatibility. A study proved that the Wolbachia infected *A. aegypti* led to decreased pathogen transfer and lifespan of the mosquitoes in Australia.[19,20]

Dengue Vaccine

Vaccination can be considered as an effective mechanism as current methods of preventive strategies for mosquito elimination have become futile.

No antivirals drugs are active against the Flavivirus and control of mosquito vector has thus become difficult. Vaccination remains the most hopeful preventive measure. Inactivated vaccine may be safe but requires booster dose; tetravalent live attenuated vaccine and chimeric vaccine has become the backbone of dengue vaccines.[21] Types of vaccines evaluated include live attenuated, live chimeric, recombinant, inactivated, subunit and DNA vaccine.[22]

The first dengue vaccine is CYD-TDV, which is a live recombinant tetravalent vaccine. It was first registered in Mexico in December 2015, and is given in a 0-6-12 months schedule.[23] Vaccines have been developed correlating to the pathogenesis of dengue. A genetically modified infectious virus clone is an advanced form. Genetic vaccination and use of recombinant virus such as attenuated adenovirus are being investigated.[24] The reactogenicity of vaccine occurs due to the adaptive or acquired immunity.[25] Challenges faced include existence of 4 DENV types, absence of validated animal model, no validated human model, incomplete understanding of the immune profile and poorly immunizing vaccine.[26] A published study shows effective results of CYD-TDV vaccine in children aged 9-16 years.[27] Other candidate vaccines with promising results in phase 1 and 2 trials include a live attenuated tetravalent dengue vaccine, and a recombinant live attenuated tetravalent vaccine.[28-30] Presently, India has two different dengue vaccine candidates, an LAV and a recombinant protein based vaccine DSV4 for testing. But a safe vaccine seems to be out of reach.[31]

MANAGEMENT IN DENGUE

The management of dengue mainly involves fluid replacement and rest. Since it is a viral infection, no antibiotics are effective against it.

Since no suitable antivirals are available, symptomatic treatment is provided in dengue. Antipyretics can be given, the use of nonsteroidal anti-inflammatory agents is to be avoided. Oral hydration is advised to all patients.

Fluid Replacement

Hydration is a necessity in dengue fever. Crystalloids are aqueous solution of mineral salts or other water-soluble molecules, whereas colloids contain large insoluble molecules.

Crystalloids or colloids are considered for fluid replacement therapy. About 0.9% normal saline or Ringer's lactate is the most commonly used crystalloid followed by dextran or gelatin in colloids. In serious circumstances, colloids are used because of their greater osmotic effect and they draw the fluid back to capillary.[32,33]

In cases of DHF I and II, 6 mL/kg/h crystalloid solution for 1-2 hours is given. If the patient shows no improvement, increase IV 10 mL/kg/h for 2 hours along with blood transfusion in case of suspected hemorrhage. In DHF III, IV crystalloid solution of 10-20 mL/kg/h is given; if there is no improvement, consider colloids/crystalloids 10-20 mL/kg over 1 hour along with blood transfusion for suspected hemorrhage. DHF IV is treated with rapid volume replacement of 10-20 mL/kg crystalloid solution as bolus over 15-30 minutes.[34] DHF requires a higher volume of fluid from the 3rd day of fever and from the 5th to 7th day, whereas for DF least amount of fluid is required on the 3rd day.[35]

A study compared two crystalloids, normal saline and lactated Ringer's solution and two colloids, dextran 70 and 3% gelatin, and identified colloid solution to be more beneficial.[36] Another study showed that dextran 70 and 6% hydroxyethyl starch were beneficial but dextran caused more adverse effects. The study also stated that Ringer's lactate is indicated for initial resuscitation in children.[37] Another possible treatment is the use of intravenous immunoglobulin (IVIg) due to its immunomodulatory effect.[38]

Corticosteroids

Corticosteroids have been used in a variety of disease conditions. It is a treatment option widely used.

These are anti-inflammatory agents, synthetic compounds similar to the natural hormones produced by the adrenal glands. In higher doses, they have immunosuppressive properties.[39]

Mechanism of action

The mechanism of action of corticosteroids involves both genomic and nongenomic pathway.

Corticosteroids bind to the glucocorticoid receptors (GR) leading to gene transcription (genomic pathway) or

production of responsive elements (nongenomic) that result in the immunomodulatory effect. Understanding the GR signaling may help in the development of more safe and effective steroid drugs.[40] The pharmacologic action includes cellular functions like development, homeostasis, metabolism, cognition and inflammation.[40,41] They are effective in thrombocytopenia as they inhibit the formation of platelet autoantibodies and reverse the adenosine diphosphate (ADP) activation of platelets leading to decreased destruction of platelets.[42,43]

Platelet count and steroids

The relation between steroids and platelet count has been explored very little. It is believed that steroids can reduce platelet destruction, thereby used in dengue where thrombocytopenia is one of the major complication in dengue.

Corticosteroids are used in immune thrombocytopenic purpura (ITP) as they reduce the rate of platelet destruction and alter the endothelial cell integrity to facilitate primary hemostasis.[44] Prednisone is the conventional treatment in ITP.[45,46] Methyl-prednisolone[45,47] and dexamethasone[45,48-50] are also used in the treatment, according to randomized trials, as they help in improving the platelet count.[45,51]

Steroids in dengue

Dengue fever has thrombocytopenia as the major complication. Steroids can be used to prevent the platelet destruction. Corticosteroids are used empirically by clinicians as they have the potential for preventing and reducing complications of dengue. The ability of corticosteroids to increase platelet count and reduce its destruction is taken into account. The WHO guidelines for dengue management do not mention corticosteroids. This is due to lack of proper evidence.

The review consists of 13 studies, out of which the majority of participants were children. The earliest evidence came from a small randomized controlled trial, where children with DSS were treated with a tapering dose of hydrocortisone for 3 days. A statistically significant mortality benefit was seen in children 8 years and above.[52] A clinical study showed no benefit with IV hydrocortisone 25 mg/kg/day.[53] This was probably due to the study being unbalanced with 7 in steroid and 19 in control group and single dose of drug.

The studies conducted were divided into three categories, according to the stage of DF when corticosteroid was administered. Table 1 summarizes the studies with the use of steroids in the early stage.

Table 1. Studies with Steroid Use in the Early Stage

Authors/Shock stage of study group	Dose and duration of drug	Results	Explanation for the results
Tam DT, et al /No shock	Low-dose (0.5 mg/kg) or high-dose (2 mg/kg) oral prednisolone for 3 days; within DF for ≤72 hours.	No significant adverse effects or prolongation of viremia. No reduction in the incidence of shock.	High-dose could reduce the risk of shock by up to 43%.
Villar LA, et al/No shock	Methylprednisolone single dose, within 120 hours of fever onset.	Reduces the incidence of bleeding and no prolongation of viremia; no significant adverse events.	Methylprednisolone has the highest receptor affinity among corticosteroids and IV root access is used. Treated early in the course of illness.
Kularatne SA, et al/No shock	IV 4 mg dexamethasone, followed by 2 mg doses 8 hourly for 24 hours.	A low-dose is used; dexamethasone was not effective in achieving a higher rise of platelet count in dengue infection.	Four-day course of high-dose dexamethasone (40 mg/day) is an effective dose. Dexamethasone 10 mg/day was used here.
Shashidhara KC, et al/ No shock	IV dexamethasone 8 mg initially, followed by 4 mg 8 hourly thereafter for 4 days.	A low-dose is used; dexamethasone was not effective in achieving a higher rise of platelet count.	Four-day course of high-dose dexamethasone (40 mg/day) is an effective dose. Dexamethasone 12 mg/day was given here.
Nguyen TH, et al/No shock	Low-dose (0.5 mg/kg) or high-dose (2 mg/kg) oral prednisolone/Fever for <72 hours.	Early prednisolone therapy has little impact on the host immune response or the clinical evolution of dengue.	After corticosteroid administration, it may take longer duration to detect changes of immune markers. In this study, it was checked on Day 1 and Day 2.

The period is between the onset of dengue symptoms to earliest plasma leakage.

The study conducted by Tam et al, had 225 Vietnamese patients with DF for <72 hours, preceding the critical phase. The patients aged between 5 to 20 years were included in the trial. They had three groups - low-dose (0.5 mg/kg), high-dose (2 mg/kg) oral prednisolone and a placebo group. The therapy continued for 3 days and the conclusion obtained was that oral prednisolone during the preliminary phase of DF is not associated with significant adverse events or clinical events nor leads to reduction in the incidence of dengue complications, but it highlighted that high-dose corticosteroids could reduce the risk of shock up to 43%.[54] The study by Nguyen et al had high-dose (2 mg/kg) and low-dose (0.5 mg/kg) of prednisolone administered to patients for 3 days. The concentration of 11 cytokines and chemokines were measured each day for 3 days and it was found that there was no attenuation of acute phase plasma cytokines by prednisolone treatment. The study concluded that there was no reduction in the severity of plasma leakage but there was no prolonged viremia in the prednisolone treated patients.[55] Two other clinical trials saw a rise in the mean platelet count following low- (4 mg initially, followed by 2 mg every 8 h for 24 h) (Kularatne et al) and high- (8 mg initially followed by 4 mg every 8 h for 4 days) doses (Shashidhara et al) of dexamethasone; however, it was ineffective in achieving a higher rise in the platelet count.[56,57]

A positive response to corticosteroid administration in the early phase was obtained from another study conducted by Villar et al that had patients in the age group of 5-15 and more than 15 years. The participants were given a single dose of methylprednisolone and the study concluded that there was a reduction in the incidence of bleeding and ascites.[58]

To summarize the studies, two trials with high and low doses of prednisolone for 3 days and two trials using IV dexamethasone did not show beneficial effects. A study administering a single dose of methylprednisolone showed promising results. No adverse events were reported in all of the trials mentioned above.

Table 2 summarizes the studies with corticosteroid use during intermediate stage.

The phase between the onset of critical stage and before the severe stage of DSS, not including Grade IV of DHF.

The study conducted by Fernando et al, used hydrocortisone 50 mg IV, 4 times a day in DHF I and II patients. Ninety-two percent showed improvement within 72 hours and none of the patients advanced into the leakage phase. Of the participants in the control group treated with standard dengue management protocols, 24% developed complications such as myocarditis,

Table 2. Studies with Corticosteroid Use During the Intermediate Stage

Authors/Shock stage	Dose and duration of drug	Results	Explanation for the results
Fernando S, et al/DHF Grade I and II	IV hydrocortisone 50 mg, 4 times a day for 3 days.	92% improved within 72 hours/24% of controls had myocarditis, hemorrhage, pneumonia.	Pharmacologically effective drug protocol maintained therapeutic drug levels.
Min M, et al/Shock	IV hydrocortisone Day 1: 25 mg/kg, Day 2: 15 mg/kg, Day 3: 10 mg/kg, for 3 days.	A statistically significant mortality benefit was seen.	Pharmacologically effective drug protocol was used.
Sumarmo et al/Shock	A single dose of IV hydrocortisone hemisuccinate, 50 mg/kg.	No value in the treatment.	No sustained effective drug dose was maintained. High-dose effect lasted only for a short period. Hydrocortisone has low receptor affinity than methylprednisolone.
Futrakul P, et al	IV methylprednisolone: 10-30 mg/kg/dose; Single or repeated dose.	9 out of 11 in treatment group survived. All patients in the control group died.	Sustained and effective drug dose was maintained. Single dose may help due to higher receptor affinity of methylprednisolone.
Futrakul P, et al	IV methylprednisolone: 30 mg/kg. Repeated doses.	Significant hemodynamic improvement.	Sustained and effective drug dose was maintained with using a drug with higher receptor affinity.

hemorrhage and pneumonia.[59,60] A study by Min et al, used tapering dose of IV hydrocortisone: 25 mg/kg on Day 1, 15 mg/kg on Day 2 and 10 mg/kg on Day 3, for 3 days in children 8 years and above. A clinically significant reduction in mortality rate was seen.[52] Two other trials by Futrakul and colleagues in 1981 and 1987 used multiple doses of IV methylprednisolone of 10-30 mg/kg and demonstrated beneficial effects. [61,62]

Another clinical trial conducted with hydrocortisone showed no beneficial effects. A single dose of hydrocortisone 50 mg/kg of body weight was administered to children with DSS. The response to therapy of 47 children in steroid group and that of 50 in control group, was virtually identical and the study concluded that hydrocortisone is of no value in the treatment of DSS.[63]

To be brief, out of the five trials in the intermediate stage, only one which used a single dose of hydrocortisone failed to exhibit beneficial effects. However, the other trials that used multiple doses showed beneficial effects. Table 3 summarizes the studies with corticosteroid use during the late stage.

A study conducted by Tassniyom et al administered a single high-dose of methylprednisolone IV 30 mg/kg or placebo in 63 children with profound dengue shock. Complications such as fever after shock, pneumonia, convulsions, cardiac arrest, pulmonary hemorrhage and positive hemoculture occurrence were not different in treatment and control groups and the study concluded that the drug has no beneficial effect in reducing the mortality in severe DSS.[64] A study by Widya and Martoatmodjo concludes that 30 mg IV hydrocortisone administered every 4-6 hours/day was ineffective; 10 patients died out of 28.[60,65]

Conversely, a study by Premaratna et al showed beneficial effects of corticosteroids. A single dose of IV methylprednisolone 1 g was given to adults in severe DSS stage. The hematological recovery and morbidity after recovery were significantly shorter in the corticosteroid-treated group.[66]

In short, two trials that used single-dose IV methyl-prednisolone and multiple doses of IV hydrocortisone did not show any beneficial effects, whereas another study using single-dose IV methylprednisolone showed beneficial effects.

From these studies, it can be summarized that IV methylprednisolone in high and multiple doses demonstrated to be the most beneficial. At high doses, steroids intercalate into the cell membrane thereby altering cellular functions and leading to a reduction in calcium and sodium cycling across immune cells. Also, high-dose steroids act in both genomic and nongenomic pathways unlike the low-dose steroids.[67] A single dose of glucocorticoid has short duration of action as the receptor occupation reverts to its original state quickly thereby implying the significance of multiple doses.[68] Methylprednisolone has a quicker penetration of cell membrane and IV shows a rapid peak.[69] High-dose methylprednisolone has more beneficial effects in thrombocytopenia.[47,70,71] The poor response of dexamethasone in trials may be due to inadequate dose and frequency. Even in ITP, a high-dose is preferred.[72]

Table 3. Studies with Corticosteroid Use in Late Stage

Authors/Shock stage	Dose and duration of drug	Results	Explanation for the results
Premaratna R, et al	IV methylprednisolone 1 g single dose.	Hematological recovery, hospital stay, morbidity after recovery were significantly shorter in the corticosteroid groups.	Single high-dose of a drug with higher receptor affinity and low mineralocorticoid action is used. Reduced confounding factors due to better fluid management in 2011 study than 1993 and 1875.
Tassniyom et al/ Profound shock	IV methylprednisolone single dose 30 mg/kg.	Did not reduce mortality in severe DSS, pneumonia, convulsion, cardiac arrest, pulmonary hemorrhage and positive hemoculture.	At profound shock stage of the illness body does not respond to conventional critical care. Fluid management methods might not be better established in 1993 than 2011 that might have masked the benefit effect of corticosteroids.
Widya MS, et al/Most patients profound shock	IV hydrocortisone 30 mg 4-6 hourly (120-180 mg/day).	No effects of corticosteroids in severe DSS.	Hypervolemia due to mineralocorticoid action of hydrocortisone could increase mortality and morbidity at this stage.

It has also been proved that high-dose dexamethasone enables early cessation of steroids without loss of response in ITP and also is used as an initial treatment option.[48,73] Another study reveals that dexamethasone is superior to prednisolone as it has higher response rates, shorter time to response and fewer bleeding events.[72]

A significant observation is that most beneficial effects of corticosteroid administration were found in intermediate stage of DF, shown in studies conducted by Fernando et al, Min et al and Futrakul and colleagues. The reason may be that at this stage the immune-mediated mechanisms, cross-reacting antibodies, cytokines and chemokines are high, which can be suppressed by adequate amount of steroids. Hydrocortisone did not show benefit in the study by Widya and Martoatmodjo possibly due to its mineralocorticoid effect that led to hypervolemia and adverse effects.

Certain studies show that corticosteroids can be beneficial in dengue, but it requires large randomized trials to prove the beneficial effects[74] and other studies show that the beneficial effects of corticosteroids can be obtained if therapeutic blood levels of these drugs are maintained.[60]

CONCLUSION

The relevance of adding steroids to dengue fever treatment is discussed in this review. It has been identified how steroids can reduce complications in dengue such as thrombocytopenia.

To summarize, corticosteroids have beneficial effects in dengue illness, primarily in the intermediate stage where the immunosuppressive mechanism of corticosteroids is put to use. High doses with multiple frequencies of corticosteroids given intravenously have better results. Although methylprednisolone has shown beneficial effects in dengue trials, dexamethasone may be a better agent. It has short onset of response and less bleeding events. Large randomized trials are required to analyze its beneficial properties.

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Evaluation of the Infertile Female

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ABSTRACT

Infertility is defined as failure to conceive after 1 year of regular unprotected intercourse and is estimated to affect 10-15% of couples worldwide. Evaluation of the female partner is started if she fails to achieve pregnancy after 12 months or more of regular unprotected intercourse. This article provides a comprehensive review of the evaluation of a woman with infertility. We discuss the history and physical examination, evaluation of ovulatory function, tubal and peritoneal factors, uterine factors, cervical factors and ovarian reserve testing in detail.

Keywords: Female infertility, ovulatory dysfunction, uterine factors, tubal and peritoneal factors, cervical factors, ovarian reserve test, basal body temperature

Infertility is defined as failure to conceive after 1 year of regular unprotected intercourse. It affects 10-15% of couples worldwide. Female factor is responsible for infertility in 35-40% of couples. Among females, the major causes of infertility include ovulatory dysfunction (30-40%), tubal and peritoneal pathology (30-40%), cervical factor (3%), uterine factor (rare) and unexplained (10%) (Fig. 1).

Usually, we start evaluation of female partner if she fails to achieve pregnancy after 12 months or more of regular unprotected intercourse. But in certain conditions earlier evaluation is warranted, which include:

- After 6 months of unsuccessful efforts in women over age of 35 years
- History of irregular menstrual cycles
- Known or suspected uterine/tubal or peritoneal disease
- History of pelvic infection
- Endometriosis, particularly Stage III-IV
- Known or suspected male subfertility.

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HISTORY AND EXAMINATION

Both the partners should be made aware of underlying causes of infertility, components of basic evaluation and encouraged for simultaneous testing.

Diagnostic evaluation should begin with thorough history and physical examination. History taking of infertile partner must include the following:

- Duration of infertility and results of any previous evaluation/treatment
- Coital frequency and sexual dysfunction
- Menstrual history (age at menarche, cycle length and characteristics, onset/severity of dysmenorrhea)
- Outcome of previous pregnancy, if any, and use of contraception
- Past or current medical and surgical illness (particularly any history of pelvic infection,

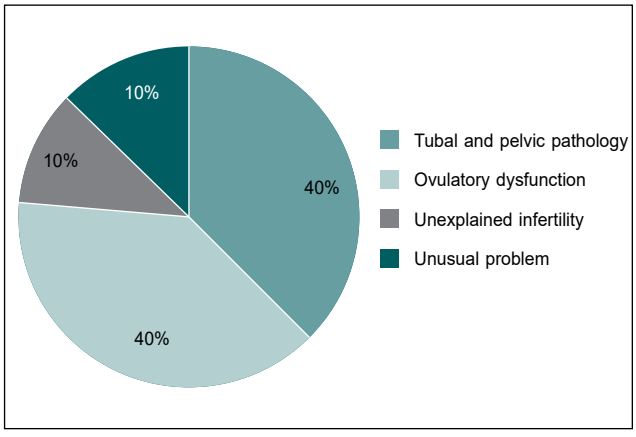

Figure 1. Cause of infertility: Women.

exposure to sexually transmitted infections, septic abortion, ectopic pregnancy, abdominal myomectomy, adnexal surgery)
- Family history of birth defects, mental retardation, early menopause or reproductive failure
- Symptoms of thyroid disease, galactorrhea, hirsutism or acne
- Pelvic or abdominal pain or dyspareunia
- Occupation and addiction history.

Physical examination should document:
- Body mass index (BMI)
- Thyroid nodule or tenderness
- Breast secretions and their character
- Signs of androgen excess
- Abdominal or pelvic mass or tenderness
- Vaginal or cervical abnormality or discharge
- Any mass, tenderness or nodularity in adnexa or cul-de-sac.

Subsequent evaluation should be carried out in a systematic and cost-effective manner to identify underlying cause.

OVULATORY FUNCTION

Ovulatory dysfunction, presenting as menstrual irregularity, is the underlying cause of infertility in approximately 15% of infertile couples and accounts for up to 40% of infertility in women. Diagnosis of ovulatory dysfunction can be made by menstrual history. Further investigations should be aimed to document ovulation and find the pathology of anovulation, if present.

Document Ovulation

A history of regular menstrual cycles occurring at interval of 25-35 days with consistent flow characteristics strongly suggests normal ovulatory function but still objective documentation in infertile women is needed. There are a number of methods to measure normal ovulatory function.

Methods to document ovulation

- Basal body temperature charts
- Urinary luteinizing hormone (LH) Kits
- Mid-luteal serum progesterone level
- Endometrial biopsy

Serial basal body temperature (BBT) measurement is a simple and inexpensive method based on thermogenic properties of progesterone. Ovulatory cycles have typical "biphasic" BBT recording, whereas anovulatory cycles have monophasic pattern. It is not the preferred method for infertile women because there can be few women who menstruate regularly but do not exhibit biphasic BBT.

Urinary LH determination is based on identification of mid-cycle LH surge and provides indirect evidence of ovulation. Since LH has a short half-life and is rapidly cleared of the urine, testing should be done on a daily basis starting 2-3 days before the surge is expected based on the cycle length. It is done using various commercially available "ovulation prediction kits" like i-know, i-can, PregaPlan, etc., which are easy to use but can have false positive and false negative results.

Serum progesterone measurement is simplest, reliable and preferred test of ovulatory function as long as it is appropriately timed. The best time to test is Day 21 of a 28-day cycle or approximately 1 week before the expected onset of next menses. A progesterone concentration of >3 ng/mL provides reliable evidence of recent ovulation, whereas value >10 ng/mL is suggestive of normal "in phase" endometrial histology.

Endometrial biopsy identifies ovulation based on characteristic secretory endometrial changes on histology induced by progesterone. Historically, it was considered "gold standard" for diagnosis of luteal phase deficiency (LPD) but not anymore. Since endometrial biopsy is an invasive test and provides not much added information over other noninvasive methods, it is no longer recommended to evaluate ovulatory or luteal function in infertile women. Its clinical use is limited to identify or exclude endometrial hyperplasia in women with chronic anovulation and to diagnose chronic endometritis. But in our Indian population where tuberculosis is an important cause of infertility, it becomes a part of routine investigations to rule out tubercular endometritis.

Serial transvaginal ultrasonography (TVUS) can be used to monitor number and size of developing follicles. It provides most accurate estimate of ovulation identified by sudden collapse of follicle, loss of clearly defined follicular margins, appearance of internal echoes and increase in cul-de-sac fluid volume. Because of associated cost and logistic demands, it is mainly used to monitor follicle growth in women receiving ovulation induction drugs.

Establish Cause for Anovulation

Patients with irregular or infrequent menses and amenorrhea have ovulatory dysfunction and do not

require any specific test to establish a diagnosis of anovulation. The ovulatory disorders have been classified by World Health Organization (WHO) into three groups (Table 1).

Therefore, in women with irregular cycles, basal (Day 2-4) serum follicle-stimulating hormone (FSH), LH, serum estradiol and prolactin levels should be done to find the cause of anovulation and to treat accordingly. Before that, pregnancy must be excluded by a urine pregnancy test. Serum thyroid-stimulating hormone (TSH) levels should be done if signs and symptoms are suggestive of it.

TUBAL AND PERITONEAL FACTORS

Tubal pathology is the most common cause (30-35%) of infertility among both young as well as older women. Tubal damage should be strongly suspected in women with history of tuberculosis, pelvic inflammatory disease (PID), septic abortion, ectopic pregnancy or tubal surgery. Other important causes of tubal and peritoneal factor infertility include inflammation and adhesions related to endometriosis, inflammatory bowel disease or surgical trauma.

Hysterosalpingography (HSG) is the traditional and standard method for evaluation of tubal patency. It is a procedure which directly visualizes uterotubal anatomy as well as tubal patency with fluoroscopic screen after injecting radio-opaque dye through cervix. It is done as an office procedure in the preovulatory phase of menstrual cycle. It is approximately 65% sensitive, 83% specific with a positive (PPV) and negative predictive value (NPV) of 38% and 94%, respectively. It's low PPV implies that when HSG reveals obstruction, it can be because of mucus plug or cornual spasm and there is high probability (approx. 60%) that tube is open but when it demonstrates patency, there is only 5% chance that tube is actually occluded.

Saline infusion sonography (SIS) involves TVUS after injecting saline into uterine cavity. Apart from delineating intrauterine pathology, it can also be used to determine tubal patency by appearance of fluid in cul-de-sac with saline infusion on TVUS. It does not differentiate between unilateral or bilateral patency.

Laparoscopy and chromotubation is the definitive test for evaluation of tubal factors. It provides both a panoramic view of pelvic reproductive anatomy as well as magnified view of uterine, ovarian, tubal and peritoneal surfaces. Apart from evaluation of tubal patency, it can also identify distal tubal occlusive disease (fimbrial agglutination, phimosis), pelvic or adnexal adhesions and endometriosis that adversely affect fertility but escape detection by HSG. It also provides advantage of treating the pathology at time of diagnosis.

The detection of antibodies to *Chlamydia trachomatis* has also been associated with tubal pathology, including tubal occlusion, hydrosalpinx and pelvic adhesions but its clinical utility has not been proved yet.

UTERINE FACTORS

Anatomic and functional abnormalities of uterus are an uncommon cause but should always be excluded as a part of infertility evaluation. The anatomic abnormalities

Table 1. WHO Classification of Ovulatory Disorders and Serum Concentration of Hormones

Hormone	Normal values	Hypogonadotropic hypogonadal anovulation (WHO Class I) 5-10%	Eugonadotropic eu-estrogenic anovulation (WHO Class II) 75-85%	Hypergonadotropic anovulation (WHO Class III) 10-20%	Hyper-prolactinemia
Day 2/3 FSH	<10 IU/L	Decreased	Normal	Increased	Normal
Day 2/3 LH	<10 IU/L	Decreased	Normal or increased	Increased	Normal
LH:FSH ratio	About 1:2	Normal	Reversed	Normal	Normal
Day 2/3 estradiol	<50 pmol/L	Decreased	Normal	Decreased	Decreased
Serum prolactin	15-20 ng/L	Normal	Normal or increased	Normal	Increased
Example		Kallmann's syndrome Excessive exercise Anorexia nervosa	Polycystic ovary syndrome	Premature ovarian failure	Pituitary micro- or macroadenoma

which adversely affect fertility include congenital malformations, leiomyomas, intrauterine adhesions and endometrial polyp. Chronic endometritis is the only functional uterine abnormality. Three basic methods for evaluation of uterine cavity are HSG, pelvic ultrasound or saline sonohysterography and hysteroscopy with each having its own advantage and disadvantages.

- Ultrasound is a noninvasive method which permits visualization of position and size of uterus, fallopian tubes and ovaries. Modern 3-D ultrasonography extends the diagnostic capabilities of ultrasonography and can generate reconstructed images in the coronal plane. It is more useful in diagnosing important uterine pathologies particularly congenital anomalies, to measure endometrial volume, locate fibroids and also defines their relationship to endometrial canal. It has diagnostic accuracy comparable to magnetic resonance imaging.
- SIS can be used for better identification of intrauterine adhesions and endometrial polyps.
- HSG accurately defines size and shape of uterine cavity. It may help in delineating any developmental uterine anomaly (unicornuate, bicornuate, septate, didelphys, etc.) and acquired abnormalities (intrauterine adhesions, endometrial polyps, submucous myomas). It has relatively low sensitivity (50%) and PPV (30%) for diagnosis of endometrial polyp and submucous myomas in asymptomatic infertile women.
- Hysteroscopy is the definitive method for evaluation and treatment of intrauterine pathology. Being more costly and an invasive method, its use is reserved for further evaluation and treatment of abnormalities detected on TVUS, SIS or HSG.

CERVICAL FACTORS

It includes abnormalities of cervical mucus production or sperm/mucus interaction which are rarely the sole cause of infertility. Traditionally, post-coital test (PCT) was considered a basic element of infertility evaluation. It is inconvenient to patient, does not predict inability to conceive and rarely changes clinical management. Therefore, PCT is no longer recommended for evaluation of infertile female.

ROLE OF OVARIAN RESERVE TESTING

Ovarian reserve describes the size and quality of the remaining ovarian follicular pool. This has become a routine element of the diagnostic evaluation of infertility but is best justified for women with any of the following characteristics:

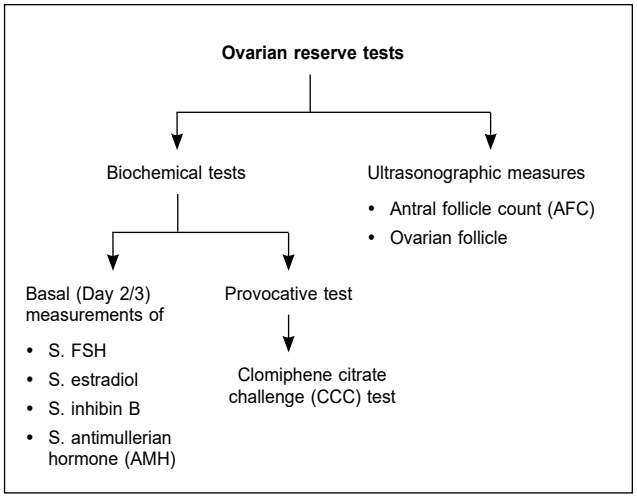

Figure 2. Ovarian reserve tests.

- Age over 35 years
- Family history of early menopause
- Previous ovarian surgery (ovarian cystectomy/ drilling, unilateral oophorectomy), chemotherapy, radiation
- Unexplained infertility
- Chronic smoking
- Demonstrated poor response to exogenous gonadotropin stimulation.

It includes a number of biochemical tests and ultrasonographic measures with each test having its own sensitivity and specificity (Fig. 2 and Table 2).

Therefore, ovarian reserve tests should always be interpreted with caution as none of the tests available at present can be recommended as a sole criteria of diminished ovarian reserve (DOR). They should only be used to obtain prognostic information and to choose the best treatment available.

KEY RECOMMENDATIONS: NICE GUIDELINES

- A careful history and physical examination can identify a specific cause of infertility and help to focus the diagnostic evaluation on the most likely cause.
- A blood test to measure serum progesterone in the mid-luteal phase (Day 21 of a 28-day cycle) is the preferred method to confirm ovulation even if women having regular menstrual cycle.
- Women with irregular menstrual cycle should be offered a blood test to measure serum gonadotropins.

Table 2. Summary of Different Ovarian Reserve Tests

Ovarian reserve test	Cut-off range	Sensitivity (%)	Specificity (%)	Comment
S. FSH (Day2/3)	10-20 IU/L	10-30	83-100	Most widely used; good reliability
S. Inhibin B	40-45 pg/mL	40-80	64-90	High inter- and intracycle variability; not used routinely
S. AMH	0.2-0.7 ng/mL	40-97	78-92	Good reliability
CCC test (Day 10 FSH)	10-22 IU/L	35-98	68-98	Higher sensitivity than basal FSH but needs drug administration
AFC (No)	3-10	40-97	78-92	Good reliability; widespread use
Ovarian volume	>3 mL	11-80	80-90	Limited clinical use

- Serum prolactin should only be offered to women who have an ovulatory disorder, galactorrhea or a pituitary tumor.
- Thyroid function test should not be offered routinely; rather should be estimated only in women with symptoms of thyroid disease.
- The routine use of endometrial biopsy and PCT of cervical mucus is no longer recommended as a part of evaluation of infertile female.
- HSG to screen for tubal patency is a reliable test, less invasive and makes more efficient use of resources than laparoscopy.
- Ovarian reserve testing should be best limited to the women at increased risk of DOR and should be interpreted with caution.

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Blood Type, Genes Linked with Risk of Severe COVID-19, Says Study

An individual's blood type and other genetic factors may be associated with the severity of COVID-19 infection, suggest European researchers in a study published in *The New England Journal of Medicine*.

The findings suggest that people with type A blood seem to have a higher risk of being infected with the coronavirus and developing worse symptoms. Investigators also found that a cluster of variants in genes involved with immune responses was more common among people with severe COVID-19… (*Reuters*)

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Sustenance in Chronic Kidney Disease: Beyond the Calorie Count

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ABSTRACT

Diet and nutrition play key roles in the management of metabolic disorders like hypertension, obesity, hyperlipidemia and diabetes. All these conditions are linked with the pathogenesis of chronic kidney disease (CKD). Patients with CKD frequently exhibit a progressive loss of muscle and fat mass that may not be related to reduced intake alone. This article provides a comprehensive overview of protein-energy wasting (PEW) in CKD, including its etiology and the obesity paradox and the nutritional guiding principles.

Keywords: Chronic kidney disease, protein-energy wasting, nutrition, deficiencies, supplementation

DWINDLING GFR BLOCKING THE EXIT OF NITROGENOUS WASTE

Diet and nutrition have an extremely pivotal role to play in the management of metabolic disorders like hypertension, obesity, hyperlipidemia and diabetes, all of which are bonded stalwartly with the pathogenesis of chronic kidney disease (CKD).

As the glomerular filtration rate (GFR) experiences a downhill movement, the nitrogenous metabolites tend to be retained, resulting in a decreased ability to regulate the levels of electrolytes and water. Alongside this, certain vitamin deficiencies can occur due to dietary changes. Adding up, protein-energy depletion is frequently observed and predicts a pitiable outcome.

THE UNMET NEEDS OF NUTRITION: PROTEIN-ENERGY WASTING

Patients with CKD, particularly more advanced stages, frequently exhibit a progressive loss of muscle and fat mass that may not be related to reduced intake alone. Because malnutrition refers to an intake that is inappropriate for the needs of the individual, it can be misleading to use this blanket term when reduced intake is not necessarily the sole cause of wasting. Protein-energy wasting (PEW) is defined as a state of nutritional and metabolic derangements in patients with CKD that may negatively affect nutritional status and lean body mass, leading to frailty.

PERCEPTION OF PROTEIN-ENERGY WASTING

Protein-energy wasting was proposed in 2007 by the International Society of Renal Nutrition and Metabolism as a notion defining the multifactorial nature of metabolic processes and nutritional consequences of uremia in CKD. PEW involves a hypermetabolic state that promotes protein catabolism, attributed to both metabolic consequences of CKD—including inflammation, oxidative stress, uremia, metabolic acidosis, diminished efficacy of anabolic hormones and a multi-morbid condition—and the catabolic nature of hemodialysis (HD), which can lead to protein losses and muscle and fat wasting (Fig. 1).

Therefore, the reduction in energy and protein intake associated with PEW is often secondary to other factors, rather than a primary consequence of inadequate access to adequate energy and protein to meet nutritional needs, as in primary malnutrition. In clinical practice, the reduction in nutritional intake and causes may be difficult to separate because they are synergistic and may exacerbate each other.

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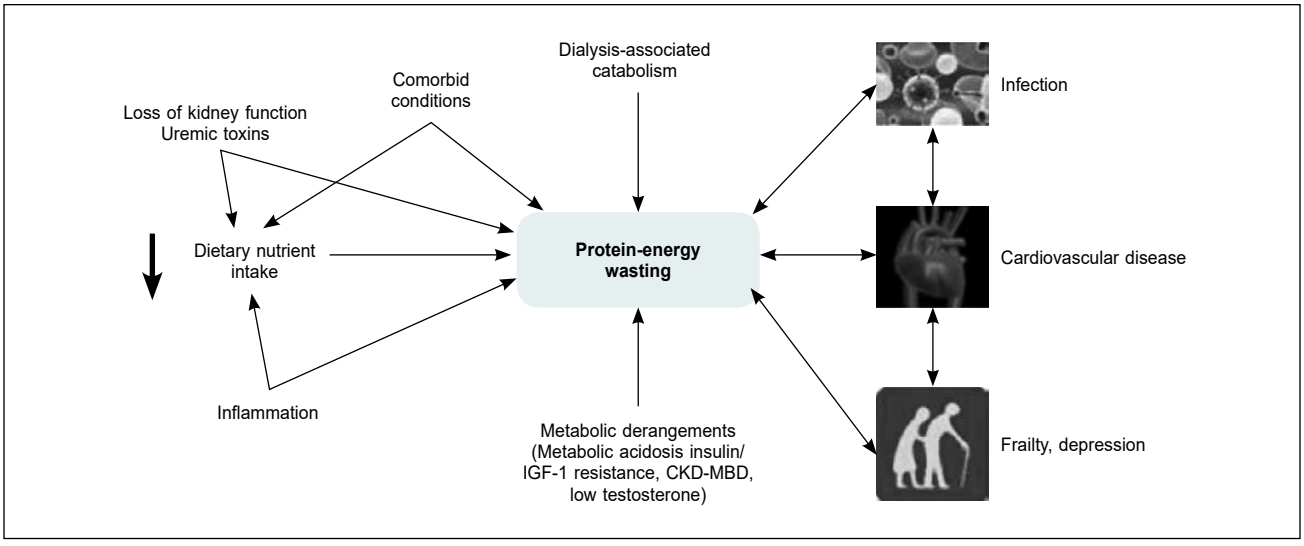

Figure 1. The conceptual model for protein-energy wasting in CKD.

CKD-MBD = Chronic kidney disease-mineral bone disorder; IGF-1 = Insulin-like growth factor 1.

PERPETRATOR OF PROTEIN-ENERGY WASTING IN CHRONIC KIDNEY DISEASE

Understanding the features that have a say in the etiology of PEW is critical to put in the picture, the suitable assessment and treatment strategies (Table 1). Furthermore, adequate nutritional intake will not alter some of the contributing factors, such as hypermetabolism secondary to inflammation, the reduction in anabolic response, the catabolic nature of HD, insulin resistance or frailty associated with reduced physical activity. A multifaceted therapeutic approach for this complex syndrome is therefore necessary.

The prevalence of PEW in dialysis patients ranges from 10% to 70%, depending on the choice of nutritional marker and the population studied. There is also diminished nutritional status before initiation of dialysis, which strongly predicts mortality on dialysis. Several factors contribute to the high incidence of PEW.

There is a spontaneous reduction in nutrient intake that parallels the decrease in GFR and is largely driven by CKD-associated anorexia. This anorexia is caused by impaired taste acuity and diminished olfactory function, medications, autonomic gastroparesis, psychological and socioeconomic factors and inadequate dialysis. Frailty, poverty, advanced age and multiple acute or chronic comorbidities also may contribute to suboptimal intake. Protein and amino acid losses occur during dialysis treatment. Metabolic acidosis and periods of acute or chronic illnesses may induce protein catabolism. This is mediated in large part through the ubiquitin-proteasome pathway of protein degradation.

Table 1. Causes of Protein-energy Wasting in CKD

Decreased protein and energy intake
• Anorexia, problem in organs involved in nutrient intake
• Dietary restrictions
• Depression, frailty, dependency
Hypermetabolism
• Increased energy expenditure
• Metabolic acidosis
• Inflammation
• Hormonal disorders
▪ Insulin resistance of CKD
▪ Increased glucocorticoid activity
Decreased anabolism
• Resistance to GH/IGF-1
• Testosterone deficiency
• Low thyroid hormone levels
Comorbidities and lifestyle
• Comorbidities (DM, CHF, depression, CAD, PVD)
• Poor physical activity
• Unhealthy dietary pattern
Dialysis
• Nutrient losses into dialysate
• Dialysis-related inflammation and hypermetabolism

CKD = Chronic kidney disease; GH = Growth hormone; IGF-1 = Insulin-like growth factor 1; DM = Diabetes mellitus; CHF = Congestive heart failure; CAD = Coronary artery disease; PVD = Peripheral vascular disease.

Chronic inflammation may contribute to both an increase in nutritional needs and anorexia. Alterations

in intestinal microbiota and increased permeability of the intestinal barrier may play a pivotal role in the pathogenesis of inflammation. Endocrine disorders, such as insulin resistance (associated with increased muscle breakdown), vitamin D deficiency and increased parathyroid hormone concentrations have long been considered contributors to PEW.

THE OBESITY PARADOX IN CKD: REVERSE EPIDEMIOLOGY

Although there is a high prevalence of PEW in patients with CKD associated with poorer outcomes, paradoxically a higher body mass index (BMI) is associated with better survival. This is termed *reverse epidemiology*.

APPRAISAL OF NUTRITIONAL STATUS

The measurement of nutritional status does not lend itself to one simple test, and a panel of measures is required.

Intake Composition

Diet history, recall and food diaries are the mainstays for estimation of dietary intake. In addition, a gradual decrease in blood urea nitrogen and reduced phosphate and potassium levels may indicate a decrease in protein intake in dialysis-dependent patients, and low serum cholesterol level may indicate a poor calorie intake. The emission of urea is easily calculated and is often used to estimate adequacy of dialysis. The protein equivalent of total nitrogen appearance (PNA) can be estimated on HD from interdialytic changes in urea nitrogen concentration in serum and the urea nitrogen content of urine and dialysate.

Index of Body Mass

The BMI (BMI = weight [kg]/height [m^2]) is the most commonly used parameter for nutritional assessment. BMI cannot distinguish muscle from fat mass and is affected by hydration status.

Composition of the Body

An assortment of techniques can make a distinction between body compartments on the basis of physical characteristics, which can provide information about nutritional state (body lean tissue and fat content) and hydration. Skinfold thickness can be used to assess body fat, and muscle mass can be assessed by measurement of mid-upper arm muscle circumference. Although these anthropometric parameters are inexpensive and relatively easy to measure, they are limited by inconsistency, both on the part of patient and examiner. Sequential measures of bioelectrical impedance are used as an appendage to the day-to-day clinical appraisal of hydration status and body composition management of patients on dialysis.

The Primeval Protein

Fluid status, impaired hepatic function, age and acute inflammatory conditions can affect albumin levels. However, despite its relatively longer half-life (20 days), albumin remains an important measure of nutritional status and health of the patient. Clinically, it may be possible to observe the growth of white nails when there has been a transient period of hypoalbuminemia. Serum transferrin is linked to body iron stores and may be altered with changes in iron status.

NUTRITIONAL GUIDING PRINCIPLES

Guideline campaigners advocate that it is important that dietary restrictions are not gratuitously made obligatory for each and every individual, rather the advice be tailored to the individual and altered as circumstances dictate (Table 2).

DYSREGULATED LIPID COMPOSITION

Although disturbances in lipid metabolism are commonly seen in CKD, there is a paucity of data on the effect of diet therapy in this group. A diet low in fat (particularly saturated fat) with an increased intake of soluble fiber may be helpful in reducing cholesterol levels, although the role of cholesterol-lowering in CKD patients is controversial. Losing weight and consuming a diet lower in sugar may improve hypertriglyceridemia, but a balance needs to be struck between healthy eating concepts and nutritional adequacy.

VITAMINS, MINERALS AND TRACE ELEMENTS

Vitamins, minerals and trace elements deficiencies are not uncommon in patients with CKD and it relates to dietary restriction, dialysate losses and the necessity of integral renal function for normal metabolism of certain vitamins. However, the dietary requirements for patients with CKD are not lucid. Protein and potassium restrictions can lead to inadequate intakes of pyridoxine, vitamin B12, folic acid, vitamin C, iron and zinc. The use of recombinant human erythropoietin may increase the requisite for iron and folic acid. In the absence of firm guidance, it is prudent to have a low threshold for commencing water-soluble vitamin

Table 2. Nutritional Recommendations for CKD

Daily intake	Predialysis CKD	Hemodialysis	Peritoneal dialysis
Protein (g/kg ideal BW) (refer to KDOQI for estimation of adjusted edema-free BW)	0.6-1.0 Level depends on the nephrologist's viewpoint. 1.0 for nephrotic syndrome.	Min ≥1.1 Recommendations are in conjunction with an adequate energy intake. Requirements may be higher during illness because of multiple comorbidities or during acute periods of infection, including peritonitis.	Min 1.0-1.2
Energy (kcal/kg BW)	35 (<60 y) 30-35 (>60 y)	35 (<60 y) 30-35 (>60 y) 30-40 kcal/kg ideal BW	35 including dialysate calories (<60 y) 30-35 including dialysate calories (>60 y)
Sodium (mmol)	<100 (more if salt wasting)	<100	<100
Potassium	Reduce if hyperkalemic	Reduce if hyperkalemic	Reduce if hyperkalemic; potassium restriction is generally not required. May need to enhance potassium intake if hypokalemic.
	If hyperkalemic, advice will be to decrease certain foods (e.g., some fruits and vegetables) and giving information about cooking methods.		
Phosphorous	Reduce because of phosphate retention. Monitor levels. Advice will be to reduce certain foods (e.g., dairy, offal, some shellfish) and processed foods with high content of added phosphates, and giving information about the timing of binders with high-phosphorus meals and snacks.		

preparations. High-dose vitamin C supplements should be avoided in CKD because of the increased risk for secondary tissue oxalate deposition. A review on fat-soluble vitamins in advanced CKD concluded that there is universal agreement that supplementation with vitamin A is generally not recommended (unless a patient is receiving total parenteral nutrition) because deficiencies are rare, dialysis losses are minimal and buildup leading to toxicity can occur.

Vitamin E has been suggested to have antioxidant properties and beneficial effects for patients with CKD. Evidences suggest that most dialysis-dependent patients have subclinical vitamin K deficiency, and there is no known toxicity but, its benefits are waiting to get approval from the clinical trials. Novel, orally administered potassium-exchanging compounds are being investigated as possible treatment options for the management of hyperkalemia. Sodium zirconium cyclosilicate and patiromer act by enhancing potassium removal, predominantly through the gastrointestinal (GI) tract.

BENEVOLENT SUPPLEMENTATION

If food fortification advice is insufficient, supplements, in the form of high-protein, high-calorie drinks, powders and puddings, should be considered. Enteral tube feeding is also an option if nutrient intake cannot be increased sufficiently by use of oral supplements. Renal-specific tube feeds and supplements are available that have lower fluid and electrolyte contents. A systematic review suggested that enteric multinutrient support increases serum albumin concentration and improves total dietary intake in patients receiving maintenance dialysis.

The GI route is the preferred choice for nutritional supplementation. However, intradialytic parenteral nutrition (IDPN) has been used to provide intensive parenteral nutrient therapy with use of concentrated hypertonic solutions infused into the venous blood line three times weekly during HD treatments for patients who cannot tolerate oral or enteral administration of nutrients. IDPN typically provides 800-1200 kcal three times weekly, in the form of glucose and fat emulsion and 30-60 g of protein and so will only supplement rather than provide full nutritional needs.

Intraperitoneal amino acids (IPAAs) can be used in peritoneal dialysis. A 1.1% amino acid solution is substituted for glucose in peritoneal dialysis (PD) fluid, and about 80% of the amino acids are absorbed in a 4-hour period. The long-term effects of IPAAs on nutritional status and clinical outcomes are not known, and the solution is often used primarily to reduce glucose exposure. Expert opinion on the use of these approaches is inconsistent. The Kidney Disease Outcomes Quality Initiative (KDOQI) has suggested that IPAAs (for PD) or IDPN (for HD) should be considered for patients

who have evidence of protein or energy malnutrition and inadequate protein or energy intake and who are unable to tolerate adequate oral supplements or tube feeding.

HUNGER SYRUPS

Megestrol acetate, a progesterone derivative, moderately improves appetite in HD patients, as shown in small studies. However, megestrol acetate has adverse effects and larger trials are required before recommendations can be made for CKD patients. More studies are also required for ghrelin, anorexigenic hormone and melanocortin-receptor antagonists.

GUT-WELL-MICROBIOME

There is accumulating evidence that the GI tract may be a major source of chronic inflammation in CKD. It is hypothesized that altered diets (low potassium, phosphorus and fiber) may affect the gut microbiome, resulting in overgrowth of bacteria that produce uremic toxins and a leaky epithelial barrier that allows toxins to get into the circulation. It has been suggested that prebiotic and probiotic formulations may lower serum levels of uremic toxins. However, more trials investigating gut-targeted therapeutics are needed before they could be recommended for use in clinical practice.

pH BALANCE

Although some trials have shown no detrimental effect of mild metabolic acidosis, many others have reported that normalization of serum bicarbonate concentration is beneficial for protein nutritional status and bone metabolism. Current guidelines recommend the correction of acidosis in dialysis-dependent patients.

CONCLUSION

Protein-energy wasting is a relatively common metabolic complication inherent to CKD. A worsening of quality of life and an increase in the risk for comorbidities, hospitalizations and death accompany the onset and progression of PEW. The cause of PEW is multifactorial, involving undernutrition (insufficient or inadequate nutrient intake) and excess protein catabolism that altogether favors the progressive and continuous loss of energy and fat fuels. This multifactorial nature makes diagnosis difficult; it must be based on the combined interpretation of complementary nutritional screening and assessment tools.

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Typhoid Fever – An Overview

Good Hygiene is the Key to Prevent Typhoid Fever

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ABSTRACT

All animals are susceptible to infection with *Salmonella*, a genus of Gram-negative, non-spore forming, usually motile, facultative anaerobic bacilli belonging to the family *Enterobacteriaceae. Salmonella* are differentiated into over 2,200 serologically distinct types (serotypes) based on differences in somatic, flagellar and capsular antigens. *Salmonella* Typhi causes the most severe form of enteric fever/typhoid fever. Unlike the other serotypes of *Salmonella*, humans are the only known host for this pathogen. The infection is commonly spread through fecal contaminated food and water. Typhoid fever has a slow, insidious onset and if untreated, lasts for weeks. The primary symptom is slowly rising fever often accompanied by abdominal pain. It ends either by a gradual resolution or in death due to complications (rupture of intestine or spleen). All infections occur almost always via oral route, usually with water or food contaminated by sewage or via hands of carrier.

Keywords: Vi polysaccharide vaccine, adenylate cyclase, randomized controlled trials, chloramphenicol, streptomycin, sulfonamide, tetracycline

Salmonella is a human and animal pathogen that causes considerable disease burden worldwide. The genus contains two species, *Salmonella bongori* and *Salmonella enterica.* In the United States, an estimated 11% of the foodborne illnesses are caused by *Salmonella.* The two most common disease manifestations of human *Salmonella* infections are gastroenteritis and typhoid fever. *Salmonella* Typhi and *Salmonella* Paratyphi A can cause typhoid fever, a more severe systemic disease. Salmonellosis outbreaks have been linked to the consumption of fruits, leafy green vegetables, sprouts, eggs, milk products and meat. Enteric fever is a systemic infection caused by *Salmonella* Typhi and Paratyphi A, B and C and is a significant cause of morbidity and mortality. Interactions between *Salmonella* spp. and the native microbial communities are hypothesized to contribute to the ability of this human pathogen to colonize. The typhoid fever surveillance in Africa program (TSAP) revealed a significant burden of *Salmonella* disease in sub-Saharan Africa. Low moisture foods (LMF), including spices and seasonings, dried protein products, such as dried eggs or dried milk and seeds, have been increasingly implicated as the source of foodborne Salmonellosis outbreaks.

Although most microbial hazards cannot grow in LMFs due to the low water activity (a_w), many pathogens can survive and remain viable for months to years in these foods, posing potential risks to consumers.

Several national and international outbreaks of foodborne illnesses, as well as product recalls, have occurred in recent years due to *Salmonella* spp. contamination of LMF products such as spices, nuts (including peanut butter), cereal products (e.g., breakfast cereals), tahini paste and chocolate, among many others.

Recent high-profile outbreaks of foodborne illness and product recalls due to microbial contamination of LMF, particularly from *Salmonella* spp., have increased global attention and response to the microbial safety of LMF.

S. enterica subspecies serovar Typhi (*S.* Typhi) is a major cause of invasive bacterial infection, particularly in children in low- and middle-income countries. Vaccines available for prevention of typhoid fever include

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Vi capsular polysaccharide vaccine (Vi-CPS) and live attenuated oral vaccine Ty21a.

Vaccination against *S.* Typhi using the Vi-CPS, a T-cell independent antigen, can protect from the development of typhoid fever. This implies that antibodies to Vi alone can protect in the absence of a T-cell-mediated immune response; however, protective Vi antibodies have not been well-characterized.

Enteric fever is principally caused by *S. enterica* serovar Typhi *(S.* Typhi*). S.* Typhi is the leading pathogen isolated from blood cultures in South Asia.

The fatality rate of enteric fever is low (<1%) but it is higher when antimicrobial therapy is delayed or unavailable.

Alternative molecular serotyping methods have been described previously, including pulsed-field gel electrophoresis, sequence-based polymerase chain reaction (PCR) (rep-PCR) and combined PCR- and sequencing-based approach that directly targets O- and H-antigen-encoding genes.

Paratyphoid fever, however, often shows milder symptoms than that of *S.* Typhi infection.

Typhoid *Salmonellae* are human-restricted, and nontyphoidal *Salmonella* (NTS) are broad host-range serovars infecting both humans and animals.

Symptoms of typhoid include fever, headache, weight loss, lethargy, stupor, malaise, leukopenia, thrombocytopenia, gastrointestinal bleeding and neurological complications.

Healthy carriers shed *S.* Typhi in their stool, which passes on the bacterium through the contamination of food and water sources.

CHRONOLOGICAL RECORD OF SIGNIFICANT EVENTS

Salmonellae are Gram-negative motile bacilli. The genus *Salmonella* belongs to the family *Enterobacteriaceae*. Daniel E Salmon first isolated *Salmonella*. In 1880, Karl Joseph Eberth described a bacillus that he suspected was the cause of typhoid.

In 1884, pathologist Georg Theodor August Gaffky (1850-1918) confirmed Eberth's findings.

British bacteriologist Almroth Edward Wright first developed an effective typhoid vaccine at the Army Medical School in Netley, Hampshire. It was introduced in 1896 and was used successfully by the British during the Boer War in South Africa.

Karl Joseph Eberth, doctor and student of Rudolf Virchow, in 1879 discovered the bacillus in the abdominal lymph nodes and the spleen. He went on to publish his observations in 1880 and 1881. His discovery was then verified and confirmed by German and English bacteriologists, including Robert Koch.

The genus "*Salmonella*" was named after Daniel Elmer Salmon, an American veterinary pathologist, who was the administrator of the USDA research program, and thus the organism was named after him, despite the fact that several scientists had contributed to the quest.

In 1909, Frederick F Russell, a US Army physician, adopted Wright's typhoid vaccine for use with the army, and 2 years later, his vaccination program became the first in which an entire army was immunized. It eliminated typhoid as a significant cause of morbidity and mortality in the US military.

As a cook of Sloane Maternity in Manhattan, Mary Mallon contaminated, over a period of 3 months, at least 25 people, doctors, nurses and staff. Two of them died. She had managed to be hired as "Mary Brown". Since then, she was stigmatized as "Typhoid Mary" and became the butt of jokes, cartoons and eventually "Typhoid Mary" appeared in medical dictionaries, as a disease carrier.

Both salmonellosis and the microorganism genus *Salmonella* derive their names from a modern Latin coining after Daniel E Salmon.

CLINICAL PRESENTATION

Without treatment, some patients develop sustained fever, bradycardia, hepatosplenomegaly, abdominal symptoms and occasionally, pneumonia. In white-skinned patients, pink spots, which fade on pressure, appear on the skin of the trunk in up to 20% of cases. In the third week, untreated cases may develop gastrointestinal and cerebral complications, which may prove fatal in up to 10-20% of cases. The highest case fatality rates are reported in children under 4 years. Around 2-5% of those who contract typhoid fever become chronic carriers, as bacteria persist in the biliary tract after symptoms have resolved.

THE MECHANISM INVOLVED IN TYPHOID FEVER/ ENTERIC FEVER

Enteric fever is endemic in many developing countries due to poor sanitation and substandard water supply.

Enteric fever is caused due to infection by the genus *Salmonella,* which comprises of *S.* Typhi, *S.* Paratyphi A, *S.* Paratyphi B, *S.* Paratyphi C. All these organisms can cause a bacteremic illness known as enteric fever.

In the initial stages of infection, the pathogen invades small and larger bowel walls, creating an inflammatory response. It is an intracellular pathogen.

The infection is spread to the body via the regional lymph nodes and bloodstream. Initial symptoms of infection are headache, fever, general malaise and abdominal tenderness. Once the organism has spread throughout the body, it reaches the gallbladder and payer's patches in the colon, initiating the diarrheal illness.

The organism can frequently be recovered from blood and stool cultures. Appropriate antibiotic use results in clinical improvement; however, stool cultures often remain positive, which can serve as a source of infection for other individuals. Some patients can develop chronic colonization of their gallbladder, biliary tree, leading to persistent shedding of the organism with potential transmission to others.

S. Typhi is a human host-restricted pathogen that is responsible for typhoid fever in approximately 10.9 million people annually. The typhoid toxin is postulated to have a central role in disease pathogenesis, the establishment of chronic infection and human host restriction.

Mucosal invasion and inflammation are clearly important, at least accounting for the bloody mucoid type of stools, which occur commonly but do not explain the copious watery stool in early stages. Observations in experimental animals of enteropathy with water and electrolyte transport defects suggest the existence of secretary mechanisms.

Production of prostaglandins and other mediators by the inflammatory tissues and toxin production by the organisms have been suggested. *Salmonella* produces an enterotoxin and a cytotoxin. The enterotoxin activates adenylate cyclase and has some physicochemical characteristics in common with cholera toxin but limited antigenic homology.

Typhoid fever is caused by the bacterium *S. enterica* subsp. *enterica* serovar Typhi. It is mainly due to the inadequate access to safe water and sanitation, which is a major problem in developing countries. The global burden of typhoid fever was estimated to be 12 million cases and 1,30,000 deaths in the year 2010. It exceeded 100 cases per 1,00,000 people/year in South East Asian countries, and has especially high burden rates in India. A recent systematic review and meta-analysis estimated the prevalence of laboratory confirmed typhoid and paratyphoid cases in India to be 9.7 and 0.9%, respectively.

NEW APPROACHES IN THE DETECTION OF *SALMONELLA*

Randomized controlled trials (RCTs) have found that people with *Salmonella* infection treated with norfloxacin versus placebo had significantly prolonged excretion of *Salmonella* species. In addition, six of nine Campylobacter isolates obtained after treatment showed some degree of resistance to norfloxacin.

Continued evolution of antimicrobial resistance among enteric pathogens has meant that agents previously found to be effective in clinical trials, such as trimethoprim-sulfamethoxazole or ampicillin, no longer show *in vivo* activity.

Molecular techniques for the detection of *Salmonella* species such as PCR, offer considerable advantages in terms of specificity, speed, and standardization over the conventional methodologies. However, it is difficult to perform PCR directly on fecal samples due to presence of inhibitory substances and large quantities of bacterial DNA extraction from feces can be improved by pre-treating the sample with polyvinylpyrrolidone (PVP).

It has been found that culture and PCR methods used for detection of *Salmonella* from clinical fecal samples were of similar sensitivity. However, culture results are available in 2-3 days, whereas those obtained by real-time PCR assays can be available within 3 hours, which can be advantageous for rapid intervention and appropriate treatment.

RECENT ADVANCES IN DIAGNOSTIC TECHNOLOGY

In enteric fever and septicemia, blood culture results are often positive in the first week of the disease.

In enteric fever, the stools yield positive results from the second or third week on. In enterocolitis, the stools yield positive results during the first week. Bone marrow cultures may be useful. Urine culture reports may be positive after the second week. A positive culture of duodenal drainage establishes the presence of *Salmonellae* in the biliary tract in carriers. EMB, MacConkey or deoxycholate medium permits rapid detection of lactose nonfermenters (not only *Salmonellae* and *Shigellae* but also *Proteus, Pseudomonas,* etc.) Bismuth sulfate medium permits rapid detection of *Salmonellae,* which form black colonies because of H2S production. Many *Salmonellae* produce H2S.

The specimen is plated on *Salmonella-Shigella* (SS) agar, hektoen enteric (HE) agar, Xylose-lysine decarboxylase (XLD) agar or deoxycholate-citrate agar, which favors the growth of *Salmonellae* and *Shigellae* over other

Enterobacteriaceae. The stool specimen is also put into selenite F or tetrathionate broth. Both of these inhibit replication of normal intestinal bacteria and permit multiplication of *Salmonellae*. After incubation for 1-2 days, this is plated on differential selective media. Suspect colonies are identified by biochemical reaction patterns and slide agglutination tests.

Hektoen enteric agar was introduced in 1968 by Sylvia King and William I Metzger. They formulated HE agar medium while working at the Hektoen Institute in Chicago, to increase the recovery of *Salmonella* and *Shigella* from clinical specimens. It is a selective as well as differential medium. HE agar is currently used as both a direct and indirect plating medium for fecal specimens to enhance the recovery of species of *Salmonella* and *Shigella* from heavy numbers of mixed normal fecal flora.

The gold standard diagnosis of enteric fever is the isolation of the organism from the blood, bone marrow, stool or urine. A number of serological assays has been overutilized in this part of the world but need to be discouraged for the diagnosis of such acute infection.

The Widal test has been in use for the past 100 years but at times, it can be misleading. Its potential to yield false-positive and false-negative results limits its use. This assay can be misleading in endemic countries and no interpretive titer should be recommended. Urinary antigen detection assays have also not been able to improve the diagnostic yield. Some rapid agglutination tests for *S.* Typhi alone are in use, but their utility cannot be evaluated due to a lack of data.

BIOTECHNOLOGY OF MOLECULAR DIAGNOSIS OF ENTERIC FEVER

Detection methods rely on traditional bacterial culture procedures that employ the use of serial enrichments with increasing selectivity culminating in the isolation of *Salmonella* on selective-differential agar plates.

Even with newer automated technologies that permit simultaneous testing of multiple analytes, at least 24 hours are needed for confirmation of *Salmonella.*

DNA fingerprinting techniques, such as pulsed-field gel electrophoresis (PFGE), ribotyping and intergenic sequence (IGS) ribotyping, have all been used to subtype *Salmonella* isolates.

For ribotyping, genomic DNA is digested, separated on an agarose gel and then hybridized to rRNA operons to visualize the banding pattern.

After comparison to a database of fingerprints species, serovar and occasionally strain identifications can be made.

The DNA fragments are separated on an agarose gel subjected to a pulsed electric field. DNA is visualized by ethidium bromide staining and fingerprints are analyzed using specific software.

PCR as a diagnostic modality for typhoid fever was first evaluated in 1993 when Song et al successfully amplified the flagellin gene of *S.* Typhi in all cases of culture proven typhoid fever and from none of the healthy controls. Studies have reported excellent sensitivity and specificity when compared to positive and healthy controls. The turnaround time for diagnosis has been less than 24 hours.

OPENING THE DEBATE ON THE MANAGEMENT OF TYPHOID FEVER/ENTERIC FEVER

Because of the efficacy and low relapse and carrier rates, associated with their use, the four quinolone drugs are now the drugs of choice in the treatment of adult typhoid fever.

However, because of cheapness, chloramphenicol will continue to be used in areas where the local strains are sensitive. Azithromycin may be in the future a useful alternative, especially in children.

Early Recognition and Management of Enteric Fever/Typhoid Fever

Salmonellae were the foremost of the food poisoning organisms for almost the whole of the 20th century. A dirty and unhygienic toilet is a source of many infectious diseases such as typhoid, cholera, hepatitis A and other diarrheal diseases, including parasitic infestations.

Hence, toilet hygiene is essential for good health. Timely and appropriate management of typhoid fever can reduce both morbidity and mortality. During the past two decades, *Salmonella enteritidis* has emerged as a leading cause of human infections in many countries, with hen eggs being a principal source of the pathogen. This has been attributed to this serovar's unusual ability to colonize ovarian tissue of hens and be present within the contents of intact shell eggs. Broiler chicken is the main type of chicken consumed as poultry in many countries. Large percentages are colonized by *Salmonellae* during grow-out and the skin and meat of carcasses are frequently contaminated by the pathogen during slaughter and processing. Considering the major role eggs and poultry have as vehicles of human cases

of salmonellosis, an assessment of different factors affecting the prevalence, growth and transmission of *Salmonella* in eggs and on broiler chicken carcasses and the related risk of human illness would be useful to risk managers in identifying the intervention strategies that would have the greatest impact on reducing human infections.

RESEARCHERS STRUGGLE TO DEVELOP A NEW TREATMENT FOR ENTERIC FEVER/TYPHOID FEVER

Patients with persistent vomiting, inability to take oral food, severe diarrhea and abdominal distention usually require parenteral antibiotic therapy, preferably in a hospital. Antibiotic therapy must be guided by *in vitro* sensitivity testing.

Chloramphenicol (500 mg 4 times daily), ampicillin (750 mg 4 times daily) and co-trimoxazole (2 tablets or IV equivalent twice daily) are losing their effectiveness due to resistance in many areas of the world, especially India and South East Asia. Fluoroquinolones are the drugs of choice (e.g., Ciprofloxacin 500 mg twice daily), if nalidixic acid screening predicts susceptibility, but resistance is common, especially in the Indian subcontinent and also in the UK.

Extended-spectrum cephalosporins are useful alternatives but have slightly increased treatment failure rate. Azithromycin 500 mg once daily is an alternative when fluoroquinolone resistance is present. *Salmonella*-resistant to chloramphenicol can respond to norfloxacin, ciprofloxacin therapy. For gastroenteritis in uncompromised hosts, antibiotic therapy is often not needed and may prolong the convalescent carrier state. For enteric fever, appropriate antibiotics include beta-lactams and fluoroquinolones.

With the limitations of the two existing *Salmonella* vaccines, particularly their lack of effectiveness in young children, along with their lack of widespread uptake in endemic countries, the *Salmonella* community and global health policymakers are keenly awaiting the arrival of new vaccines against *Salmonella.* Vaccine is indicated for those persons who travel or live in areas where typhoid fever is endemic. Multidrug resistance transmitted genetically by plasmids among the strains of *S.* Typhi had been reported for the first time in 1972 from Mexico. The transmissible plasmids carry R determinants to chloramphenicol, streptomycin and sulfonamide and tetracycline. Multiple drug resistance has become a problem in India and South East Asia. Chloramphenicol-resistant typhoid fever had appeared first in epidemic form in Kerala (Calicut), India in 1972. The drug-resistant strains of *S.* Typhi that had been reported from India were originally confined to include phase D1-N, but later to types C5, A and O.

Prevention

Handwashing with soap and water is the simplest and also the most economical way to remove dirt and prevent the transmission of harmful microorganisms and control the spread of infection. But, it is important to choose the right type (quality) of soap. The quality (or grading) of soap is determined by the total fatty matter (TFM), defined as the total amount of fatty matter (fatty acids - oleic, stearic and palmitic), which can be separated from a sample after splitting with mineral acid (hydrochloric acid).

Hand hygiene is inexpensive and forms an integral part of infection control practices in healthcare. Our hands are home to two types of bacterial flora - the resident flora and the transient flora.

The resident flora is found in the deeper layers of skin. Proper sewage disposal, correct handling of food and good personal hygiene are important for prevention. Between 1995 and 2008, Bangladesh made significant progress in providing improved sanitation services throughout the country.

Vaccination is recommended for people who travel from developed countries to endemic areas including Asia, Africa and Latin America.

AN OPINION ARRIVED AT THROUGH A PROCESS OF REASONING

Outbreaks make the news, but most cases occur in individuals or as sporadic events.

Current surveillance systems remain insensitive to diffuse and sporadic cases and resources for laboratory investigations are limited. Food-borne illnesses are an important public health challenge. The new discoveries are probably a result of - 1) Recent acquisition of key virulence factors and 2) Detection of newly developed laboratory methodologies.

There is a need for education programs that inculcate the importance of good agriculture practices, as well as safe post-harvest handling and preparation of food.

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Adjunctive CGRP to Botox Treatment Safe, Effective for Migraine Prevention

Adjunctive preventive therapy with a calcitonin gene-related peptide monoclonal antibody (CGRP-mAb) medication has been found to be safe and effective in patients with chronic migraine who achieve a partial response to onabotulinumtoxinA (Botox) treatment.

In a study presented at the virtual American Headache Society (AHS) Annual Meeting 2020, it was noted that the CGRP-mAbs significantly reduced the number of headache days and pain severity and that the adverse event rates were similar to those reported in previous trials of these medications… (*Medscape*)

Adverse Events with Biologics Increase with Age among Rheumatic Disease Patients

Among patients with rheumatic diseases, age and female sex appeared to be the key factors associated with the development of a first adverse event after initiating biologic treatment, suggests new research.

In comparison with young patients (those below 25), the adjusted incidence rate ratio for a first adverse event was 1.42 for those considered elderly (ages 65-75) and 1.89 for those considered very elderly (over age 75), reported researchers in *Arthritis Research & Therapy…* (*Medpage Today*)

First Therapy for Rare Disease that Causes Low Phosphate Blood Levels, Bone Softening Approved

The US FDA has granted approval to burosumab-twza injection for the treatment of patients aged two and above with tumor-induced osteomalacia (TIO).

This rare disease is characterized by the development of tumors that can weaken and soften the bones. The tumors associated with TIO release a peptide hormone-like substance - fibroblast growth factor 23 (FGF23) - that lowers phosphate levels… (*FDA*)

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.

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

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

Governing Council Members

Sumi Malik
Vivek Kumar
Karna Chopra
Dr Veena Aggarwal
Veena Jaju
Naina Aggarwal
Nilesh Aggarwal
H M Bangur

Advisors

Mukul Rohtagi
Ashok Chakradhar

Executive Council Members

Deep Malik
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Study on Correlation Between MELD Score and Hematological Abnormalities in Predicting Prognosis in Patients with Chronic Liver Disease

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ABSTRACT

Abnormalities in hematological indices are frequently encountered in cirrhosis of liver. Multiple causes contribute to the occurrence of hematological abnormalities. Recent studies suggest that the presence of hematological cytopenias is associated with a poor prognosis in cirrhosis. This study was conducted on 43 patients with chronic liver disease to assess the hematological abnormalities. We found 37 (90%) patients had hemoglobin <12 g/dL. Macrocytic anemia was the predominant type, followed by normocytic normochromic and microcytic type. Twenty-four patients had platelets <1.5 lakh/dL; 28 patients had prolonged prothrombin time (PT) and international normalized ratio (INR). Twelve patients showed peripheral smear picture suggestive of pancytopenia. We observed patients with anemia had model of end-stage liver disease (MELD) score above 15% compared to patients without anemia. We also observed patients with MELD score above 20% had mean platelets of 1.5 lakh/dL compared to lower score. Thirty-eight patients had splenomegaly. We also observed that mean platelet count in patients with hepatic encephalopathy was low and they also had prolonged PT.

Keywords: Anemia, cirrhosis, hematological spectrum in cirrhosis

The liver is the largest organ in the body and amongst the most complex organs that has a wide range of functions. It has a major role to play in the metabolism of carbohydrates, proteins and lipids, inactivation of various toxins, metabolism of drugs, hormones, synthesis of plasma proteins and maintenance of immunity. The liver has a significant role in maintenance of blood homeostasis - from being a primary site of hematopoiesis in fetal life to maintenance of hematological parameters in postnatal life. It stores iron, folic acid and vitamin B12, and secretes clotting factors and inhibitors. Therefore, a range of hematological abnormalities are encountered in association with liver diseases.[1]

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Decompensated chronic parenchymal liver disease is one of the most common diseases encountered in day-to-day practice. Because of chronic disease many hematological abnormalities are present in these patients. The hematological abnormalities in a chronic disease add morbidity to the primary pathology and increase the mortality. Hence, it becomes necessary to investigate the hematological abnormalities and hemostatic abnormalities to decrease the comorbidity. Abnormalities in hematological parameters are commonly seen in patients with cirrhosis. Abnormal hematological indices (HIs) in cirrhosis have a multifactorial pathogenesis that includes sequestration due to portal hypertension, altered bone marrow stimulating factors, bone marrow suppression due to viruses, toxins or excess alcohol consumption, etc.[2-4]

Abnormalities in HIs are associated with an increased risk of complications such as bleeding and infection.

Various studies on patients with varying stages of cirrhosis have shown a prevalence of hematological abnormalities ranging from 6% to 77%.[4-6]

In an analysis of homogenous patients with compensated Child-Pugh Class A/B cirrhosis, 84% were found to have abnormalities in the HIs, defined as a platelet count of

≤150 × 10^9/L, white blood cell (WBC) count of ≤400 × 10^9/L or hemoglobin level ≤135 g/L for men and 115 g/L for women. Thirty-two percent of these patients had a combination of cytopenias.[7] Thrombocytopenia was the most common single abnormality and thrombocytopenia and leukopenia was the most common combined abnormality.[8]

The study was conducted at RajaRajeswari Medical College and Hospital, Bangalore. The study was conducted to assess the hematological abnormalities and derangements and the nature of hematological abnormalities mainly to reduce the morbidity. Broadly the hematological abnormalities are viewed under abnormalities in red blood cells (RBCs), WBCs, platelets and coagulation profile.

MATERIAL AND METHODS

This study was conducted at RajaRajeswari Medical College and Hospital, Bangalore. Institutional Ethical Committee clearance was obtained before the study. Informed consent was obtained from all patients who met with inclusion criteria.

Inclusion Criteria

- Patients above 18 years.
- Patients presenting with signs and symptoms of chronic liver disease.
- Patients with ultrasound evidence of chronic liver disease with portal hypertension.

Exclusion Criteria

- Patients with underlying malignancy or known primary hepatocellular carcinoma.
- Patients with primary coagulation disorder or primary abnormalities of hemostatic function.
- Patients with acute hepatic failure.
- Patients with pre-existing anemia due to other causes.
- Patients suffering from end-stage medical diseases like chronic obstructive pulmonary disease, coronary artery disease, cardiac failure, chronic kidney disease.

All patients who met with inclusion criteria were evaluated with detail history and clinical examination. Blood sample was taken for assessment of liver function tests, complete hemogram, coagulation profile, peripheral blood smear, renal function tests and ultrasound abdomen and baseline upper gastrointestinal (GI) endoscopy were done for all patients. Results were analyzed with statistics.

RESULTS

We conducted the study on 43 patients with clinical and sonological diagnosis of chronic liver disease with various etiologies. In all, data were available for 41 patients. Hematological parameters, including anemia, leukocyte count, prothrombin time (PT) and platelet count were assessed in the subjects and were categorized under the different groups of model of end-stage liver disease (MELD) score. The relationship of these variables with MELD score was studied and statistical analysis was done.

This was an observational noninterventional correlational clinical study. Maximum number of patients was in 41-50 years and 30-40 years of age groups. Only 6 patients were above 50 years. Eighty-eight percent of patients were males and 12% were female. Alcohol consumption (38 patients) was common etiology for all these patients and 3 patients had cirrhosis of cryptogenic origin. Fifty percent of patients had history of alcohol consumption for more than 10 years. Ascites, jaundice, generalized weakness and edema of limbs were common symptoms at admission.

Nine patients had bleeding manifestations and 37 patients had hemoglobin <12 g/dL (Table 1). Macrocytic anemia was predominant type. Thirteen patients had leukopenia, 8 patients had leukocytosis and 20 patients had normal leukocyte count. Thrombocytopenia was observed in 24 patients. Twenty-eight patients had prolonged PT and international normalized ratio (INR) (Table 2). Elevated total bilirubin was observed in 16 patients; 36 patients had serum albumin <3 g. Enlarged spleen of more than 10 cm was observed in 38 patients (Table 3). We also observed peripheral smear suggestive of pancytopenia in 12 patients. We found 16 patients with upper GI evidence of varices. Most of patients with platelets <1.5 lakhs/dL had findings of upper GI bleed, but only 2 patients with platelets above 1.5 lakh had upper GI bleed. There was significant drop in hemoglobin and in platelets in patients with MELD score above 20%. Mean corpuscular volume (MCV) was prolonged in patients with MELD score above 20%. This finding was statistically significant. In our study, only 2 patients had MELD score <9%. Most other patients had score above 20% and about 7 patients had very high score (Table 4).

We also found there was increase in PT in patients who had MELD score above 15%. Mean duration of alcohol consumption was also >15 years in patients with MELD score above 20%. There was significant rise in MELD score with fall in hemoglobin. Mean platelet count

Table 1. Clinical Investigations

Variables	No. of patients (n = 41)	Percentage (%)
MCV		
<80	3	7.3
80-95	15	36.6
>95	23	56.1
Hemoglobin (g/dL)		
<10	25	61.0
10-12	12	29.3
12-14	2	4.9
>14	2	4.9
PS		
Macrocytic	23	56.1
Microcytic	7	17.1
Normocytic	11	26.8
Total count		
<4000	13	31.7
4000-11000	20	48.8
>11000	8	19.5
Platelets		
<0.50	2	4.9
0.50-1.50	22	53.7
>1.50	17	41.5
ESR		
<35	11	26.8
35-60	26	63.4
>60	4	9.8

MCV = Mean corpuscular volume; PS = Peripheral smear; ESR = Erythrocyte sedimentation rate.

Table 2. Coagulation Profile

	No. of patients (n = 41)	Percentage (%)
PT, INR		
<20	13	31.7
20-40	27	65.9
>40	1	2.4
Raised INR		
<3 sec	0	0.0
3-5 sec	22	53.7
>5 sec	19	46.3

PT = Prothrombin time; INR = International normalized ratio.

Table 3. Spleen Size in Patients Studied

	No. of patients (n = 41)	Percentage (%)
No	1	2.4
<10	2	4.9
10-15	34	82.9
>15	4	9.8

Table 4. MELD Score Distribution of Patients Studied

MELD	No. of patients	Percentage (%)
1-9%	2	4.9
10-19%	11	26.8
20-29%	21	51.2
30-39%	7	17.1
Total	**41**	**100.0**

was <1.5 lakhs/dL in patients with MELD score above 15%. We observed low mean serum albumin and total protein among patients with high MELD score; this observation was statistically significant (Table 5). Only 2 patients had MELD score <10%. Rest all patients had high score. MELD score above 30% was observed in 7 patients. We observed Child-Pugh score of category B in 19 patients and category C was seen in 7 patients. Most of the patients with high MELD score presented with jaundice, ascites and edema. Few patients had bleeding symptoms. There was significant correlation between high MELD score and hepatic encephalopathy in our patients.

DISCUSSION

The vital functions of many organs in the body depend directly or indirectly on the liver. The hematopoietic system is an exception. Beginning early in fetal life, it exerts a profound influence on the formation and maintenance of blood. It acts as a hematopoietic organ and after birth it plays an active and important role in the production of many elements necessary for homeostasis and hematopoiesis. Indirectly, when the liver is damaged by either acute or chronic disease, the effect

Table 5. Comparison of Clinical Variables According to MELD Score of Patients Studied

Variables	MELD				P value
	1-9%	10-19%	20-29%	30-39%	
Age (years)	47.00 ± 0.00	52.00 ± 14.30	48.90 ± 12.43	45.29 ± 10.64	0.731
Duration	15.00 ± 0.00	18.36 ± 10.22	14.19 ± 10.25	9.14 ± 8.01	0.294
MCV	87.00 ± 0.00	95.09 ± 3.86	94.33 ± 12.34	93.71 ± 13.73	0.808
Hemoglobin (g/dL)	12.50 ± 0.00	10.23 ± 1.91	9.32 ± 2.30	10.74 ± 2.96	0.187
Total count	5700.00 ± 424.26	7514.55 ± 5256.15	6200.00 ± 3932.43	10500.00 ± 6318.49	0.222
Platelets	2.63 ± 0.33	1.72 ± 0.95	1.52 ± 0.87	1.59 ± 1.07	0.440
ESR	42.50 ± 17.68	48.64 ± 13.42	46.09 ± 14.49	48.43 ± 16.83	0.948
PT INR	16.00 ± 0.00	21.36 ± 3.61	23.65 ± 6.00	28.43 ± 27.45	0.521
INR	1.11 ± 0.01	1.69 ± 0.48	1.95 ± 0.57	2.51 ± 2.52	0.348
Total bilirubin	1.40 ± 0.00	2.95 ± 1.75	6.06 ± 4.37	17.23 ± 14.96	0.001**
OT	23.00 ± 0.00	57.18 ± 19.43	79.48 ± 55.37	117.71 ± 55.73	0.034**
PT	13.00 ± 0.00	21.55 ± 6.85	31.81 ± 19.65	66.00 ± 46.35	0.002**
Total protein	8.20 ± 0.00	6.36 ± 0.84	6.15 ± 0.74	6.03 ± 0.85	0.008**
Albumin	3.90 ± 0.00	2.24 ± 0.54	2.25 ± 0.41	2.49 ± 0.82	0.001**
Sodium (mEq/L)	133.00 ± 7.07	135.73 ± 4.52	131.81 ± 3.54	127.57 ± 1.51	0.001**
Potassium	4.60 ± 0.00	4.27 ± 0.45	4.05 ± 0.52	3.81 ± 0.54	0.142

**Statistically significant.

on these functions may be catastrophic. Liver plays a major role in carbohydrate, lipid and protein metabolism. Its role in hematological manifestations is also important. Loss of liver function can manifest as subtle metabolic abnormalities and derangements in hematological parameters, which can ultimately culminate in grave complications. Liver plays a major role in maintaining the hematological parameters and maintain the homeostasis. Liver stores iron, vitamin B12 and folic acid, which are necessary for normal hematopoiesis. Liver also secretes the clotting factors and inhibitors, and keeps the homeostasis in equilibrium. Chronic liver disease is usually accompanied by hypersplenism. Diminished erythrocyte survival is frequent. Dietary deficiencies, alcoholism, bleeding and difficulties in hepatic synthesis of proteins used in blood formation or coagulation add to the complexity of the problem.

In our study, we found anemia and thrombocytopenia as two major hematological abnormalities. And presence of these abnormalities can affect prognosis of patients which was observed by elevated MELD score. And thus, these abnormalities can contribute to patient's mortality. We also observed significant relation between prolonged PT and increase in MELD and Child-Pugh score. Once again, presence of thrombocytopenia and prolonged PT can contribute to development of hepatic encephalopathy and adverse prognosis. We observed most of the patients with thrombocytopenia and prolonged PT had evidence of upper GI bleed, which could lead to the development of hepatic encephalopathy and anemia.[9,10] Hence, identification and treatment of all abnormal HIs are a vital part of the management of patients with chronic liver disease. Similar results were observed is previous studies by Selvamani et al. Among the 100 patients, 52 patients had normochromic and normocytic anemia, 30 patients had microcytic anemia and 16 patients had macrocytosis. Two had dimorphic anemia and thrombocytopenia was found in 46 patients.[9] Rajkumar Solomon et al, in their study, found 50% of the patients had thrombocytopenia (<1 lakh). Out of the 13 patients who had an upper GI bleed, 3 patients had normal

platelet counts and the remaining had counts <1 lakh. They also found that most of the patients with thrombocytopenia had prolonged PT.[1]

CONCLUSION

Apart from serum protein, albumin, which reflects synthetic function of liver, alteration in hematological parameters are telltale signs of chronicity of liver disease. Efforts can be made to normalize the hematological parameters, so that we can reduce the mortality and morbidity of these patients effectively.

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UN and Partners Launch Guidelines to Address Needs of Most Vulnerable Groups During COVID-19

Vulnerable groups, especially women, displaced people, migrants, elderly and people with disabilities, may experience the most adverse impacts of COVID-19.

The Eastern Mediterranean RCCE Working Group, an inter-agency coordination platform that provides technical support to COVID-19 preparedness and response in the region, has released new guidelines titled "COVID-19: How Can Risk Communication and Community Engagement Include Marginalized and Vulnerable People in the Eastern Mediterranean Region". The practical guidelines describe the vulnerability of marginalized groups to the COVID-19 pandemic and explain how national and local efforts can address them… (*WHO/EMRO*)

Sewage Study in Italy Shows COVID-19 was There in December 2019

Scientists in Italy found traces of the new coronavirus in wastewater collected from Milan and Turin in December 2019. The finding suggests that COVID-19 was already circulating in northern Italy before China reported the first cases. The Italian National Institute of Health assessed 40 sewage samples collected from wastewater treatment plants in northern Italy from October 2019 to February 2020. The samples taken in Milan and Turin on December 18 demonstrated the presence of the SARS-CoV-2 virus… (*Reuters*)

Headache may Predict Clinical Evolution of COVID-19

Headache may be a key symptom of COVID-19 and may predict the disease's clinical evolution in individual patients, suggests new research.

An observational study of over 100 patients revealed that headache onset could occur during the presymptomatic or symptomatic phase and could resemble tension-type or migraine headache. Headache itself was found to be associated with a shorter symptomatic period, while headache and anosmia (loss of sense of smell) were associated with a shorter hospitalization period. The findings were presented at the virtual American Headache Society (AHS) Annual Meeting 2020… (*Medscape*)

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The Usefulness of Ultrasound Guidance in Fresh Embryo Transfers: A Retrospective Study

ALKA GAHLOT*, ML SWARANKAR†, RAVIKANT SONI‡

ABSTRACT

Objective: To evaluate retrospectively the efficacy of ultrasound-guided embryo transfer method on pregnancy and implantation rate and compare with clinical touch method. **Material and methods:** The results of 582 cycles from our *in vitro* fertilization and embryo transfer (IVF-ET) program conducted at Jaipur Fertility Centre, an Infertility Unit of Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan were analyzed retrospectively and comparison was made between those carried out using ultrasound guidance and those by clinical touch method. **Results:** Higher pregnancy and implantation rates (37.19% and 19.66%, respectively) were found in the group using the transabdominal ultrasound guidance during ET compared with those in the group using the clinical touch method (30.92% and 16.22%, respectively). The difference was not statistically significant. **Conclusion:** Older women (>35 years) and in the subgroup when the clinician rated the transfer procedure as easy with some difficulty, there appeared to be a substantial improvement in the pregnancy rate and the difference was statistically significant. We believe that ultrasound-guided ET should be used in these subgroups.

Keywords: Clinical touch, embryo transfer, *in vitro* fertilization, retrospective study, ultrasound-guided, air bubble

Transabdominal ultrasound-guided embryo transfer (ET) has been described by various authors since 1985 to improve the pregnancy rate.[1-4] However, significantly higher pregnancy rates following transabdominal ultrasound guidance have not been consistently demonstrated. Lindheim et al, first reported that ultrasound guidance improved pregnancy outcome only in easy transfer.[5] Subsequently, two studies demonstrated significant differences between the clinical touch method and transabdominal ultrasound-guided ET retrospectively[6] and prospectively.[7]

Most studies trying to address the issue of whether ultrasound guidance is beneficial to ET conclude that although pregnancy rates may not be significantly raised, ultrasound guidance provides both the clinicians and patients with greater degree of confidence in the ET procedure.[3,4,8] We divided our study population according to: i) Number of embryo transferred; ii) age of patient; and iii) ease of transfer to delineate a subgroup of patients that would particularly benefit from their embryo being transferred under ultrasound guidance.

MATERIAL AND METHODS

A retrospective study of *in vitro* fertilization and embryo transfer (IVF-ET) cycles from June 2011 to August 2012 was performed. Between June 2011 to December 2011 the clinical touch method had been adopted for 262 cycles in our IVF-ET program. Between January 2012 and August 2012, 320 cycles of IVF-ET were performed under transabdominal ultrasound guidance. During both periods, there was no change in ovarian stimulation method, oocyte retrieval, culture media and culture system. For ET, Wallace and Cook echo tip catheters were used. Exclusion criteria were: age 45-year-old, more than three previous assisted conception cycles and transfer requiring general anesthesia for the patients. One clinician and three ultrasonographers were involved in the study. All ultrasonographers were specialists in infertility. An ultrasound machine with 3.75 MHz transabdominal probe was used on all women in ultrasound group.

Controlled ovarian hyperstimulation (COH) was carried out in more than 85% of patients with

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recombinant follicle-stimulating hormone (FSH) and human menopausal gonadotropin (hMG) with half-dose of gonadotrophin-releasing hormone (GnRH) agonist after down regulation with GnRH agonist in the preceding late luteal phase. Rest of the patients were induced by short protocol with GnRH agonist along with recombinant FSH or hMG. Follicular growth was followed by transvaginal ultrasonography and once adequate follicular maturation was obtained, human chorionic gonadotropin (hCG) was administered and oocyte retrieval was performed about 36 hours later under transvaginal sonographic guidance and general anesthesia. ET was carried out on Day 3 or Day 5 after oocyte retrieval. Frozen ETs were excluded from the study.

THE EMBRYO TRANSFER PROCEDURE

We carried out all the ET in the operation theater. Three embryos were usually prepared for transfer. In case, where numbers of embryos formed were less than three, less number of embryos, i.e., one or two were transferred. The patients arrived with semi-filled bladder in ultrasound-guided group and with empty bladder in clinical touch group. In both clinical touch and ultrasound group, the clinicians started the ET in the same way, i.e., cleaning the external genitalia with a dry swab before insertion of a sterile speculum into the vagina. The external cervical os was then cleaned with a dry cotton swab and mucus in the cervical canal was removed with a mucus extractor. Embryos were loaded into Wallace sure view and Cook echo tip catheter. The catheter was then handed over to the clinician who inserted it through the cervical canal. At this stage, there was a difference between the two groups.

In the clinical touch group, when the clinician was satisfied with that he had placed the catheter as close to the fundus as possible without touching it, the plunger was depressed; but in the ultrasound group, the ultrasonographer used a transabdominal ultrasound to guide the clinician in the positioning of the tip of the catheter to ~15 mm from the fundus of the uterine cavity. The plunger was then depressed and the air bubbles observed to be expelled from the catheter tip. The embryos were injected over 30 seconds, allowing observation of the movement of the air bubbles into uterine cavity. Removal of the catheter was also monitored by ultrasound and retention of the air bubbles was observed in the fundal position. The catheter was carefully checked under microscope and the embryo retained within the lumen or adherent to the surface of the catheter were reharvasted. The embryo can be clearly identified by air bubbles inserted on either side, which are seen as bright echoes on the ultrasound image.

The clinician was then required to rate the ET procedure in terms of ease of transfer before they left the ET room. The rating system guidelines were:

- **Very easy:** Transfer catheter went straight through the cervix.
- **Easy with some difficulty:** Required the separation of the transfer catheter to advance the sheath of a stiffer catheter to facilitate the transfer.
- **Difficult:** Required in tenculum in addition to those requirement in easy category.

A positive pregnancy outcome was a positive blood pregnancy test performed 2 weeks after the ET and an ultrasound scan showing at least one sac in the uterine cavity 2 weeks after the positive pregnancy test. Statistical analysis: A p value <0.05 was considered to be statistically significant.

RESULTS

The pregnancy rate and implantation rate appeared higher in the ultrasound-guided group but not significant statistically (Tables 1 and 2).

When the analysis was performed controlling for the number of embryos transferred, there was no significant difference in the two groups whether one, two, three

Table 1. Clinical Data of IVF Cycles in Clinical Touch and Transabdominal Ultrasound Groups

Variables	Clinical touch (n = 262)	Ultrasound-guided (n = 320)
Age in years	34.2	33.9
Primary infertility (%)	142/262 = 54.2	165/320 = 51.6
Mean infertility duration in years	6.0	5.6
Cause of infertility		
Unexplained (%)	44/262 = 16.8	63/320 = 19.7
Male (%)	92/262 = 35.1	112/320 = 35
Only female (%)	98/262 = 37.4	127/320 = 39.7
Combined (%)	28/262 = 10.7	18/320 = 5.6
Mean number of embryos available	7.8	6.9
Mean number of embryos transferred	2.56	2.37
Mean number of oocyte retrieved	13.2	12.3
Days after retrieval	3.1	3.2

No significant difference was observed between the two groups.

Table 2. Outcome of ETs Performed with Clinical Touch and Ultrasound Guidance

	Clinical touch (n = 262)	Ultrasound-guided (n = 320)	P value
Pregnancy rate (%)	81/262 = 30.92	119/320 = 37.19	0.134 NS
Implantation rate (%)	109/672 = 16.22	149/758 = 19.66	0.103 NS

NS = Not significant.

Table 3. Outcome of ET in Subgroups

Pregnancy rate in subgroups	Clinical touch (n = 262)	Ultrasound-guided (n = 320)	P value
Number of embryo transferred			
One	3/21 = 14.3%	15/55 = 27.27%	0.327 NS
Two	15/72 = 20.8%	24/92 = 26.1%	0.549 NS
Three	63/169 = 37.3%	80/173 = 46.24%	0.116 NS
Age of patients			
≤35-year-old	53/141 = 37.6%	69/186 = 37.1%	0.981 NS
>35-year-old	28/121 = 23.14%	50/134 = 37.31%	0.021 S
Ease of ET			
Very easy	65/174 = 37.4%	85/225 = 37.8%	0.986 NS
Easy with some difficulty	12/62 = 19.35%	25/68 = 36.8%	0.045 S
Difficult	4/26 = 15.38%	9/27 = 33.33%	0.231 NS

NS = Not significant; S = Significant.

Table 4. Pregnancy Rate According to the Position of the Air Bubbles

	Distance of air bubbles from fundus (mm)						No air bubbles	Total
	0-5	6-10	11-15	16-20	21-25	26-30		
Total	13	34	49	14	6	5	4	**125**
Pregnancy	4	13	21	5	2	1	0	**46**
Pregnancy rate (%)	30.77	38.24	42.86	35.71	33.33	20	0	**36.8**

embryos were transferred. When controlled for age of women (≤35 and >35 years old) again the results were not significantly different in ≤35 years of age group but they were statistically significant in age group >35 years old (23.14% vs. 37.31%, respectively). Pregnancy rate in 'easy with some difficulty' ultrasound group was 36.8% vs. 19.35% in comparison to clinical touch group (statistically significant $p < 0.05$). It may be due to precise recognition of position of uterus in ultrasound-guided cases. If we only examined the cases, which were rated 'difficult' the difference in favor of the ultrasound group appeared nonsignificant (Table 3).

Out of 320 ultrasound-guided ET, in 125 patients, distance of air bubbles from fundus was noted. Pregnancy rate according to the position of the air bubbles was calculated. Maximum pregnancy rate was achieved when the distance of air bubble was between 11-15 mm from the fundus. Four cycles were excluded from this analysis because there was no description of the location of air bubbles in these cases (Table 4).

DISCUSSION

Since the IVF pregnancy was achieved, some aspects of the technique have remained largely unchanged,

whilst other have been constantly evolving, the most significant development being in ovulation induction, the use of intracytoplasmic sperm injection (ICSI) and in the development of culture media. Despite these improvements, the majority of the transferred embryos fail to implant. This failure may be due to poor quality embryo, lack of uterine receptivity or the technique of ET itself.[9,10] Defining the factors that are important for successful ET after IVF has been a major issue. Based on the questionnaires distributed amongst highly experienced IVF clinical, Kovacs summarized the answers.[11] The factor that got highest votes was the need to remove hydrosalpinx before treatment. The other important factors in order of priority included absence of bleeding, type of catheter used, not touching the fundus, avoid the use of a tenaculum, removal of all mucus from the cervix, ultrasound details of the cavity before treatment, leaving the catheter in place for at least 1 minute, 30 minutes rest after transfer, dummy transfer before treatment, ultrasonic monitoring of transfer and antiprostaglandins to prevent contractions. Although the clinician rated the importance of ultrasound guidance as 11th of 12 factors, the role of ultrasound monitoring during transfer should receive more emphasis. The cause of low priority of this factor might be due to the inconvenience and inaccuracy of transabdominal ultrasound guidance.

Generally, the positions of air bubble indicate the position of the embryos. It was recommended that the tip of the catheter be positioned 15 mm from the fundus of the uterine cavity to avoid placement of embryos close to the uterine fundus.[7] In our study, the point of placement of embryo was also 15 mm from the fundal limit of the uterine cavity. We could transfer the embryos to the precise place under transabdominal ultrasound guidance. There was no pregnancy in four cases in which air bubbles could not be identified. It is likely that these embryos were misplaced probably due to uterine contractions or technical errors. In two cases embryos remained in the lumen of catheter. In other cases, we suppose that the catheter was inadvertently abutting the internal tubal os and the bubbles disappeared in the tubal canal. Furthermore, we experienced some cases in which the air bubbles moved towards the cornue or the cervix from the position of the tip of the catheter. These observations also suggest that adequate monitoring by ultrasound guidance is very important during ET.

Evidence emerging from 17 to 20 randomized controlled trials comparing ultrasound guidance versus the 'clinical touch' method for ET have been evaluated. Clinical pregnancy rates were found to be statistically significant higher (odd ratio [OR] 1.31-1.50) with transabdominal ultrasound guidance.[7,12] It has been reported that high frequency uterine contractions on the day of embryo transfer hinder IVF-embryo transfer outcome.[13] It was reported that tactile assessment of catheter placement was unreliable.[14]

The outer guiding catheter inadvertently abutted the fundal endometrium or the internal tubal os and intended the endometrium. The transfer catheter was seen to be embedded within the endometrium. Transabdominal ultrasound-guided ET can minimize these endometrial traumas and thus reduce the uterine contractions. As transabdominal ultrasound can supply fine picture of the flexion of the uterus and the curve of the uterine endometrial midline, the clinician can insert the catheter smoothly without endometrial trauma under the monitoring, and stop the catheter before reaching the fundus. If the curve of the uterine endometrial midline is sharp, we stop the outer sheath before intending the endometrium and advance only the inner catheter, which is softer than the outer sheath, up to 15 mm from the uterine fundus. These atraumatic procedures probably contributed to successful ET in the present study because bleeding from the endometrium or the uterine cervix is a significant negative factor for ET, as suggested by Kovacs.[11]

The procedure was readily accepted by the patients who were reassured by the visualization of the transfer process. The acceptance by the clinician was also high with no significant added time, and the procedure was done with more confidence as the catheter is advanced to the fundus of the uterus under ultrasound scan guidance. Furthermore, ultrasound-guided ET may have two additional advantages over clinical touch ET when considering that: i) Blind catheter placement has been shown to result in a malposition of the catheter in >25% of cases, thus indicating that tactile assessment of ET catheter position is unreliable[14] and ii) the depth of the embryo replacement into the uterine cavity influences implantation rates, with high pregnancy rates obtained when the embryos are replaced 15-20 mm from the fundal endometrial surface.[7] Ultrasound assistance in the ET is a pivotal tool for improving pregnancy rate in assisted reproduction irrespective of whether embryos are fresh or frozen and replaced in spontaneous, stimulated or artificially prepared cycles. A report showing that ultrasound-guided ET improves outcome in patients with previous failed IVF cycles provides further evidence in this regard.[12]

CONCLUSION

There was no significant difference in the pregnancy rate when the number of embryos transferred was controlled. Based on the results obtained from the present study, transabdominal ultrasonography guidance appears to be an essential factor for improving the results of ET especially in case of easy with some difficulty ET and in older women.

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Over 14,000 New Cases, COVID Count Nears 4 Lakh in India

New Delhi: India's COVID-19 caseload was close to crossing the 4 lakh mark, as new cases hit a record high of 14,574 on 19th June. Delhi with 3,137 new cases and Maharashtra with 3,827, both recorder their highest daily numbers, taking the total to more than 3.95 lakh.

The total number of COVID-19 cases reported in June thus far have crossed the 2 lakh mark, with total number of cases standing at 2,10,655 on 19th June, according to state governments' data. Cases recorded in the month of June now account for 53% of all coronavirus infections detected so far in India… (*ET Healthworld – TNN*)

Dementia Tied to Previous Migraine History

Migraine patients reported a higher rate of subsequent dementia compared to people who did not have a history of migraine, reported a population-based longitudinal study in Denmark that was presented at the virtual American Headache Society annual scientific meeting.

People with a hospital diagnosis of migraine in midlife, at ages 31-58, were found to have a 50% higher dementia rate after 60 years of age compared to people without a migraine diagnosis… (*Medpage Today*)

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Stroke in Hanging: Ischemic or Thrombotic?

KA VIVEK*, N VIJAYAKUMAR†, R UMARANI‡

ABSTRACT

Hanging is among the most common methods of committing suicide in India, as reported in recent data published by National Crime Records Bureau. Neurological injury in such cases occurs due to compression of the neck. We present the case of a 52-year-old male who presented to the emergency with an alleged history of attempted suicide by hanging with nylon thread. Patient was started on supportive therapy, and 24 hours following admission, he became stable with normal blood pressure without any antihypertensive medications. However, on Day 3 of admission, he developed weakness of left upper limb and lower limb and deviation of angle of mouth to the left side. Repeat CT imaging of brain showed two hypodense foci in right caudate nucleus, head of adjacent internal capsule and a focus in right lentiform nucleus and posterior limb of internal capsule. MRI of brain, including MRA, showed an acute infarct with restricted diffusion in right lentiform nucleus, caudate nucleus, with filling defect in proximal M1 segment of right middle cerebral artery (MCA) suggestive of thrombus and attenuated signal was also noted in distal branches of right MCA. This case highlights the neurological complication following suicidal hanging and a structured approach to it.

Keywords: Suicidal hanging, neuroimaging, CT, MRI, stroke, hypoxia, thrombosis

Suicidal hanging is among the most common methods of committing suicide in India according to recent data published by National Crime Records Bureau, where neurological injury occurs due to compression of the neck. The neck is the target organ for hanging. Easy accessibility, rounded contours, minimum bony shields, the small diameter and unsafe location of the airway, vital blood vessels and spinal cord make it susceptible to life-threatening injuries by hanging, which has been practiced as a popular method of committing suicide since ancient times.

The jugular veins are the first structures to get compressed (force of 2 kg) followed by the carotid arteries (5 kg), causing cerebral edema and hypoxic brain damage, respectively. Compression of the airways needs greater force (15 kg), which can lead to severe hypoxia and death. Neurological outcomes in hanging vary from death, permanent hypoxic brain damage to complete recovery.

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In the reviewed literature, the neuroimaging findings in hanging have consistently been described as bilateral hemorrhagic and/or ischemic lesions in the thalamus, cerebellum and other areas of the basal nuclei. Unilateral lesions seem to be a very rare event and to the best of our knowledge, very few cases have been reported.

We report a case of suicidal hanging where the patient survived an initial brain insult, but later developed a neurological deficit in the form of hemiplegia due to an infarct in the right lentiform nucleus, caudate nucleus and corona radiata. Patient recovered with supportive treatment. This case highlights the neurological complication following suicidal hanging and a structured approach to it.

CASE REPORT

A 52-year-old male presented to the emergency with an alleged history of attempted suicide by hanging with nylon thread. After few seconds of suspension, he fell down, and was rushed to the hospital. There was no history of seizure, bleeding from nostrils, eyes and mouth. There were no pre-existing comorbid conditions.

At the time of admission, patient was conscious and oriented. The pulse rate was 110/min, blood pressure was 170/100 mmHg, respiratory rate was 18/min and oxygen saturation by pulse oximeter was 98%. Local examination revealed one circumferential shallow

abraded ligature mark over anterior aspect of the neck. There was no cyanosis or subconjunctival hemorrhages. Nasal mucosa, post pharyngeal wall and bilateral tympanic membrane were not congested. Neurological examination was normal except for bilateral extensor Babinski response. Fundus was normal. Both pupils were mid-dilated and responding to light. All biochemical investigations and baseline computed tomography (CT) imaging of brain was normal, and there were no fractures of the cervical spine. Patient was started on supportive therapy, and 24 hours following admission, patient became stable with normal blood pressure without any antihypertensive medications.

On Day 3 of admission, patient developed weakness of left upper limb and lower limb and deviation of angle of mouth to the left side. Neurological examination revealed hemiparesis of left upper limb and lower limb with a power of 3/5. Tone was increased, reflexes were diminished on both left upper limb and lower limb. Extensor plantar was present on the left side and right side plantar was not elicitable; left upper motor neuron (UMN) type of facial nerve palsy was also present.

Urgent repeat CT imaging of brain (Fig. 1a) showed two hypodense foci in right caudate nucleus, head of adjacent internal capsule and a focus in right lentiform nucleus and posterior limb of internal capsule.

Magnetic resonance imaging (MRI) of brain (Fig. 1b), including magnetic resonance angiography (MRA), showed an acute infarct with restricted diffusion in right lentiform nucleus, caudate nucleus, with filling defect in proximal M1 segment of right middle cerebral artery (MCA) suggestive of thrombus and attenuated signal was also noted in distal branches of right MCA. Magnetic resonance venography (MRV) had no evidence of venous thrombosis. Cardiac evaluation including echocardiogram was found to be normal.

Patient was treated with fluid restriction, mannitol, intravenous antibiotics, low molecular weight heparin, physiotherapy and other supportive measures. Patient gradually improved and was discharged on Day 9, with advice to continue physiotherapy.

DISCUSSION

The factors that contribute to death after suicidal hanging include pulmonary complications and neurological complications. *Pulmonary complications* include pulmonary edema and bronchopneumonia, secondary to aspiration. The edema may be due to a centrally mediated sympathetic discharge or due to negative intrathoracic pressure, which is generated as the person

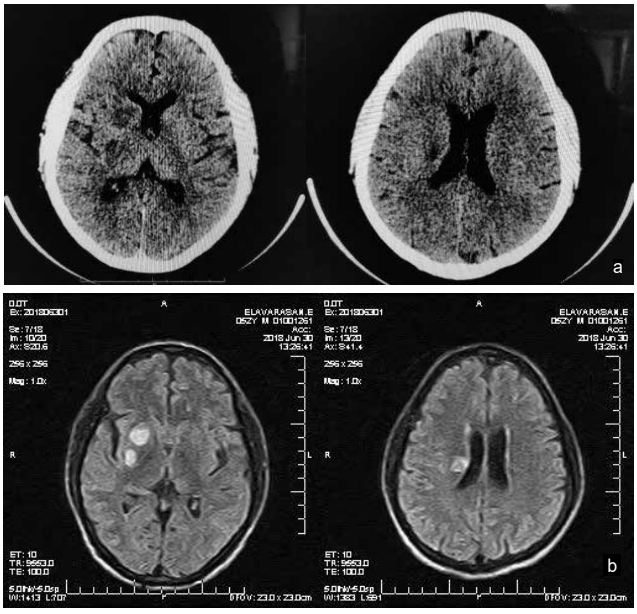

Figure 1 a and b. CT imaging of brain showing two hypodense foci in right caudate nucleus, head of adjacent internal capsule and a focus in right lentiform nucleus and posterior limb of internal capsule **(a)**. MRI showing acute infarct with restricted diffusion in right lentiform nucleus and caudate nucleus **(b)**.

attempts to inspire through an obstructed airway. *Neurological complications* include transient hemiparesis, spinal cord syndromes, focal cerebral deficits, cerebral edema, various nerve palsies and larger infarctions. Other complications like hyperthermia, subarachnoid hemorrhage, pneumoperitoneum, ruptured esophagus may also occur. Some factors such as systolic blood pressure <90, Glasgow coma scale score ≤8, anoxic brain injury on CT scan and injury severity score >15 have been found to be significantly associated with mortality in hanging.

In suicidal hanging, there is slower development of *cerebral hypoxia and ischemia*, with both the events being strongly dependent on the materials, location and the method of suicide attempt. This cerebral hypoxia and ischemia can be attributed to the mechanical compression and obstruction of the airway and vasculature of the neck. Further, airway can be compromised by the upward displacement of the tongue and epiglottis, jugular vein occlusion by mild neck closure and vertebral artery occlusion by spinal injury. These combined factors can easily lead to acute cerebral hypoxia. In rare instances, direct injury to the spinal cord and brainstem can also occur.

The most sensitive areas of hypoxic and ischemic damage are the cerebral cortex, border zones between arterial territories, Ammon's horn, Purkinje cells, particularly the basal ganglia. In the early stages, ischemic neuronal

changes are demonstrated by cytotoxic edema (swelling of neurons, glia and endothelial cells) and failure of the sodium ion exchange pump. Sodium accumulates within the cell and water follows this movement to maintain the osmotic equilibrium. The venous hypertension and stasis of blood flow caused by the acute bilateral compression of the internal jugular veins result in hydrostatic transudation of intravascular contents and subsequently rapid occurrence of hypoxia and infarction.

Bilateral involvement is the common finding in hypoxic ischemic injury in suicidal hanging. However, unilateral involvement of brain in the form of hemiplegia due to thrombotic stroke can occur rarely. Traumatic thrombosis of internal carotid artery is reported as being caused by one of the four mechanisms:

- Injury to intrapetrous or cavernous part of the carotid artery during the basal skull fracture
- Injury to point of emergence of carotid artery from the cavernous sinus as a result of strain
- A direct blow to the neck or trauma to peritonsillar area by a foreign object carried in the month
- Stretching of the carotid artery by hyperextension and lateral flexion of neck.

The pathophysiology of thrombosis is due to adherence of platelets to the endothelium with subsequent aggregation, which releases thromboplastin leading to initiation of coagulation cascade.

The neuroimaging in hypoxic ischemic brain injury is often symmetrical, diffuse, low-density lesions found in the watershed areas of the brain. However, in thrombotic injury, the CT and MRI findings are consistent with the vascular territory of the vessels involved. MRA and MRV may show filling defects with attenuated signals.

CONCLUSION

The mechanism of injury, pathophysiology, clinical features and neuroimaging are distinct and different in both cerebral hypoxic ischemic injury and traumatic thrombotic injury to the brain in patients with suicidal hanging. Detailed neurological examination daily to look for subtle changes in clinical features in the patient, repeated neuroimaging studies including MRA and MRV, would help in early diagnosis of thrombotic episodes in suicidal hanging and for early medical management, and if required, surgical management.

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Senior-Loken Syndrome Complicated by Panuveitis: A Diagnostic Challenge

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ABSTRACT

Senior-Loken syndrome is a rare autosomal recessive syndrome affecting eyes and kidneys. The kidney condition nephronophthisis, classified as medullary cystic kidney disease, begins in childhood with symptoms of polydipsia and polyuria, which are secondary to defective urinary concentrating ability. Nephronophthisis progresses to end-stage renal disease during the second decade. The retinal lesions are variable, ranging from severe infantile onset retinal dystrophy to more typical retinitis pigmentosa. Other associated features observed in this entity are cerebellar, skeletal and dermatological anomalies. Here, we report a case of SLS in which eye involvement is complicated, rather masqueraded, by panuveitis, causing diagnostic dilemma. There may be a role of autoimmunity in the pathophysiology of the syndrome.

Keywords: Panuveitis, nephronophthisis, retinitis pigmentosa, Senior-Loken syndrome

Senior-Loken syndrome (SLS) is a rare autosomal recessive disorder described by Senior and Loken in 1961 in children. It is broadly a ciliopathy and consists of retinopathy and nephronophthisis. Retinopathy in SLS is variable, including retinitis pigmentosa, retinal dystrophy, Leber amaurosis.[1] Nephronophthisis is a chronic tubulointerstitial nephritis leading onto inability to concentrate urine due to which polyuria and polydipsia occur initially and finally leads to end-stage renal disease (ESRD) by second decade.[2] Clinically, it is diagnosed on the basis of ocular examination and renal assessments. Ocular examination includes fundus examination, refraction testing, visual acuity examination, color testing, electroretinography; whereas renal assessment includes urine analysis, renal function test, ultrasonography and kidney biopsy.[3]

Here, we report a case of SLS involving kidneys in the form of ESRD and eyes in the form of retinitis pigmentosa with other manifestations including skeletal defects and bilateral sensorineural hearing loss. What makes the case different is associated bilateral panuveitis which created the diagnostic dilemma along with an extensive search for the autoimmune etiology, which could not be ascertained.

CASE REPORT

A 19-year-old female presented with history of progressive loss of vision for the last 6 years and progressive hearing loss for last 2 years. For eye condition, she was diagnosed as a case of idiopathic panuveitis in another hospital and was given treatment in the form of steroids, which she stopped 1 year back on her own. She also had multiple seizure episodes of generalized tonic-clonic in type followed by loss of consciousness. There was no history of fever, headache, loose stool, vomiting, jaundice and head trauma.

On examination, she was confused, dyspneic, pale with puffy face and edema over both feet. She was hypertensive with blood pressure of 170/100 mmHg. Lab investigations revealed deranged renal parameters with blood urea of 215 mg/dL and serum creatinine of 8.1 mg/dL, with severe anemia (hemoglobin - 4.6 g/dL), hypocalcemia (serum calcium <5.0 mg/dL), hyperphosphatemia (serum phosphorus - 6.0 mg/dL), metabolic acidosis with pH - 7.11, PCO_2 - 25.5 mmHg and bicarbonate - 7.9 mmol/L. Her serum sodium level was 128 mEq/L and had hyperkalemia with serum potassium >6.0 mEq/L. Her ECG showed sinus tachycardia with

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tall T waves secondary to hyperkalemia. Her chest X-ray revealed bilateral symmetrical opacities suggestive of uremic lung with scoliosis of thoracic spine (Fig. 1).

On ultrasonography, her kidneys were found to be contracted with size of right kidney measuring 6.2 × 2.7 cm and left kidney measuring 6.0 × 2.5 cm with loss of corticomedullary differentiation. Urine complete examination revealed albuminuria without red blood cell cast or dysmorphic red cells. She was treated as a case of ESRD with uremic lung with hypocalcemic seizure. Patient was managed with regular hemodialysis and showed significant improvement in metabolic derangements including metabolic acidosis, hyperkalemia, renal function tests and clinical improvement with relieved shortness of breath and no recurrence of seizure. Her ophthalmologic examination at our institute revealed changes suggestive of retinitis pigmentosa in both eyes with old uveitis (Fig. 2 a and b).

To further evaluate, magnetic resonance imaging (MRI) brain was done, which was suggestive of mild cerebral atrophy. Pure-tone audiometry was done which suggested mild-to-moderate sensorineural hearing loss. Cardiac and hepatic involvement was ruled out with the help of echocardiography and ultrasonography abdomen, respectively. She was advised antinuclear antibody (ANA), c-ANCA, p-ANCA, rheumatoid arthritis factor and C-reactive protein to look for small vessel vasculitis, which turned out to be negative. Mantoux test for tuberculosis, Venereal Disease Research Laboratory (VDRL) for syphilis were also negative. Hence, other possible causes of bilateral panuveitis were ruled out.

To summarize, this was a case of SLS where eye involvement in the form of retinitis pigmentosa which was masquerading as bilateral panuveitis with progressive vision loss despite steroid therapy and progressive kidney disease, which remained undiagnosed until ESRD.

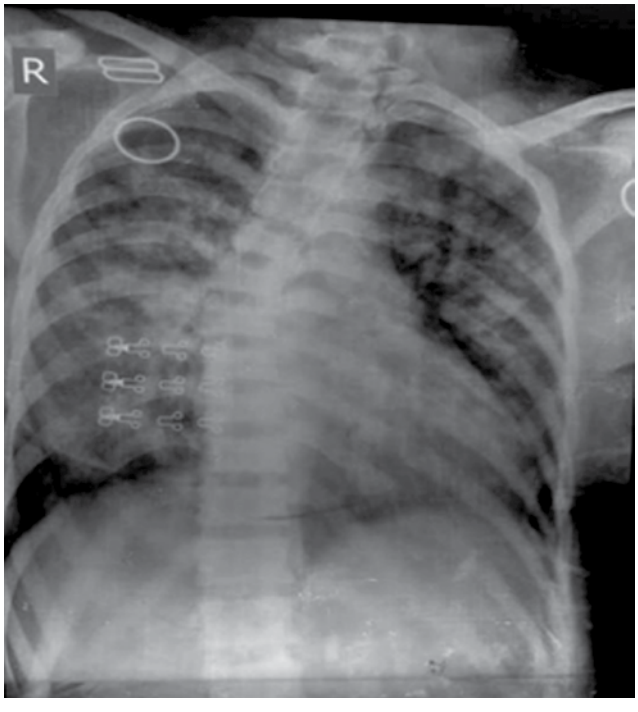

Figure 1. Chest X-ray showing bilateral pulmonary infiltrate with scoliosis.

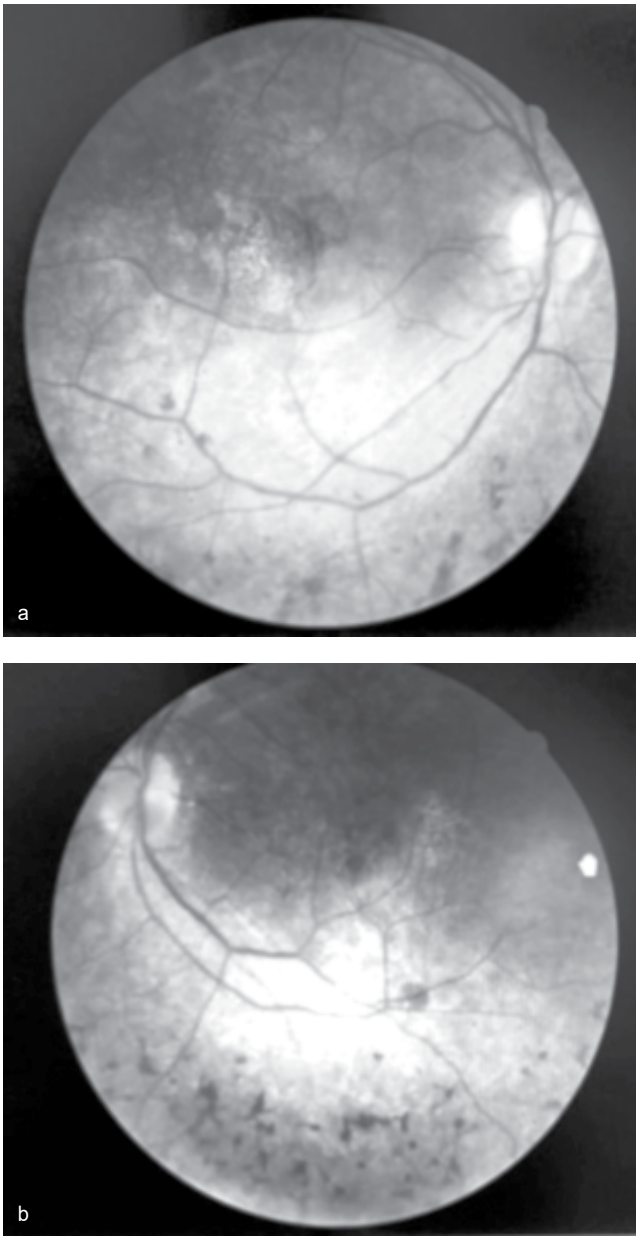

Figure 2 a and b. Fundus of right and left eye, respectively, showing retinitis with bony spicules.

DISCUSSION

Senior-Loken syndrome is a rare autosomal disease with incidence of 1/1,00,000 population and is more common in consanguineous marriage. Other synonyms for this disease are juvenile nephronophthisis with Leber amaurosis, renal retinal syndrome and renal dysplasia and retinal aplasia. Renal nephronophthisis is a ciliopathy due to genetic mutation of *NPHP* gene, which leads to renal cystic dysplasia or cystic kidney. On the basic of median age of presentation, nephronophthisis is categorized into three variants: 'Infantile' at the age of 1 year, 'juvenile' at the age of 13 years and 'adolescent' at the age of 19 years.[4]

It has been shown that SLS is caused due to mutations in several genes known as nephrocystins, which encode proteins that are presented in the primary cilium of kidney cells and in the connecting cilium of photoreceptor cells.[5] Various identified genetic variants as cause of SLS include *NPHP* 1-6, *NPHP10, NPHP13, NPHP15, TRAF3IP1* and the recently identified heterozygous splice site sodium channel and clathrin linker 1 (*SCLT1*) variants.[6] Gene responsible for infantile variant *NPHP2* is localized on chromosome 9q22-q31, for juvenile variant *NPHP1* on chromosome 2q12-q13 and for adolescent variant *NPHP3* is localized on chromosome 3q21-q22.[7] A triad of renal interstitial fibrosis, interstitial infiltration and renal tubular cell atrophy with cyst development is found on histology of renal tissue.[8] Ocular involvement presents as variable forms like tapetoretinal degeneration, Leber's congenital amaurosis, retinitis pigmentosa, Coat's disease, keratoconus, cataract, retinal dystrophy.[9] Other eye manifestations include nystagmus, vision loss in infancy or childhood, hyperopia and photophobia.[3] Other than renal and ocular involvement there are dermatological manifestations as well, like madarosis, skeletal manifestations like small hands, scoliosis and cerebellar involvement, obesity, liver fibrosis.[3,10] For end-stage renal failure, patient should undergo hemodialysis; however, renal replacement therapy appears to be the best option for end-stage renal failure and also there is poor prognosis for ocular manifestations.[11]

In our case, lack of cyst does not exclude the diagnosis of nephronophthisis. Hyperechogenic kidneys with reduced or normal size are consistent with the diagnosis of nephronophthisis.[12] Bilateral sensorineural hearing loss in our case favors underlying ciliopathy; scoliosis of spine is also a positive finding. This case remained undiagnosed due to coexistent panuveitis and patient presented to us with ESRD. Coexistent panuveitis and retinitis pigmentosa are rare though, can occur. In this case, association of SLS with idiopathic panuveitis, with some improvement in vision with steroid therapy, may indicate role of autoimmunity in pathogenesis and thus the role of immunosuppressive therapy for the treatment of this genetic disorder.

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Tubercular Retropharyngeal Abscess with Compressive Cervical Myelopathy with Tuberculous Meningitis

ABHIJIT GAIKWAD*, NEETU AGGRAVAL*

ABSTRACT

Tuberculosis (TB) is the commonest infection in a developing country like India. One of the many presentations of TB is meningitis, but tubercular retropharyngeal abscess is a very rare presentation of TB. A retropharyngeal abscess is an immediate life-threatening emergency, with potential airway compromise and other catastrophic complications including compressive myelopathy. We report clinical, radiological and histological findings in a symptomatic 17-year-old female who presented with quadriparesis due to cervical compressive myelopathy due to tubercular retropharyngeal abscess with tuberculous meningitis.

Keywords: Tubercular retropharyngeal abscess, tuberculous meningitis, compressive high cervical myelopathy

India is the country with highest burden of tuberculosis (TB). The World Health Organization (WHO) statistics of 2015 give estimated incidence of 2.2 million cases of TB in India out of global incidence of 9.6 million cases. TB most commonly involves lungs. Common sites of extrapulmonary TB are lymph nodes, osteoarticular areas, abdominal organs and central nervous system. In view of its unusual presentation, diagnosis of extrapulmonary can be difficult and high index of suspicion is required. Though tuberculous meningitis is common, its association with tubercular retropharyngeal abscess is rare. Again, tubercular retropharyngeal abscess are mainly secondary to TB spine due to spread of infection hematogenously via Batson's plexus. Here we want to draw attention to a rare presentation of TB as tuberculous meningitis with tubercular retropharyngeal abscess causing compressive cervical myelopathy and nontraumatic atlanto-axial dislocation. Chronic tubercular retropharyngeal abscess is rare in immunocompetent adults, especially without spine involvement. Tubercular retropharyngeal abscess requires prompt diagnosis and early management, which frequently involves surgical drainage with antibiotics and antitubercular treatment.

CASE REPORT

A 17-year-old, right-handed female came with complaints of weight loss since 2 months. Patient also had headache since 2 months, which was mostly localized in character to posterior part. There was history of low-grade, on and off fever, with no diurnal variation since 2 months. Patient developed neck pain for 1 month which was gradual in progression and developed painful restricted neck movements since few days. Patient consulted local doctors for the same complaints and had received symptomatic treatment. Patient developed sudden onset of right-sided hand weakness while doing her routine activities since 7 days followed by left leg stiffness while walking since 7 days. She was brought to the hospital where she was admitted. Basic investigation was done including CT scan of brain, which was normal. She developed all four-limb weakness followed by breathlessness since 2 days and developed sudden onset of altered sensorium since 1 day and hence was referred to higher center for further management.

Patient was evaluated and investigated. There was no history of cough, hemoptysis, chest pain, foreign body impaction, ear discharge, odynophagia, dental

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extraction, vomiting or convulsions. There was no history of TB in past. On clinical examination, there were no signs of anemia, jaundice, cyanosis or clubbing. Vitals were stable with pulse - 72 /min, blood pressure - 122/70 mmHg and respiratory rate - 16 cycles/min. There was no bony tenderness or swelling in cervical spine but the neck movements were painful and restricted. Nervous system examination revealed that the patient was rousable. There was no cranial nerve involvement. Tone was increased in all four limbs. Deep tendon reflexes were exaggerated in all four limbs. Ankle clonus and Babinski's sign were positive; power was 2/5 in all four limbs. Examination of cardiovascular and respiratory system did not show any abnormality.

On investigation, hemoglobin was 11.2 g/dL and white blood cell (WBC) count was 11, 500/mm^3. Renal function tests and liver function tests were within normal limits. Erythrocyte sedimentation rate (ESR) was 102 mm 1st hour. Chest X-ray was suggestive of normal findings. Ultrasonography (USG) abdomen was done and findings were within normal limits. Fundoscopic examination of bilateral eyes was normal. Patient's X-ray neck was done and was suggestive of atlanto-axial dislocation (Fig. 1). Lumbar puncture was done after taking valid consent and was suggestive of neutrophilic predominance but raised adenosine deaminase (ADA) level. Patient was started on CAT 1 AKT. Magnetic resonance imaging (MRI) brain with cervical spine screening was done and was suggestive of large retropharyngeal abscess compressing corticomedullary junction and from C1 to C3 level with significant cord edema (Fig. 2). ENT Surgeon and Neurosurgeons were consulted and transoral incision and drainage of retropharyngeal abscess was done. Patient was tracheostomized in view of respiratory failure due to diaphragmatic involvement and was kept on ventilatory support in intensive care unit (ICU). No surgical intervention could be done for spine stabilization and patient's neck was immobilized with hard cervical collar as a conservative management. Pus was examined for routine microscopy and was found to have lymphocytic predominance. GeneXpert for pus aspirated from retropharyngeal abscess showed *Mycobacterium tuberculosis* (MTB) and hence diagnosis of tubercular retropharyngeal abscess was established.

Patient was continued on CAT 1 AKT as GeneXpert for MTB was done and no rifampicin resistance was detected. Pus culture for MTB was negative. Patient regained consciousness within 3 days of starting antitubercular therapy. Patient developed ventilator-associated pneumonia and started on higher antibiotics

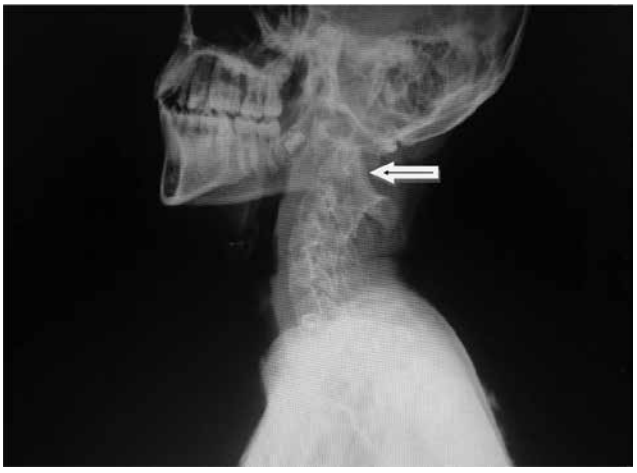

Figure 1. X-ray cervical spine suggestive of atlanto-axial dislocation.

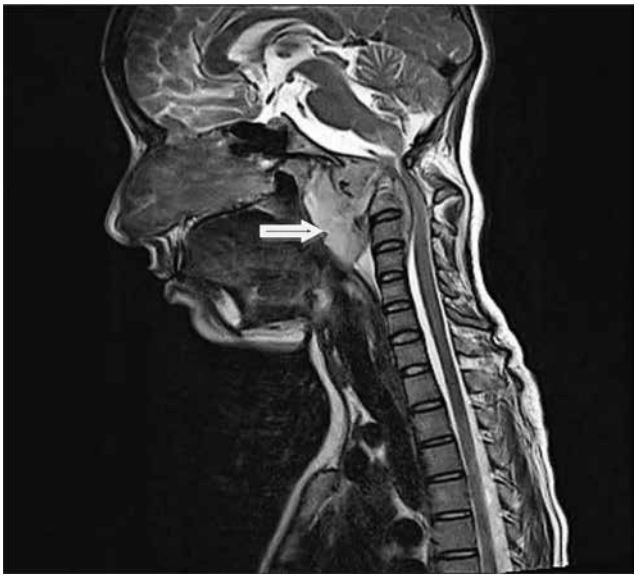

Figure 2. T2-weighted MRI cervical spine suggestive of large retropharyngeal abscess compressing corticomedullary junction and cervical cord.

accordingly tracheal culture sensitivity report. But in spite of all measurements patient could not be survived and died due to sepsis and shock.

DISCUSSION

A retropharyngeal abscess in an infection in one of the deep spaces of neck. An abscess in this location is an immediate life-threatening emergency, with potential for airway compromise and other catastrophic complications. Complications of retropharyngeal abscess are secondary to mass effect, rupture of abscess or spread of infection. The rupture of abscess can cause aspiration of pus, resulting in asphyxia or pneumonia. Infection can spread, resulting in inflammation and

destruction of adjacent tissue. Posterior spread of infection can result in osteomyelitis, and erosion of spinal column causing subluxation or dislocation as in our case where she developed atlanto-axial dislocation due to posterior spread of abscess. Chronic retropharyngeal abscess occurs in adults and cause is almost always TB. Retropharyngeal TB is a rare presentation of extrapulmonary TB and its association with tuberculous meningitis in absence of pulmonary involvement is very rare. Retropharyngeal abscess in adults is usually secondary to tubercular involvement of cervical spine. Symptoms in adults are sore throat, fever, odynophagia, neck pain and dyspnea as in our case. Route of spread of TB could be due to retropharyngeal space, via lymphatics, to persistent retropharyngeal lymph node. A hematogenous spread can also occur from pulmonary TB or from any other site.

The diagnosis of tubercular retropharyngeal abscess is based on careful patient history and examination along with a high index of clinical suspicion.

The diagnosis of retropharyngeal abscess is further supported by radiological imaging, which plays an important role in assessing extent of disease and possible damage to important structures, such as cervical spine. A CT scan accurately differentiates cellulitis from abscess with accuracy of 89%. MRI provides a better delineation of soft tissues in the neck and is very useful in assessing vascular complications such as internal jugular vein thrombosis. Pathophysiology explained for atlanto-axial dislocation may be inflammatory ligamentous laxity of transverse ligament and atlanto-axial joint. No single report has been reported in Indian patients with nontraumatic atlanto-axial dislocation due to tubercular retropharyngeal abscess without pulmonary involvement as per best of our knowledge.

In a case of tubercular retropharyngeal abscess with neurological complications, recovery does occur following prompt drainage and antitubercular therapy. In our case, trans-oral drainage of abscess was done and decompression was achieved.

As in any abscess, mainstay of treatment of tubercular retropharyngeal abscess is drainage of pus. Surgical drainage of pus through oral, cervical or combined oral and cervical route has been described. Therapeutic ultrasound-guided aspiration has been used successfully and can be repeated if necessary. The standard recommended regimen is 6 months of isoniazid and rifampicin, supplemented in the first 2 months with pyrazinamide and ethambutol for pulmonary TB. For extrapulmonary TB including bone involvement recommended duration of antitubercular medication is 9-12 months.

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Brain Activation in Unresponsive Patients with Acute Brain Injury: Words of Caution

AMIT AGRAWAL*, LUIS RAFAEL MOSCOTE-SALAZAR†, RAVISH KENI‡

Functional and structural integrity of severely injured brain remains a challenge for clinicians and neuroscientists.[1] New studies[2] are further expanding our understanding on noninvasive methods to evaluate the structural integrity of brain functions.[1,3] Apparently, it has been presumed that the patients have normal hearing; however, auditory response has been shown to be reduced after brain injury in many clinical studies.[4,5] There is a need to identify the presence or absence of pre-existing hearing impairment to find out its impact on brain activation. It needs to be further clarified whether evoked potential can help us to confirm the integrity of hearing. It is also important to note that apparently global insult due to systemic factors (cardiac arrest) causes more damage than more focal insult (TBI > SAH). There is a further need to understand the severity of injury, e.g., imaging evidence of global versus focal injuries, dominant versus non-dominant side lesions. Studies have shown promising results as majority of the patients at follow-up though dependent were alive. How to interpret and apply these findings on individualized basis is the next challenge.

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COVID-19 Antibodies may Disappear After 2-3 Months, Says Study

People who develop antibodies after getting infected with the coronavirus may not keep them for more than a few months, particularly if they had no symptoms to begin with, suggests a Chinese study.

Previous studies had revealed that most people who became infected developed antibodies. Investigators in China assessed 37 people who became infected with the coronavirus and showed symptoms and 37 people who became infected and showed no symptoms. Eight weeks after recovery, antibody levels declined to undetectable levels in 40% of asymptomatic people and 13% of symptomatic patients, according to the study published in *Nature Medicine*… (*Medscape*)

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Can a Registered Medical Practitioner Compel or Force his Patient to Purchase the Drug/Medicine from him Only?

KK AGGARWAL*, IRA GUPTA†

No, the registered medical practitioner cannot compel or force his patient to purchase the drug/medicine from him only. Though as per Item No. 5 of the Schedule K of the Drugs and Cosmetics Rules, 1945 and Clause 6.3 of the Code of Medical Ethics, the registered medical practitioner is entitled to supply the drugs to his patients which have been prescribed by him.

However, the registered medical practitioner cannot compel or force the patients or his relatives/friends to purchase or take the medicine from the said registered medical practitioner as held by the **Hon'ble National Consumer Disputes Redressal Commission in its landmark judgment dated 22.07.2014 titled as Fortis Health Management (North) Ltd. vs Meenu Jain & Anr.**

In the case titled as **Fortis Health Management (North) Ltd. vs Meenu Jain & Anr.,** on 25.05.2009, Meenu Jain was admitted to Fortis Escort Hospital, Jaipur, Rajasthan (OP) for treatment of Guillain–Barré syndrome (GBS). The Complainant signed a general consent for admission. On 25.06.2009, the patient was on ventilator and administered life-saving drug injection Iviglob Ex, five doses daily, for 5 days. The cost of each injection- MRP was Rs. 18,990/-. Those injections were provided by hospital pharmacy and the Complainant was successfully treated and discharged on 13.06.2009. The total sum of Rs. 6,82,965/- as hospitalization charges were paid by the Complainant without any protest.

The Complainant alleges that, he was told that the cost per injection was Rs. 9,000/-. The Complainant 2 requested the hospital authorities that the injection Iviglob Ex was available at 30-40% discount in the other medical shops in the market and he may be permitted to purchase the injections from outside, but his request was not considered and he was forced to purchase the injections from the hospital itself.

The Hon'ble Commission held that:

"8. We find that, the Complainant singed the consent and the counseling form, but it is also important to understand the state of mind of the Complainant 2 as his wife Meenu Jain was in a critical condition in OP Hospital. The OP was in a dominating position over the Complainants. Also, the Complainants agreed to pay the expenses of drugs and medicines and other consumables as per rates of the hospital, but it is also an admitted fact that the hospital authorities did not permit the Complainant to purchase the injection "Iviglob Ex" from outside, despite repeated verbal requests. Those injections were allegedly available in the market at lesser price and he was forced to buy the injections from the hospital itself. Thus, the hospital authorities indirectly imposed unjustified and unreasonable conditions on the Complainant to purchase the injections from the hospital, for the treatment of the patient. The counsel for OP argued that, to ensure quality and genuineness of the drugs, the OP did not permit the patients to buy the drugs from outside which is not at all convincing and reasonable. The OP sold the injections at the maximum retail price (MRP), and not charged any excess amount.

9. We have given a thoughtful consideration and feel that the patient was suffering from GBS, a serious disease, and was in a critical condition. No doubt, the OP Hospital has treated her and cured her. We know that, the corporate hospitals purchase the medicines, surgical items, consumables, in bulk. Certainly huge margin is available, while procurement. OP has not produced it's purchase bills of those injections. In the open market, certainly the distributors or Pharmacy shops offer discounts on the medicines. The injection Iviglob Ex is a very expensive drug, which will be available at discounted price in open market, hence the OP should have allowed at least marginal discount of about 10-20%. The corporate hospitals should not be a commercial/business centres for profiteering from the exploitation of such critical patients, who have to pay sky rocketing hospital bills. Regarding contention of OP about spurious drugs, the OP was at liberty to explain the pros and cons of drugs brought from outside market, and after due consent from the complainants, they could have administered the injections."

*President, HCFI
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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Pregnancy and COVID-19

- Pregnant women should follow the same recommendations as nonpregnant persons to avoid exposure to the coronavirus disease (COVID) virus.
- Pregnant health workers in the third trimester, especially those ≥36 weeks pregnant, must stop face-to-face contact with patients.
- Clinical manifestations of COVID-19 in pregnant women are similar to those in nonpregnant individuals.
- A positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generally confirms the diagnosis of COVID-19; however, false-positive and false-negative tests are possible.
- Pregnancy does not seem to make an individual more prone to infection or worsen the clinical course, and most infected mothers recover. However, severe disease can occur that may necessitate maternal intensive care unit (ICU) admission and need for extracorporeal membrane oxygenation.
- Infected women, particularly those who develop pneumonia, may have an increased frequency of preterm birth and cesarean delivery. These complications are likely associated with severe maternal illness as intrauterine infection does not appear to occur, but this is still being investigated. A few possible early newborn infections and one possible placental infection have been reported thus far.
- The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have issued guidance regarding prenatal care during the COVID-19 pandemic.
- For the general population, the Centers for Disease Control and Prevention (CDC) recommend that glucocorticoids must be avoided in COVID-19-positive persons owing to the potential for adverse effects on the course of the disease. There are clear benefits of antenatal betamethasone administration between 24+0 and 33+6 weeks of gestation in patients at risk of preterm birth within 7 days. Therefore, ACOG recommends its use for standard indications to pregnant patients with suspected or confirmed COVID-19.
- For most women with preterm COVID-19 and nonsevere illness with no medical/obstetric indications for prompt delivery, delivery is not indicated and would ideally occur sometime after a negative test result is obtained or isolation status is lifted, thus limiting the risk of postnatal transmission to the neonate. Early delivery may be helpful in severely ill patients at least 32-34 weeks of gestation with COVID-19 pneumonia.
- In areas with active infection, testing all patients upon presentation to labor and delivery (or the day before if a scheduled admission) seems reasonable, if testing is available. In a city with a high infection prevalence, a high proportion of asymptomatic patients (13.5% in one study) admitted for delivery tested positive, which has clinical implications for triage, staff and newborn care.
- Management of labor is generally not altered in women giving birth during the COVID-19 pandemic or in women with confirmed or suspected COVID-19. There has been no evidence of detection of SARS-CoV-2 in vaginal secretions or amniotic fluid, so rupture of fetal membranes and internal fetal heart rate monitoring may be performed for usual indications, though data are scarce. COVID-19 is not an indication to alter the route of delivery. The partner/support person should be screened in accordance with hospital policies and those with any symptoms consistent with COVID-19, exposure to a confirmed case within 14 days, or a positive test for COVID-19 within 14 days should not be attend the labor and birth.
- In patients with known or suspected COVID-19, neuraxial anesthetic is not contraindicated and has several advantages in laboring patients.

The Society of Obstetric Anesthesia and Perinatology suggests that the use of nitrous oxide be suspended for labor analgesia in these patients on account of insufficient data about potential aerosolization of nitrous oxide systems.

- During delivery of patients with known or suspected COVID-19, some institutions choose to prohibit delayed cord clamping in term infants, in whom the benefits are modest, in order to minimize newborn exposure to any virus in the immediate environment and to limit the chances that the newborn will require phototherapy for jaundice.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for treatment of postpartum pain; however, anecdotal reports suggest possible negative effects of NSAIDs in patients with COVID-19. Considering the uncertainty, paracetamol (acetaminophen) should be used. If NSAIDs are needed, use the lowest effective dose.
- Infants born to mothers with known COVID-19 are COVID-19 suspects and should undergo testing, be isolated from other healthy infants, and cared for according to infection control precautions for patients with confirmed or suspected COVID-19.
- Whether a mother with known or suspected COVID-19 needs to be separated from her infant is determined on a case-by-case basis. If the infant tests positive, separation is not needed. If separation is indicated (mother is on transmission-based precautions) but not implemented, other measures may be put to use to limit potential mother-to-infant transmission, including physical barriers and ≥6 feet separation, personal protective equipment (PPE) and hand hygiene, and utilization of other healthy adults for infant care (feeding, diapering, bathing).
- The virus has only been found in one sample of breast milk, but data are limited.
- Droplet transmission to the newborn could occur through close contact during feeding.
- In mothers with confirmed COVID-19 or symptomatic mothers with suspected COVID-19, direct contact can be minimized if the infant is fed expressed breast milk by another caregiver until the mother recovers or has been proven uninfected, provided that the other caregiver is healthy and follows hygiene precautions. In these cases, the mother should wear a mask and thoroughly clean her hands and breasts before pumping; the pump parts, bottles and artificial nipples should be cleaned as well. If she breastfeeds the infant directly, similar personal hygienic precautions should be followed.
- Remdesivir is the most promising drug and has been used without reported fetal toxicity in some severely ill pregnant women.

(Source: UpToDate)

Migrating Citizens of India: Let Them Go with Respect

Over 5 crore or 50 million people are in process of migration from metro cities to their own native place in villages. Around 8% of migrants are found to be positive in Bihar when checked in various shelter places. It only means that required physical distance is not being followed by them in the transit.

If this continues, we expect that the doubling time of COVID-19 will remain around 13 days and in the next 2 weeks, we will end up with 2,00,000 cases in the country.

The answers are:

- As per new guidelines, in a shelter home, the minimum space requirement has been increased to 75 square feet from existing 50 square feet. Same is the requirement for any person staying in any house.
- In shelter rooms, number of people required to live per room or a house will get reduced by 30%.
- Similarly, in any closed environment like in ill-ventilated factory, the number of people working at one given time will reduce by 30%.
- About 30% people will have no choice than to go back to their native place.
- If they have to go back, send them with dignity.
- We have done so for Kota residents and getting people from other countries to India.
- Why can't we have similar arrangements for laborers?
- What is the need of checking their physical parameters at the travel origin, the same should be done at the destination? How does it matter about their health status at the point of origin, they can hide it by taking anti-fever medicine?
- About 90% of people remove their mask while talking; it will be better if they travel using a face shield along with the mask.

What are the Common Lab Findings?

Lymphopenia is the most common laboratory finding seen in 83% of hospitalized patients. Worsening lymphopenia is a bad sign.

Procalcitonin is usually normal on admission, but the levels may increase among those admitted to the ICU.

Findings associated with more illness severity: Lymphopenia, neutrophilia, elevated levels of serum alanine aminotransferase and aspartate aminotransferase, elevated lactate dehydrogenase (LDH), high C-reactive protein (CRP) level and high ferritin levels.

Elevated D-dimer (>1 μg/mL), elevated prothrombin time (PT), elevated troponin, elevated creatine phosphokinase (CPK), acute kidney injury are linked to mortality.

Elevated D-dimer and lymphopenia have been tied to mortality.

Progressive decline in the lymphocyte count and rise in the D-dimer over time have been noted in nonsurvivors compared with more stable levels in survivors.

Markers of inflammation or coagulation (D-dimer level >1 μg/mL on admission, elevated fibrin degradation products, prolonged activated partial thromboplastin time [aPTT] and PT) are linked to death.

IL-6 and D-dimer

Cohort drawn from two New York-Presbyterian hospitals: Estimation of inflammation through interleukin (IL)-6 concentrations and thrombosis through D-dimer concentrations revealed a 10% increased risk for death with every 10% increase of IL-6 (adjusted hazard ratio [aHR], 1.11; 95% confidence interval [CI], 1.02-1.20) or D-dimer concentration (aHR, 1.10; 95% CI, 1.01-1.19).

D-dimer Cut-off

D-dimer = 2.0 μg/mL (fourfold increase) on admission might be the optimum cut-off to predict in-hospital mortality.

(*Zhenlu Zhang Laboratory Medicine, Wuhan Asia Heart Hospital. No.753 Jinghan Avenue, Wuhan, China, 430022*).

Coagulation Testing

- PT and aPTT normal or slightly prolonged.
- Platelet counts normal or increased (mean: 3,48,000/μL).
- Fibrinogen elevated (mean: 680 mg/dL; range: 234-1,344).
- D-dimer elevated (mean: 4,877 ng/mL; range: 1,197-16,954).

Other assays

- Factor VIII activity increased (mean: 297 units/dL).
- Von Willebrand factor (VWF) antigen elevated considerably (mean: 529; range 210-863), consistent with endothelial injury or perturbation.
- Minor changes in natural anticoagulants:
  - Small reduction in antithrombin and free protein S
  - Small rise in protein C.

TEG findings

- Reaction time (R) decreased, consistent with increased early thrombin burst, in 50% of patients.
- Clot formation time (K) reduced, in line with increased fibrin generation, in 83%.
- Maximum amplitude (MA) increased, consistent with greater clot strength, in 83%.
- Clot lysis at 30 minutes (LY30) reduced, in line with reduced fibrinolysis, in 100%.

Laboratory Features Linked with Severe COVID-19[1-6]

Abnormality	Probable threshold
Increase in:	
D-dimer	>1,000 ng/mL (normal range: <500 ng/mL)
CRP	>100 mg/L (normal range: <8.0 mg/L)
LDH	>245 units/L (normal range: 110-210 units/L)
Troponin	>2 × the upper limit of normal (normal range for troponin T high sensitivity: females 0-9 ng/L; males 0-14 ng/L)
Ferritin	>500 μg/L (normal range: females 10-200 μg/L; males 30-300 μg/L)
CPK	>2 × the upper limit of normal (normal range: 40-150 units/L)
Decrease in:	
Absolute lymphocyte count	<800/μL (normal range for age ≥21 years: 1,800- 7,700/μL)

These laboratory features are linked with severe disease in patients with COVID-19; however, they have not been shown to have a prognostic value. These thresholds are used to identify patients at risk for severe disease; they are deduced from published cohort data and individualized to the reference values used at particular

laboratory. The specific thresholds are not well-known and may not be applicable if laboratories use other reference values.

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(*Source: UpToDate)*

Can Oral Rinses Help Stop the Spread of COVID-19?

The SARS-CoV-2 virus is surrounded by a lipid envelope. The spike glycoproteins are inserted into this bio-membrane. The membrane can be disrupted. A known virucidal strategy against several coronaviruses is to interfere with their lipid envelope. The coronavirus can replicate in the salivary glands and throat. Additionally, a high viral load in the mouth may contribute to the spread of disease in early stages of infection.

Oral rinses target the lipid envelope around SARS-CoV-2.

A review of over 100 articles suggests that some oral rinses may help check the spread of SARS-CoV-2. Even a transient decrease in the levels of the shed virus may affect the transmission of disease to vulnerable people or to healthcare professionals who routinely work in the upper airway, such as ear, nose and throat surgeons, anesthetists and dentists. The review was published online May 14 in *Function*.

Some studies have led to a consensus view that enveloped viruses, including the SARS-CoV-2, are highly sensitive to 60-70% ethanol, which can result in almost immediate inactivation.

- In the context of ethanol, most studies have assessed the utility of higher concentrations while few have evaluated the lower concentrations commonly found in commercially available mouthwashes. The research conducted with lower ethanol concentrations has yielded promising results. Two such trials, both, *in vitro*, yielded positive outcomes in terms of virus denaturation.
- A 2007 study revealed that 20% ethanol completely inactivated three enveloped viruses – sindbis, herpes simplex-1 and vaccinia. Another study published 10 years later revealed that exposure for 30 seconds to a dilution of 34% ethanol could prevent coronavirus replication.
- In 1995, 26.9% ethanol *plus* essential oils were tested against herpes, influenza, rotavirus and adenovirus *in vitro*. Herpes and influenza, both enveloped, were shown to be significantly affected, while adenovirus and rotavirus (not enveloped) were not. Investigators thus speculated that oral rinse may have the potential to alter the viral lipid envelope.
- A 2010 follow-up study by the same investigators (unpublished) showed that a 30-second *in vitro* exposure to 21.6% ethanol with essential oils resulted in over 99.99% reduction of infectivity of H1N1 influenza.
- These studies thus provide proof-of-concept that mouthwashes containing essential oils with 21-27% ethanol have the potential to inactivate enveloped viruses, both in the lab and in humans, likely by causing damage to the lipid envelope.
- Chlorhexidine has been shown *in vitro* to decrease the viral concentration of enveloped viruses. Chlorhexidine formulations can retain their oral antimicrobial activity for up to 12 hours. The researchers note that combining them with ethanol may help in reducing viral load over longer periods.
- Povidone-iodine has also been studied in a few human studies, which revealed that repeated gargling can limit the incidence of both bacterial and viral infection.
- Rinsing with chlorinated water or hypertonic saline is also an option and has shown positive result in a pilot study from Japan.
- Hydrogen peroxide tends to disrupt the lipid membranes induced by oxygen free radical.

Previous studies revealed that coronavirus 229E and other enveloped viruses are inactivated at hydrogen peroxide concentrations of approximately 0.5%. Hydrogen peroxide concentrations >5% can damage soft and hard tissues, but little damage has been reported with the 1-3% concentration range which is commonly used in mouthwashes.

- Quaternary ammonium compounds are microbicidal agents that interfere with protein or lipid components on the cell surface. Cetylpyridinium chloride is one such compound which is active *in vitro* and *in vivo* against influenza through direct attack on the viral envelope.

Research still needs to answer several questions, including the following:

- Can viral load in the oropharynx be decreased by means of oral rinsing?
- If yes, which oral rinse might be clinically effective?
- Would a combination of agents in lower amounts be better tolerated, reduce adverse effects and remain effective?
- What combinations, contact times and frequency of use might yield antiviral activity and reduce infectivity of SARS-CoV-2?

In a review published earlier this year, Stephen J Challacombe, PhD, King's College London, United Kingdom, and colleagues assessed current evidence and noted that povidone-iodine stands the best chance of reducing cross-infection.

Healthcare workers are at a high risk and it seems justified to go ahead and use it.

Challacombe also recommends 1.5% hydrogen peroxide despite the fact that it is not known whether it is inactivated in the presence of other organic matter. Chlorhexidine has been studied less, though its virucidal properties make it an attractive possibility in this context.

(Medscape)

Myocardial Injury among Hospitalized Patients with COVID-19 Associated with Higher Risk of Death

Myocardial injury is prevalent among patients hospitalized with COVID-19 and is associated with higher risk of mortality, according to a study published in the *Journal of the American College of Cardiology*.

Anuradha Lala, MD, Icahn School of Medicine at Mount Sinai, New York, NY mentioned that they had found that 36% of patients hospitalized with COVID-19 had elevated troponin levels and were at higher risk of death. These findings are consistent with reports from China and Europe and are of significance for clinicians. "If COVID-19-positive patients arrive in the emergency room and their initial test results show troponin levels are elevated, doctors may be able to better triage these patients and watch over them more closely, but this remains a testable hypothesis," said Dr Lala.

Researchers assessed the electronic health records of around 3,000 adult patients with confirmed COVID-19 who were admitted to 5 New York City hospitals within the Mount Sinai Health System from February 27 to April 12, 2020. The median age was 66 years and about 60% were male. One-quarter of all patients self-identified as African American and 27% self-identified as Latino. About 25% of the patients had a history of heart disease and 25% had cardiovascular disease risk factors.

All patients had a blood test for troponin levels within 24 hours of admission, of which 64% had normal levels (0.00-0.03 ng/mL), 17% had mild elevation (>0.03-0.09 ng/mL) and 19% had higher elevation (>0.09 ng/mL). Higher troponin levels appeared to be more prevalent among patients aged above 70 and having known conditions such as diabetes, hypertension, atrial fibrillation, coronary artery disease and heart failure.

Patients with milder forms of myocardial injury were found to be linked with lower odds of hospital discharge and a 75% higher risk of death compared to patients with normal levels. Patients with higher troponin concentrations had a 3 times higher risk of death compared with those with normal levels. After adjusting for relevant factors, including heart disease, diabetes and hypertension, troponin was found to have an independent association with risk of death. More specifically, it appears that heart injury is a more important indicator in predicting risk of death than a history of heart disease.

(*Reference: https://www.sciencedirect.com/science/article/abs/pii/S0735109720355522***)**

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Indian Journal of Clinical Practice, Vol. 31, No. 1, June 2020

News and Views

Is It Time to Switch from TSH to T4 for Assessment of Thyroid Function?

When it comes to assessment of thyroid function, thyroid hormone levels, particularly free thyroxine (FT4) levels, consistently show more robust associations with a range of clinical conditions compared to the standard measure of thyroid-stimulating hormone (TSH), reported a systematic review and meta-analysis of over 50 studies published in *Thyroid*.

Investigators stated that there was no indication of, or reference to, any work to suggest that TSH levels consistently indicate thyroid status of any organ or tissue more strongly than thyroid hormone levels… (*Medscape*)

Steroids, But Not Anti-TNF, Linked to Severe COVID-19 in IBD Patients

Increasing age, comorbidities and corticosteroids as well as other anti-inflammatories seem to be correlated with severe coronavirus disease 2019 (COVID-19) infection in inflammatory bowel disease (IBD) patients, but tumor necrosis factor (TNF) antagonists appeared not to be linked to severe COVID-19, suggested an analysis of a large geographically diverse registry of pediatric and adult IBD patients.

Risk factors for severe COVID-19 among IBD patients included systemic corticosteroids: adjusted odds ratio (aOR) 6.9 (95% confidence interval [CI] 2.3-20.5); sulfasalazine or 5-aminosalicylate use: aOR 3.1 (95% CI 1.3-7.7); two or more comorbidities: aOR 2.9 (95% CI 1.1-7.8) and increasing age: aOR 1.04 (95% CI 1.01-1.02), reported researchers in *Gastroenterology*.

Safety and Efficacy Tretinoin 0.05% Lotion in Moderate-to-severe Acne Vulgaris in Adult Females

A tretinoin 0.05% lotion formulation has shown to be effective and well-tolerated, especially in adult female acne patients. Patients with more severe disease might show clinically significant improvement with topical monotherapy. Topical retinoids might provide realistic treatment options in these patients.

An analysis was done to evaluate the safety and effectiveness of once-daily tretinoin 0.05% lotion in adult females with moderate or severe acne. Post hoc analysis of two multicenter, randomized, double-blind, vehicle-controlled phase 3 studies were done. Adult females aged 18 years or more with moderate (n = 551) and severe (n = 55) acne were randomized to receive tretinoin 0.05% lotion. Once-daily application of the lotion was advised for 12 weeks.

Evaluation of efficacy included changes in baseline inflammatory/non-inflammatory lesions, treatment success (2-grade reduction in Evaluator's Global Severity Score [EGSS] and almost clear) and quality of life (QoL) using the validated Acne-QoL survey. Safety, adverse events (AEs) and cutaneous acceptability were also evaluated.

Efficacy in adult females with moderate acne (EGSS = 3) treated with tretinoin 0.05% lotion was significantly better than reported with vehicle at Week 12. Mean percent reduction in inflammatory and non-inflammatory lesion counts was 58.5% and 55.5%, respectively, as compared with vehicle which was 50.3% and 39.8% with vehicle ($p = 0.039$ and $p < 0.001$).

Treatment success was attained by 25.4% of participants by Week 12, compared with 15.4% with vehicle ($p = 0.006$). Tretinoin 0.05% lotion was more effective in adult females with severe acne (EGSS = 4). Mean percent reduction in inflammatory and non-inflammatory lesion counts was 59.0% and 58.8%, respectively as compared with vehicle which was 53.5% and 45.5%. Treatment success was attained by 17.9% of subjects compared with 4.5% with vehicle, with 46.6% of participants achieving at least a 2-grade improvement in EGSS by Week 12.

Improvement in QoL with tretinoin 0.05% lotion was significant as compared with vehicle in adult females with moderate acne, but not in severe acne. The AEs were mild and temporary. Local cutaneous safety and tolerability assessments were mild-to-moderate and had improved by Week 12.

The analysis concluded that tretinoin 0.05% lotion was significantly more effective than vehicle in gaining treatment success and reducing inflammatory and non-inflammatory lesions in adult females with moderate acne to severe acne. Also, it was well-tolerated with mild adverse events.

Source: Harper JC, Baldwin H, Stein Gold L, et al. J Drugs Dermatol. 2019;18(11):1147-54.

PDE5 Inhibitor Tadalafil for Chronic Prostatitis/ Pelvic Pain

Daily administration of the phosphodiesterase type 5 (PDE5) inhibitor tadalafil led to a significant reduction in symptoms caused by chronic prostatitis, also known as chronic pelvic pain syndrome (CP/CPPS), in a small group of men treated with PDE5 inhibition for a mean of 1.3 years.

The study included 25 men diagnosed with CP/CPPS. Continued use of tadalafil at 5 mg/day for at least 3 months decreased the National Institute of Health total chronic prostatitis syndrome index (CPSI) score by a mean of -12.9 compared with baseline ($p < 0.001$), suggested researchers in *Translational Andrology and Urology*.

Pruritus in Autoimmune Connective Tissue Diseases is a Characteristic Symptom

Autoimmune connective tissue diseases (ACTDs) are a wide range of diseases that are featured by immune dysregulation. They often have multisystem involvement with noticeable skin manifestations. One of the most common symptoms in these diseases is pruritus. Pruritus has a significant impact on the QoL of patients.

A review study was done to illustrate the frequency, location, severity and timing comparative to disease onset of pruritus in various ACTDs. A chart review of all patients was seen in the Rheumatology-Dermatology Clinic at Massachusetts General Hospital.

Itch was a distressing symptom in 83% of dermatomyositis (DM), 61% of systemic lupus erythematosus (SLE) complained of itching, 59% of Sjogren syndrome (SJO) reported itching, 22% of systemic sclerosis (SSc) reported itching and 60% of mixed connective tissue disease. In DM and SLE, itch corresponded the course of inflammatory skin manifestations in 83% and 45%, respectively. Itch in DM was more extreme and more treatment resistant in 12% of DM vs. 1% in SLE. In comparison, itch in SSc and SJO occur later in the disease course, 86% vs. 42%, respectively.

The review concluded that in all ACTDs, itch was common and is mostly underevaluated and undertreated. Pruritus is more common and severe in DM than in SLE. Also, pruritus treatment in ACTDs is challenging, and at times multi-modal therapy is necessary.

Source: Yahya A, Gideon PS. J Drugs Dermatol. 2019;18(10):995-8.

High-intensity Exercise Builds Bone in Older Men

A high-intensity exercise program, already known to improve bone density and performance in women, has been found to be effective in older men with low bone density, suggested the LIFTMOR-M study, and published in the journal *Bone*.

The protocol involves barbell-based weightlifting and impact training involving jumping chin-ups. Investigators noted that after 8 months, those in the high-intensity resistance and impact (HiRIT) group had improved medial femoral neck cortical thickness, compared to controls (5.6% vs. –0.1%) and isometric axial compression (IAC; 5.6% vs. 0.7%). Those in the HiRIT group maintained distal tibia trabecular area, while the control group had a loss (0.2% vs. –1.6%)… (*Medscape*)

Are ACE Inhibitors Protective Against Severe COVID-19?

A nationwide US observational study has suggested that angiotensin-converting inhibitor (ACE) inhibitors may be protective against severe illness in older people with COVID-19, propelling a randomized clinical trial to test the strategy.

Furthermore, a new meta-analysis of all the available data on the use of ACE inhibitors and angiotensin receptor blockers (ARBs) in COVID-19–infected patients has revealed that these drugs are not associated with more severe disease and do not heighten the susceptibility to infection. The observational study, published on the MedRxiv preprint server, noted that the use of ACE inhibitors was tied to an almost 40% lower risk for COVID-19 hospitalization for older people enrolled in Medicare Advantage plans… (*Medscape*)

FDA Approves Apomorphine Sublingual Film for 'Off' Episodes in PD

The US Food and Drug Administration (FDA) has granted approval to apomorphine hydrochloride sublingual film for acute, intermittent treatment of 'off' episodes in patients with Parkinson's disease (PD).

This is the first approval for a sublingual therapy for this indication, described as the reappearance or worsening of PD symptoms that have otherwise been controlled with standard care with levodopa/carbidopa… (*Medscape*)

Sleep Disturbance may Predict Rapid Cognitive Decline in AD

Excessive sleep disturbances are associated with increased cognitive decline in patients with Alzheimer's disease (AD), suggests new research presented on AAN.com

as part of the American Academy of Neurology (AAN) 2020 Science Highlights.

Records from the National AD Coordinating Center (NACC) datasets for over 400 patients with autopsy-confirmed AD, all initially cognitively intact, revealed that those who experienced nighttime behaviors (NTB) at baseline had a significantly higher rate of cognitive decline compared to those without NTB… (*Medscape*)

Does Miscarriage Predict Type 2 Diabetes?

Later life diabetes risk was associated with a history of miscarriage, with what could be considered a dose response; reported a Danish study online in *Diabetologia*.

Women had a higher likelihood of later developing type 2 diabetes if they had ever lost a pregnancy compared with women who had never experienced a pregnancy loss, reported researchers. The odds of later developing diabetes increased if the woman lost more pregnancies compared to women who had been pregnant but never miscarried: One pregnancy loss: Odds ratio (OR) 1.18 (95% CI 1.13-1.23); Two pregnancy losses: OR 1.38 (95% CI 1.27-1.49); Over three pregnancy losses: OR 1.71 (95% CI 1.53-1.92)… (*Medpage Today*)

Mother's Oral Fluconazole Use Tied to Bone and Muscle Defects in Baby

Use of oral fluconazole in pregnancy has been linked with increased risk for congenital bone and muscle abnormalities in a population-based cohort study.

Investigators noted that mothers who took low-dose fluconazole during the first trimester had 30% higher likelihood of delivering infants with musculoskeletal malformations (relative risk [RR] 1.30, 95% CI 1.09-1.56). The findings were published in *The BMJ*… (*Medpage Today*)

'Clear Signature' of ALS Found in Children's Teeth

Adults who develop amyotrophic lateral sclerosis (ALS) metabolize metals differently compared to those who do not develop the neurodegenerative disease, and the signs are seen in teeth during childhood, suggests new research.

Investigators noted increased uptake of a mix of metals, including chromium, manganese, nickel, tin and zinc, in the teeth of those who developed ALS. Senior author Manish Arora, PhD, MPH, Vice Chair, Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York City, stated that the study findings suggested that metal dysregulation during specific periods in childhood and early adolescence are tied to onset of ALS decades-later. The findings were published online May 21 in *Annals of Clinical and Translational Neurology*.

Remdesivir Data from NIAID Trial Published

Peer-reviewed findings have been published recently from one of the key trials of remdesivir, possibly the most promising antiviral agent for COVID-19, confirming topline results announced a month ago.

Hospitalized patients with COVID-19 administered remdesivir had a median recovery time of 11 days compared to 15 days with placebo (rate ratio for recovery 1.32, 95% CI 1.12-1.55, $p < 0.001$), reported John Beigel, MD, of the National Institute of Allergy and Infectious Diseases (NIAID), and colleagues. Mortality estimates by 14 days were lower for the remdesivir group compared to placebo, though nonsignificant (hazard ratio [HR] for death 0.70, 95% CI 0.47-1.04), reported researchers in the *New England Journal of Medicine*.

Social Isolation Linked with Higher Risk of Cardiovascular Events, Death

Social isolation is associated with a heightened risk of a cardiovascular event of more than 40%, and of all-cause mortality around 50%, suggests new research presented at the 6th Congress of the European Academy of Neurology (EAN) 2020 virtual/online meet.

Investigators analyzed data from 4,139 participants (age range 45-75 years [mean 59.1 years]), who were recruited into the large community-based Heinz Nixdorf Recall (HNR) study. After adjusting for age, sex and social support, social isolation was found to be significantly associated with an increased risk of cardiovascular events (HR, 1.44; 95% CI, 0.97-2.14) and all-cause mortality (HR, 1.47; 95% CI, 1.09-1.97)… (*Medscape*)

FDA Approves Solifenacin Succinate for a Form of Bladder Dysfunction in Pediatric Patients 2 Years and Above

The US FDA has approved solifenacin succinate oral suspension for the treatment of neurogenic detrusor overactivity (NDO), a form of bladder dysfunction related to neurological impairment, in children 2 years of age and older.

Solifenacin succinate tablets were approved in 2004 for the treatment of overactive bladder in adults 18 years and older. This is the first FDA-approved drug for NDO patients as young as 2 years of age… (*FDA*)

Hypertension is Closely Linked with Aldosterone Levels

A new research has revealed that people with hypertension may also have an underrecognized hormonal issue - primary aldosteronism.

A cross-sectional study of over 1,800 adults noted that urinary aldosterone levels were closely linked with hypertension. Higher stages of hypertension, including resistant hypertension, had a positive correlation across the spectrum of urinary aldosterone levels - Normotension: urinary aldosterone 6.5 μg/24 h (95% CI 5.2-7.7 μg/24 h); Stage 1 hypertension: 7.3 μg/24 h (95% CI 5.6-8.9 μg/24 h); Stage 2 hypertension: 9.5 μg/24 h (95% CI 8.2-10.8 μg/24 h); Resistant hypertension: 14.6 μg/24 h (95% CI 12.9-16.2 μg/24 h). The findings were published in *Annals of Internal Medicine*.

Single Negative Colonoscopy Predicts Low Colorectal Cancer Risk

A single negative screening colonoscopy is linked with long-lasting, significant reductions in the incidence of, and mortality from, colorectal cancer (CRC), provided the colonoscopy is of high quality, suggests a new study published online May 25 in the *Annals of Internal Medicine*.

The population-based study demonstrated a durable reduction in CRC risk over 17.4 years of follow-up. Compared with the general population, individuals with a negative colonoscopy had a 72% lower incidence of CRC and CRC mortality was 81% lower over a period of 5.1-10 years.

New Guidance to Optimize Antipsychotic Treatment

A new consensus statement recommends monitoring antipsychotic blood levels, also known as therapeutic drug monitoring (TDM), to guide treatment decisions and optimize safety and efficacy.

The joint statement by experts from the American Society of Clinical Psychopharmacology (ASCP) and the Germany-based Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie, recommends antipsychotic TDM, especially for specific patient groups and for patients with suspected nonadherence. The guidance is published online in the *Journal of Clinical Psychiatry*.

SGLT2 Inhibitors vs. GLP-1 Agonists for Diabetes in Real-World Study

Drug adherence, healthcare use, medical costs and heart failure rates were found to be better among patients with type 2 diabetes who were newly prescribed a sodium-glucose cotransporter 2 (SGLT2) inhibitor compared to a glucagon-like peptide 1 (GLP-1) receptor agonist in a real-world, observational study.

Investigators stated that the findings suggest potential benefits of SGLT2 inhibitors, especially where risk related to heart failure is an important consideration. The findings were presented at the virtual American Diabetes Association (ADA) 80th Scientific Sessions… (*Medscape*)

FDA Approves Nivolumab for Second-line Esophageal Cancer

The FDA has granted approval to single-agent nivolumab as a second-line treatment for advanced esophageal squamous cell carcinoma, irrespective of PD-L1 expression.

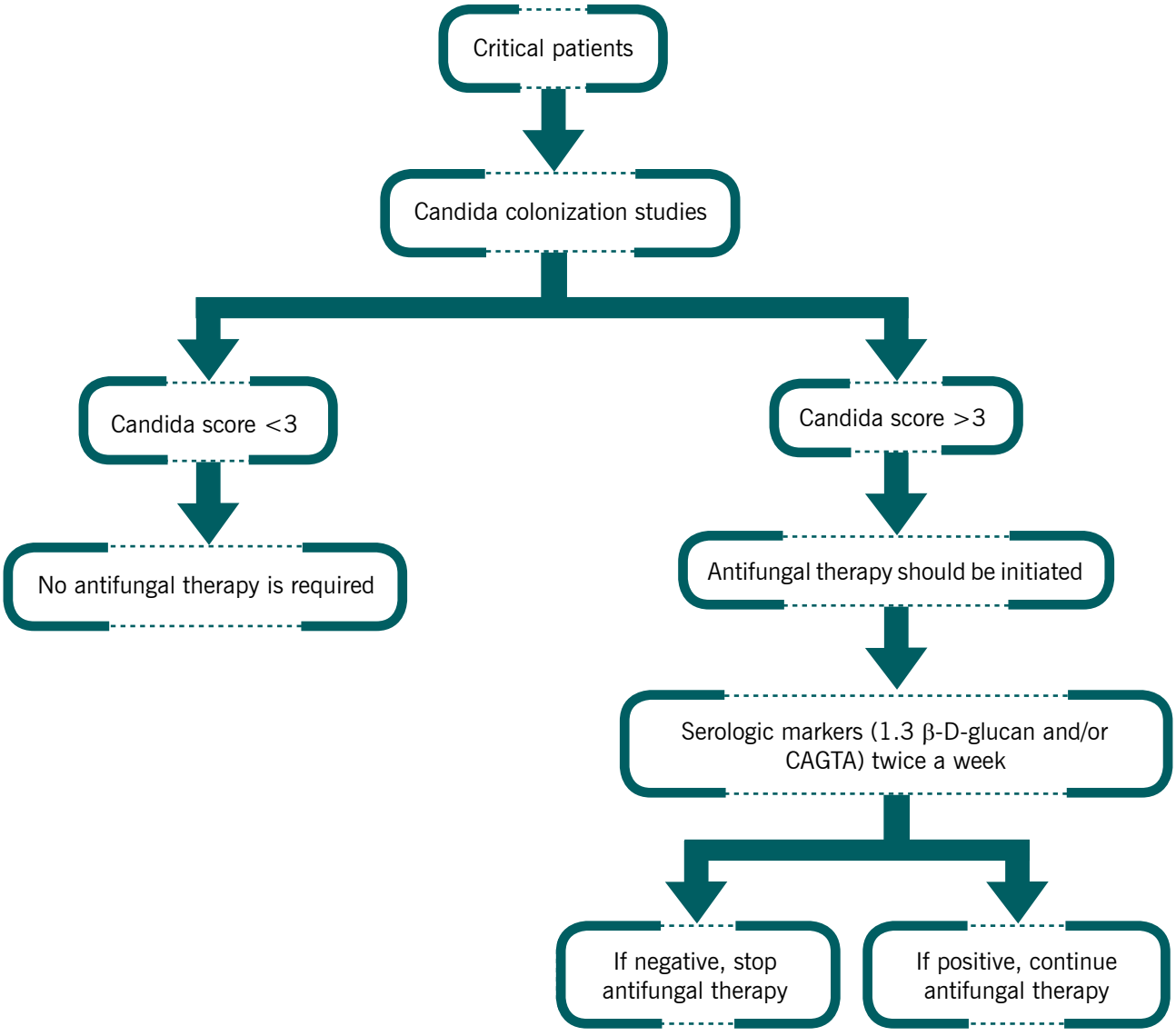
Treatment with the drug is indicated for patients with unresectable, recurrent or metastatic disease after progression on a fluoropyrimidine- and platinum-based chemotherapy. The approval came after findings from a phase III trial, ATTRACTION-3 that randomized 419 patients with advanced esophageal squamous cell carcinoma to either nivolumab (240 mg intravenously every 2 weeks) or investigator's choice of a taxane chemotherapy. There was no difference in progression-free survival between the two study arms; median overall survival improved from 8.4 months with chemotherapy to 10.9 months with nivolumab, with the benefit seen across all subgroups and regardless of tumor PD-L1 expression (HR 0.77, 95% CI 0.62-0.96, p = 0.0189)… (*Medpage Today*)

Mortality Differs by LVEF Between Women and Men

A real-world, observational study has found clinically significant sex-based differences in left ventricular ejection fraction (LVEF) related to mortality.

The analysis from the ongoing National Echo-cardiography Database of Australia (NEDA) involved 4,99,153 participants who underwent echocardiography in routine clinical practice. An LVEF <50% was more than twice as common in men compared to women, seen in 17.6% and 8.3%, respectively. Women had a higher average LVEF - 64.2%, compared to 59.5% in men. The overall 1- and 5-year all-cause mortality rates were 5.8% and 18.4%. Cardiovascular-related mortality was noted in 7.1% of women with median 5.6 years of follow-up and in 8.1% of men with 5.5 years of follow-up. The findings were presented at the European Society of Cardiology Heart Failure Discoveries virtual meeting… (*Medscape*)

Invasive Candidiasis



CAGTA: *Candida albicans* germ tube antibody.

Adapted from Candel FJ, Pazos Pacheco C, Ruiz-Camps I, et al. Update on management of invasive candidiasis. Rev Esp Quimioter. 2017;30(6):397-406.

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Why Do We Offer Food to God in Every Pooja?

KK AGGARWAL

We follow a ritual of offering 'bhog' to the deity we worship. The ritual also involves sprinkling water all around the place where we sit down to eat food. Many people have advocated that the sprinkling of water is related to preventing ants and insects from approaching the food. But in spiritual language there is a deeper meaning to these rituals.

Bhagwad Gita and Yoga Shastras categorize food into three types corresponding to their properties termed as gunas. Depending upon satoguna, rajoguna and tamoguna, the food items are categorized as satwik, rajsik or tamsik. Satwik foods provide calmness, purity and promote longevity, intelligence, strength, health, happiness and delight. Fruits, vegetables, leaves, grains, cereals, milk, honey, etc., are examples of satwik food. These items can be consumed as they are. One can also live on satwik food for life. Rajsik food items possess attributes of negativity, passion and restlessness. Hot, spicy and salty food items with pungent, sour and salty taste promote rajas qualities. Tamsik foods have attributes of inducing sleep, ignorance, dullness and inertia. The examples of tamsik food are meat, onions, garlic, left-over food, etc.

Only satwik food is offered to God. Rajsik and tamsik food is never offered as bhog. The only persons who were offered tamsik and rajsik food in Ramayana were Ahi Ravana and Kumbhkaran. Both of them were of an evil nature. Kumbhkaran signified tamas and Ahi Ravana, rajas or aggression. Tamsik and rajsik food can be converted into satwik by slow heating, sprouting or keeping them in water overnight. The examples are sprouted wheat, chana (chickpeas), etc.

A mixture of honey, milk, ghee, curd and sugar is called panchamrut and is a routine offering to the God. All the five components have satwik properties and their consumption promotes health. In Ayurveda, there is a saying that any food item, which grows under the ground, is tamsik in nature and one, which comes from the top of the tree or plant like leaves, flower and fruits are satwik in nature. Satwik food is usually fresh, seasonal and locally grown.

Human beings are made up of body, mind and soul and soul is equated to consciousness or God. Whatever offered to external God, if, is offered to the internal God or consciousness, leads to inner happiness. The ritual, therefore, of offering food to God before eating forces us to either eat only satwik food or to include a substantial portion of satwik food in our meals. It helps a person convert his meal into a pure satwik one or at least adding satwik items.

Sprinkling water around the plate is considered an act of purification.

Many people confuse bhog with chadhava or offerings to the deity. While bhog is shared with God, chadhava is the offering of your illness or negative thoughts to the God and you go back with prasada of inner happiness. Many people counter the above argument by saying that alcohol is offered to Bhairon, viewed as a demon God, which means alcohol, is good for health. I personally feel that alcohol is offered to Bhairon not as a bhog but as an offering which means that people who are addicted to alcohol go to Bhairon and give their share of alcohol to him, so they can de-addict themselves.

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Group Editor-in-Chief, IJCP Group

Indian Journal of Clinical Practice, Vol. 31, No. 1, June 2020

Addiction to Worry

Carole started counseling with me because she was depressed. She had been ill with chronic fatigue syndrome for a long time and believed her depression was due to this. In the course of our work together, she became aware that her depression was actually coming from her negative thinking – Carole was a constant worrier. Many words out of her mouth centered on her concerns that something bad might happen. "What if I never get well?" "What if my husband gets sick?" "What if I run out of money?" (Carole and her husband ran a very successful business and there was no indication that it would not go on being successful). "What if my son gets into drugs?" "What if my kids don't get into good colleges?" "What if someone breaks into the house?"

Her worry was not only causing her depression, but was also contributing to her illness, if not actually causing it. Her worry caused so much stress in her body that her immune system could not do its job of keeping her well. Yet even the awareness that her worry was causing her depression and possibly even her illness did not stop Carole from worrying. She was addicted to it. She was unconsciously addicted to the sense of control that worry gave her.

I understood this well because I come from a long line of worriers. My grandmother's whole life was about worrying. She lived with us as I was growing up and I don't remember ever seeing her without a look of worry on her face. Same is with my mother – constant worry. Of course, I picked up on it and also became a worrier. However, unlike my mother and grandmother, who worried daily until the day they died, I decided I didn't want to live that way. The turning point came for me the day my husband and I were going to the beach and I started to worry that the house would burn down and my children would die. I became so upset from the worry that we had to turn around and come home. I knew then that I had to do something about it.

As I started to examine the cause of worry, I realized that worriers believe that worry will stop bad things from happening. My mother worried her whole life and none of the bad things she worried about ever happened. She concluded that nothing bad happened because she worried! She really believed that she could control things with her worry. My father, however, never worried about anything, and nothing bad ever happened to him either. My mother believed that nothing bad happened to my father because of her worry! She really believed until the day she died (from heart problems that may have been due to her constant worry) that if she stopped worrying, everything would fall apart. My father is still alive at 92, even without her worrying about him!

It is not easy to stop worrying when you have been practicing worrying for most of your life. In order for me to stop worrying, I needed to recognize that the belief that worry has control over outcomes is a complete illusion. I needed to see that not only is worry a waste of time, but that it can have grave negative consequences on health and well-being. Once I understood this, I was able to notice the stomach clenching that occurred whenever I worried and stop the thought that was causing the stress.

Carole is in the process of learning this. She sees that her worry makes her feel very anxious and depressed. She sees that when she doesn't worry, she is not nearly as fatigued as when she allows her addiction to worry to take over. She sees that when she stays in the moment rather than projecting into the future, she feels much better. The key for Carole to stop worrying is in accepting that worry does not give her control.

Giving up the illusion of control that worry gives us is not easy for anyone who worries. Yet there is an interesting paradox regarding worry. I have found that when I am in the present moment, I have a much better chance of making choices that support my highest good than when I'm stuck thinking about the future. Rather than giving us control, worry prevents us from being present enough to make loving choices for ourselves and others. Worrying actually ends up giving us less control rather than more!

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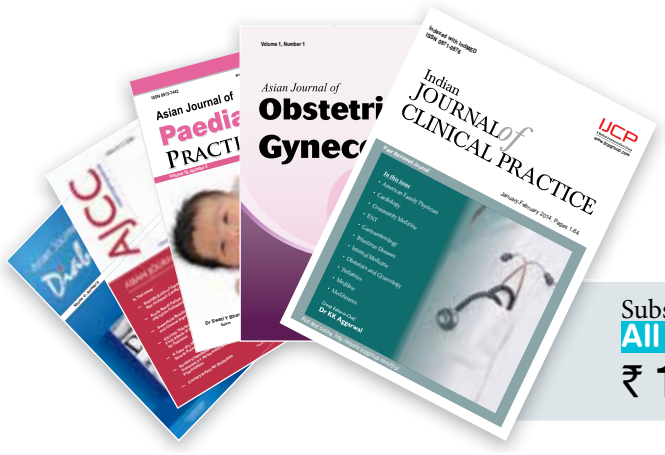

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Lighter Side of Medicine

HUMOR

HOTEL SECURITY

A friend and I stayed at a Chicago hotel while attending a convention. Since we weren't used to the big city, we were overly concerned about security.

The first night we placed a chair against the door and stacked our luggage on it. To complete the barricade, we put the trash can on top. If an intruder tried to break in, we'd be sure to hear him.

Around 1 am there was a knock on the door. "Who is it?" my friend asked nervously.

"Honey," a woman on the other side yelled, "you left your key in the door."

ACTIVATE YOUR PHONE LINES

A young businessman had just started his own firm. He had just rented a beautiful office and had it furnished with antiques. He saw a man come into the outer office. Wishing to appear the hot shot, the businessman picked up the phone and started to pretend he had a big deal working.

He threw huge figures around and made giant commitments. Finally, he hung up and asked the visitor, "Can I help you?"

"Yeah, I've come to activate your phone lines."

OUTSTANDING

A man is driving down a country road, when he spots Santu standing in the middle of a huge field of grass. He pulls the car over to the side of the road and notices that Santu is just standing there, doing nothing, looking at nothing.

The man gets out of the car, walks all the way out to our Santu and asks him, "Ah excuse me Sir, but what are you doing?"

Santu replies, "I'm trying to win a Nobel Prize." "How?" asks the man, puzzled.

"Well I heard they give the Nobel Prize to people who are outstanding in their field."

GET ME A BATTLESHIP

After lunching at the Algonquin Hotel, Robert walked through the lobby, out the front door, and said to the uniformed man on the sidewalk, "My good man, would you please get me a taxi?"

The man immediately took offense and replied indignantly, "I'm not a doorman! I happen to be a rear admiral in the United States Navy."

Robert instantly quipped: "All right then, get me a battleship."

HOW WOULD WE KNOW?

A man was complaining to a railroad engineer. What's the use of having a train schedule if the trains are always late?

The railroad engineer replied, "How would we know they were late, if we didn't have a schedule?"

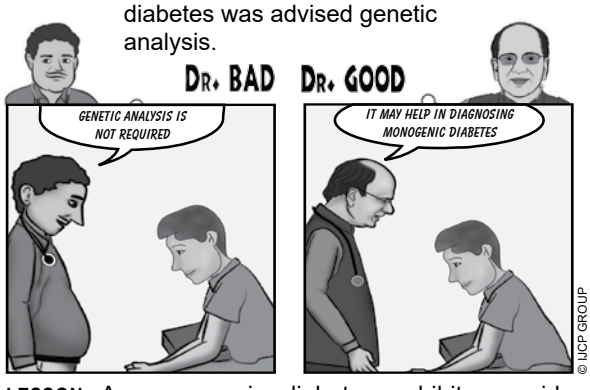
SPOON OUT FIRST?

Doctor, Doctor! I keep getting pain in the eye when I drink coffee!

Doc: Have you ever tried taking the spoon out FIRST?

Dr. Good and Dr. Bad

SITUATION: An individual initially diagnosed with type 1 diabetes was advised genetic analysis.



LESSON: As monogenic diabetes exhibits a wide phenotypic spectrum, it is usually misdiagnosed as type 1 or type 2 diabetes. Although clinical and biochemical parameters can indicate monogenic diabetes, genetic analysis is required for establishing a definitive diagnosis.

Swiss Med Wkly. 2017;147:w14535.

IJCP SUTRA: *"If you are anemic and you ordinarily eat meat, increasing the amount of meat you consume is the easiest way to increase the iron your body receives."*

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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.

Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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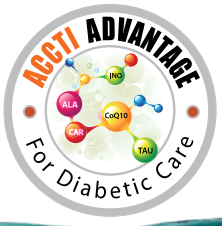

Indications

Prediabetes and diabetes.

Directions for use:
2 scoops (approx. 25 g) of Quista DN powder to be added into 200 mL of lukewarm/chilled toned milk or water and stirred briskly until well mixed.

Recommended servings:
Twice daily in between meals or at bedtime, or as directed by your healthcare professional. One serving of Quista DN in 200 mL of toned milk provides 212 kcal.

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