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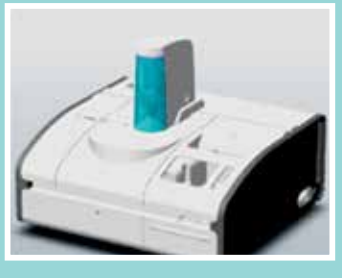

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CMAAO Coronavirus Facts and Myth Buster: Long COVID – NICE Guideline

NICE ISSUES RAPID GUIDELINE ON LONG COVID

- People may have ongoing symptomatic coronavirus disease 2019 (COVID-19) if they have symptoms 4-12 weeks after the onset of acute symptoms.
- People may have post-COVID syndrome if their symptoms do not resolve after 12 weeks.
- The rapid guideline on managing the long-term effects of COVID-19, or 'long COVID', has been issued by NICE in collaboration with the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP).
- The guideline was published as the NHS announced that patients with long-term symptoms of COVID-19 could access specialist help at an increasing number of clinics across England.
- One in 5 individuals with COVID-19 develop longer term symptoms. Nearly 1,86,000 individuals experience health problems for up to 12 weeks, suggests the Office for National Statistics (ONS).
- The ONS estimates that around 9.9% of people who had COVID-19 continued to be symptomatic after 12 weeks.
- The most common symptoms included fatigue, cough and headache.
- The NICE guidance covers the care of people having signs and symptoms that develop during or after an infection consistent with COVID-19, continuing for over 4 weeks, and that cannot be explained by an alternative diagnosis. The recommendations are based on current evidence and expert consensus.
- The guideline makes recommendations in several other important areas, such as assessing people with new or ongoing symptoms after acute COVID-19; investigations and referral; planning care; management, including self-management, supported self-management and rehabilitation; follow-up and monitoring; service organization.

The following clinical definitions were used for the initial illness and long COVID at different times:

- **Acute COVID-19:** Signs and symptoms of COVID-19 for up to 4 weeks.
- **Ongoing symptomatic COVID-19:** Signs and symptoms of COVID-19 from 4 to 12 weeks.
- **Post-COVID-19 syndrome:** Signs and symptoms developing during or after an infection consistent with COVID-19, continuing for over 12 weeks that cannot be explained by an alternative diagnosis.

COMMON SYMPTOMS OF ONGOING SYMPTOMATIC COVID-19 AND POST-COVID-19 SYNDROME

Symptoms after acute COVID-19 are variable. The most commonly reported symptoms include (but are not limited to) the following:

Respiratory symptoms

- Breathlessness
- Cough

Cardiovascular symptoms

- Chest tightness
- Chest pain
- Palpitations

Generalized symptoms

- Fatigue
- Fever
- Pain

Neurological symptoms

- Cognitive impairment ('brain fog', loss of concentration or memory issues)
- Headache
- Sleep disturbance
- Peripheral neuropathy symptoms (pins and needles, numbness)
- Dizziness
- Delirium (in older populations)

Gastrointestinal symptoms

- Abdominal pain
- Nausea
- Diarrhea
- Anorexia and reduced appetite (in older populations)

Musculoskeletal symptoms

- Joint pain
- Muscle pain

Psychological/Psychiatric symptoms

- Symptoms of depression
- Symptoms of anxiety

Ear, nose and throat symptoms

- Tinnitus
- Earache
- Sore throat
- Dizziness
- Loss of taste and/or smell

Dermatological

- Skin rashes

Investigations and Referral

These recommendations are aimed at healthcare professionals carrying out initial investigations in primary care or community services for people with new or ongoing symptoms 4 weeks or more after the onset of suspected or confirmed *acute COVID-19*.

3.1 People with *ongoing symptomatic COVID-19* or suspected *post-COVID-19 syndrome* to be urgently referred to the relevant acute services if there are signs or symptoms that could be caused by an acute or life-threatening complication, including (but not limited to):

- Severe hypoxemia or oxygen desaturation on exercise
- Signs of severe lung disease
- Cardiac chest pain
- Multisystem inflammatory syndrome (in children).

3.2 Tests and investigations tailored to people's signs and symptoms to be offered to exclude acute or life-threatening complications and find out if symptoms are likely caused by ongoing symptomatic COVID-19, post-COVID-19 syndrome or a new, unrelated diagnosis.

3.3 If there is suspicion of another diagnosis not related to COVID-19, investigations and referral to be offered in accordance with relevant national or local guidance.

3.4 Blood tests to be offered that may include a full blood count, kidney and liver function tests, C-reactive protein (CRP) test, ferritin, B type natriuretic peptide (BNP) and thyroid function tests.

3.5 If appropriate, an exercise tolerance test may be offered that suits the person's ability (for example the 1-minute sit-to-stand test). During the exercise test, level of breathlessness, heart rate and oxygen saturation must be recorded. An appropriate protocol must be followed to conduct the test safely.

3.6 For individuals with postural symptoms, such palpitations or dizziness on standing, lying and standing blood pressure and heart rate recordings (3-minute active stand test, or 10 minutes if postural tachycardia syndrome, or other forms of autonomic dysfunction are suspected) to be done.

3.7 A chest X-ray to be done by 12 weeks after acute COVID-19 if the individual has not had one and has continuing respiratory symptoms. Chest X-ray

appearances alone should not guide the need for referral for further care. A plain chest X-ray may not be sufficient to rule out lung disease.

3.8 People with ongoing symptomatic COVID-19 or suspected post-COVID-19 syndrome to be referred urgently for psychiatric assessment if they have severe psychiatric symptoms or have a risk of self-harm or suicide.

3.9 National or local guidelines on referral to be followed for individuals with anxiety and mood disorders or other psychiatric symptoms. Referral to be considered for the following:

- Psychological therapies if the person has common mental health symptoms, such as symptoms of mild anxiety and mild depression *or*
- To a liaison psychiatry service if the person has more complex needs (particularly if there is a complex physical and mental health presentation).

3.10 After acute or life-threatening complications and alternative diagnoses are excluded, referral to an integrated multidisciplinary assessment service (if available) to be considered any time from 4 weeks after the onset of acute COVID-19.

3.11 Do not exclude people from referral to a multidisciplinary assessment service or for further investigations or specialist input on the basis of absence of a positive SARS-CoV-2 test.

(*Excerpts from Medscape; https://www.nice.org.uk/guidance/NG188*)

■■■■

Second Dose of Covishield to be Administered Between 4 and 6 Weeks: DCGI

In its permission to the Serum Institute of India for manufacture for sale or distribution of Covishield, the DGCI stated that the second dose has to be administered between 4 and 6 weeks of the first dose. The regulator further stated that data is available for administration of the second dose up to 12 weeks following the first dose from the overseas studies.

According to the permission document, the firm must ensure that the factsheet for the vaccine recipient or attendant is provided before vaccine administration. It further stated that the vaccine is meant for the active immunization of the individuals above 18 years of age for the prevention of COVID-19 when administered in two doses. The order specified that the shelf-life is 6 months when stored at 2-8°C… (*HT – ANI*)

Diet Restricts GERD Beyond Acid Suppressants

Adhering to an anti-reflux lifestyle may prevent many symptoms of gastrointestinal reflux disorder (GERD) in women, suggest data from Nurses' Health Study II. The decreased risk was observed even in regular users of acid suppressants, including proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs).

Andrew T Chan, MD, MPH, of Massachusetts General Hospital in Boston, and colleagues noted that the possible explanations for this could be reduction in lower esophageal sphincter tone, increases in gastroesophageal pressure gradients and mechanical factors, such as hiatal hernia. The results support the significance of lifestyle modification in managing GERD, reported researchers in *JAMA Internal Medicine*. Researchers used an anti-reflux lifestyle score (range 0-5) consisting of five variables including normal weight, defined as BMI of 18.5 to <25.0; never smoking; moderate-to-vigorous physical activity for at least 30 minutes in a day; not more than two cups of coffee, tea or soda per day; eating a prudent diet. In comparison with women who did not adhere to anti-reflux lifestyle factors, the multivariable HR for GERD symptoms was 0.50 (95% CI 0.42-0.59) among those with five anti-reflux lifestyle factors… (*Medpage Today*)

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

PARWINDER KAUR*, SILKY MAHAJAN†, KANWAL MASIH‡

ABSTRACT

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

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

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

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

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

MATERIAL AND METHODS

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

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

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

RESULTS

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

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

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

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

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

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

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

Table 1. Cytomorphological Pattern Observed on Lymph Node Aspirates

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

Table 2. Pattern of Cases in Various Cytomorphological Tubercular Lymphadenopathy

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

CONCLUSION

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

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

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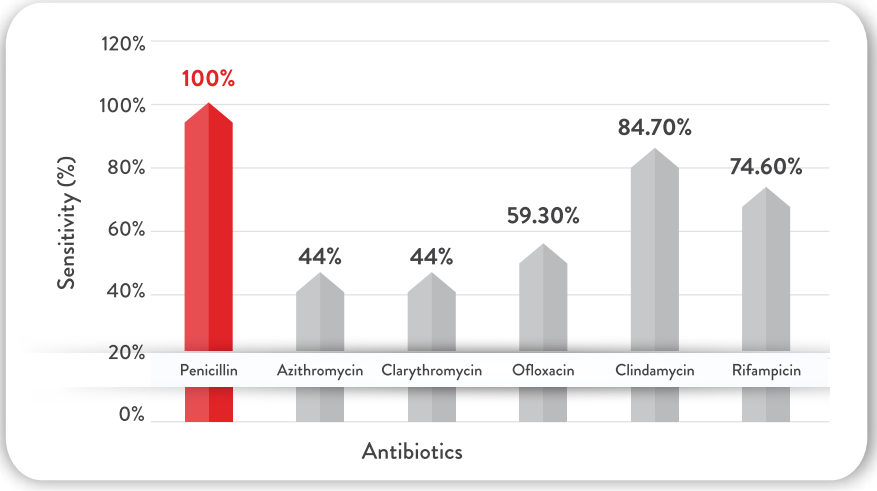
Group A streptococcus is **100% sensitive to penicillin G** making it a treatment of choice in GABHS* pharyngitis[2]



Penicillin is recommended by various National and Global bodies in the management of GABHS* pharyngitis[3]

Dosage^: Pentids™ 200/400: 1 Tablet TID
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IND2172909 23 Dec 2020

TM: Trademark, TID: Three times a day, BID: Twice a day.
*GABHS: Group A -haemolytic streptococcus, ^As per Pentids PI

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Abridged Prescribing Information: COMPOSITION: Pentid 200: Each uncoated tablet contains Penicillin G Potassium I.P. 200,000 units (2Lac (2 L) units = 125 mg). Pentids 400: Each uncoated tablet contains Penicillin G Potassium I.P. 400,000 units (4 Lac (4 L) units = 250 mg). Pentid 800: Each uncoated tablet contains Penicillin G Potassium I.P. 800,000 units (8Lac (8 L) units = 500 mg) **INDICATIONS:** Treatment of infections caused by susceptible strains of the designated microorganisms, such as Streptococcal infections (mild to moderate upper respiratory tract infections including scarlet fever and mild erysipelas), Pneumococcal infections (mild to moderate respiratory tract infections, including otitis media), Staphylococcal infections (mild infections of skin and soft tissue), N.gonorrhoeae (disseminated gonococcal infections), Corynebacterium diphtheriae (diphtheria), Fusospirochetosis (Vincent's infection) of the oropharynx, Prevention of recurrence of rheumatic fever or cholera, athrax, botulism, gas gangrene, tetanus. **DOSAGE:** As directed by the Physician. General recommended dosages are: Streptococcal infections: 2 L – 4 L units , every 6-8 hrs for 10 days. Pharyngitis in children: 0.4 L to 0.8 L units /kg/day, divided every 6 hrs, for 10 days. Pneumococcal infections: 4 L to 8 L units, every 6 hrs, until afebrile at least 2 days. Staphylococcal infections : 4 L to 8 L units, every 6-8 hrs. Fusospirochetosis (Vincent's infection of the oropharynx, mild to moderate): 4 L to 8 L units, every 6-8 hrs. Prevention of recurrence of rheumatic fever or cholera: 2 L – 4 L units, orally 2 times /day on a continuing basis. **CONTRAINDICATIONS:** A history of a hypersensitivity reaction to any penicillin or any component of the formulation. **WARNINGS AND PRECAUTIONS:** Keep out of reach of children. Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Serious and occasionally fatal hypersensitivity reactions and Pseudomembranous colitis have been reported in patients on penicillin therapy. Periodic assessment/monitoring of patients advised. **PREGNANCY/LACTATION:** To be used only if clearly needed. **DRUG INTERACTIONS:** Concurrent use of bacteriostatic antibacterials (i.e., chloramphenicol, erythromycin, sulfonamides or tetracyclines) may antagonize the bactericidal effect of penicillin. Penicillin blood levels may be prolonged by concurrent administration of probenecid. Aspirin, phenylbutazone, sulfonamides, indomethacin, thiazide diuretics, furosemide and ethacrynic acid may prolong the serum half-life of penicillin. A few Drug/Laboratory Test Interactions have also been reported. **ADVERSE EFFECTS:** Generally well tolerated. Adverse effects reported include fever, malaise, myalgia, arthralgia, abdominal pain, hypersensitivity reactions, urticaria, pruritus, skin rashes, fever, laryngeal edema, bronchospasm, hypotension, vascular collapse and Jarisch-Herxheimer reaction. **How supplied:** Strip of 10 tablets **STORAGE:** Store in a cool, dry place, protected from light. For full prescribing information, please contact: Medical Sciences Division, Abbott Healthcare Pvt. Limited, Floor 17, Godrej BKC, Plot No. C – 68, BKC, Near MCA Club, Bandra (E), Mumbai – 400 051.
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Patient-Ventilator Asynchrony: Etiology and Solutions

VITRAG H SHAH*, ARIJIT SAMANTA†, SUMIT RAY‡

ABSTRACT

Patient-ventilator asynchrony is one of the most cited reasons for giving sedation during mechanical ventilation. Various studies show that 40-50% of increase in sedative dosing is done to curb asynchrony. The acute respiratory distress syndrome (ARDS) network protocol for lung protective ventilation directs the clinician to adjust the ventilator settings or give sedation when there are more than three breaths stacking (double triggers) per minute. This review article discusses the etiology behind patient-ventilator asynchrony and the proposed solutions.

Keywords: Patient-ventilator asynchrony, breath initiation, endexpiratory pressure, neuromuscular blockers

Patient-ventilator asynchrony is one of the most important reasons for patient discomfort. It leads to increased morbidity as well as mortality. It thus becomes essential to understand patient-ventilator interaction and asynchrony for better patient management and outcome.

There are two pumps working during mechanical ventilation. One is mechanical ventilator which is controlled by the physician and another is patient's own respiratory muscle pump which is controlled by the patient. Any mismatch between these two pump leads to patient-ventilator asynchrony. Commonly, the terms used to describe this asynchrony on the ventilator are: "Patient is agitated/restless/fighting the ventilator".

Managing asynchrony is a challenge for the intensivist as it has several significant consequences, which are as follows:

- Increased anxiety and discomfort to the patient
- Increased work of breathing
- Increased requirement for sedation
- Difficult and prolonged weaning
- Prolongation of ventilator days
- Prolonged intensive care unit (ICU) and hospital stay
- Higher incidence of ventilator-associated pneumonia
- Increased need for tracheostomy.

Figure 1 illustrates the vicious cycle post initiation of mechanical ventilation in a patient due to asynchrony that may lead to increased morbidity and mortality.

Figure 2 illustrates that decreasing asynchrony helps in many ways to improve outcome and decrease morbidity.

DEFINITION

When timing of ventilator cycle is not simultaneous with the timing of patient's respiratory cycle, patient-ventilator asynchrony occurs. Any mismatch between neural Ti/Te (Ti - Inspiratory time, Te - Expiratory time) and ventilator Ti/Te or any mismatch between patient's demand and ventilator supply leads to patient-ventilator asynchrony.

When patient's inspiratory effort is not followed by a ventilator breath, it is considered as **ineffective triggering**, this is detected by "a decrease in a pressure of ≥0.5 cm along with increase in air flow without triggering an inspiration."

When a single inspiratory effort by the patient is followed by two ventilator breaths, it is called **double triggering**. This is detected by two delivered breaths separated by an expiratory time less than 50% of mean inspiratory time.

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When there is ventilator breath without any inspiratory effort by patient, it is **auto triggering**.

When inspiratory time is less than 50% of mean inspiratory time, it is called **premature cycling.**

When inspiratory time is more than double of mean inspiratory time, it is called **delayed cycling.**

Asynchrony Index

The asynchrony index is the total number of asynchronies (including all types of asynchronies) divided by the total triggered as well as ineffectively triggered breaths.

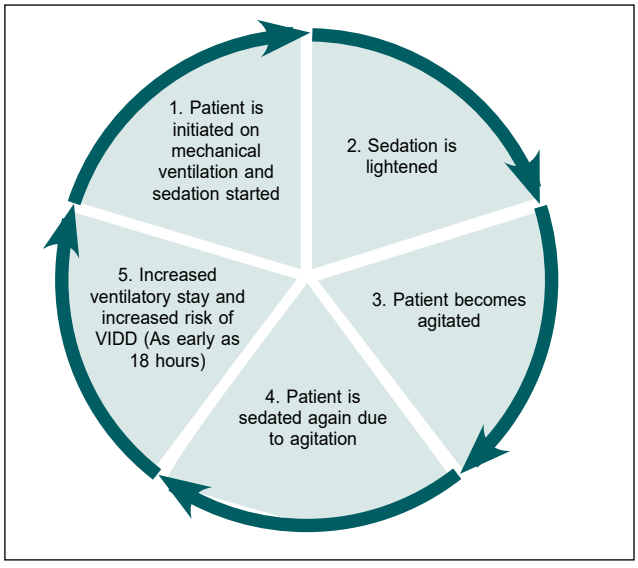

Figure 1. The vicious cycle post initiation of mechanical ventilation in a patient due to asynchrony that leads to increased morbidity and mortality.

VIDD = Ventilator-induced diaphragmatic dysfunction.

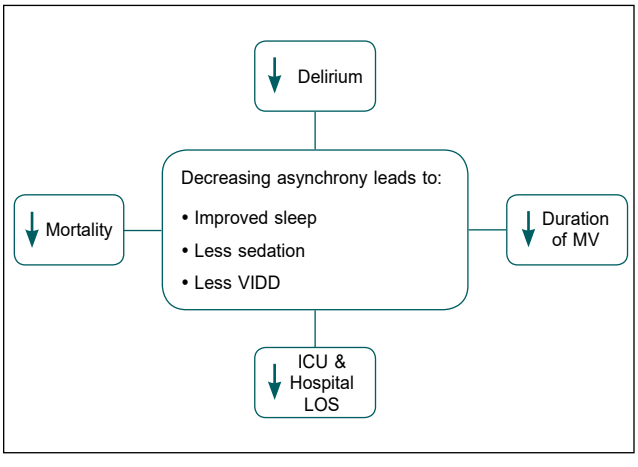

Figure 2. Decreasing asynchrony helps improve outcome and decrease morbidity.

MV = Mechanical ventilation; ICU = Intensive care unit; LOS = Length of stay.

The ineffective triggering index is the total number of ineffectively triggered breaths divided by the total triggered and ineffectively triggered breaths.

EPIDEMIOLOGY

Ventilator asynchrony is a common but an under-recognized as well as an undertreated entity. Multiple studies have suggested that 20-30% of patients experience asynchrony in more than 10% of their breaths, among which, ineffective triggering (70-80%) and double triggering are the most common asynchronies. Ineffective triggering is especially more common in patients of chronic obstructive pulmonary disease (COPD), occurring in nearly 80% of them.

Multiple types of asynchrony may be present simultaneously. Studies show that asynchrony index >10% is associated with prolonged ventilator days and prolonged ICU as well as hospital stay (Fig. 3). It also significantly increases weaning time and leads to weaning failure.

Patient-ventilator asynchrony is one of the most cited reasons for giving sedation during mechanical ventilation. Various studies show that 40-50% of increase in sedative dosing is done to curb asynchrony. The acute respiratory distress syndrome (ARDS) network protocol for lung protective ventilation directs the clinician to adjust the ventilator settings or give sedation when there are more than three breaths stacking (double triggers) per minute. While patient agitation and anxiety lead to asynchrony, the reverse is also true. That asynchrony leads to agitation and anxiety which most of the times is inappropriately managed with sedation and neuromuscular blockers. Studies

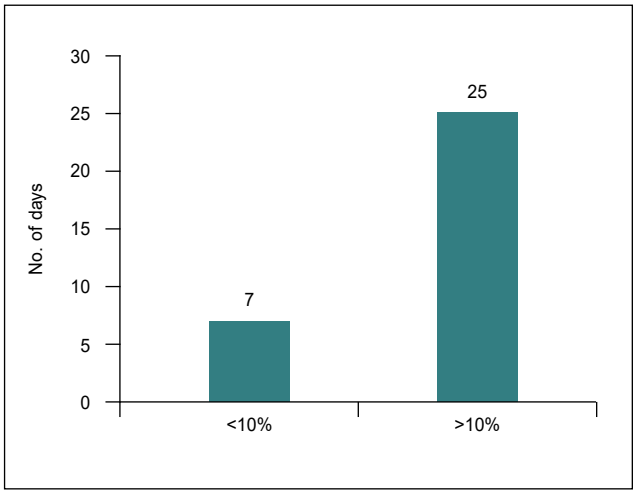

Figure 3. Prolonged ventilator days with asynchrony index >10%.

show that changing ventilator settings in response to patient's breathing pattern is more effective, as well as more rational, than, increasing sedation. Routine use of sedation and neuromuscular blockers should be discouraged for managing asynchrony. They should be used only if asynchrony index >10% after optimizing ventilator settings.

CONTRIBUTING FACTORS

There are various patient-related, disease-related as well as ventilator-related factors which contribute to asynchrony (Table 1).

TYPES AND CLASSIFICATION OF VENTILATOR ASYNCHRONY

Asynchrony can be classified based on trigger, flow and cycling. Trigger asynchrony occurs in trigger phase while flow and cycling asynchrony occur in post trigger phase (Table 2).

GRAPHICAL REPRESENTATION OF COMMONLY OCCURRING ASYNCHRONY

Asynchrony is usually identified clinically (facial expressions, signs of respiratory distress, palpation of chest and abdomen to look for efforts by patients, etc.) and by the simultaneous examination of ventilator waveforms. Esophageal pressure monitoring is used infrequently to identify asynchrony, mainly, being restricted to research settings to estimate pleural pressure.

Commonly occurring asynchrony have been illustrated with graphical examples here (Figs. 4-7).

Table 1. Factors Contributing to Asynchrony

Patient-related/ physiological	Disease-related	Ventilator-related
• Anxiety	• High resistance (e.g., COPD)	Inappropriate ventilator settings of trigger, rise time, level of pressure support, cycling, inspiratory flow, respiratory rate, tidal volume, inspiratory time, etc.
• Pain	• Low compliance (e.g., ARDS)	
• Fever	• Auto-PEEP (e.g., COPD)	
• Delirium	• Decreased/ Increased respiratory drive due to central and neuromuscular problems	

COPD = Chronic obstructive pulmonary disease; ARDS = Acute respiratory distress syndrome; PEEP = Positive end-expiratory pressure.

FOUR PHASES OF THE VENTILATORY CYCLE

As shown in Figure 8, breath cycle can be divided into four phases: Breath initiation (Trigger), breath delivery

Table 2. Types of Ventilator Asynchrony

Trigger asynchrony	Flow asynchrony (breath delivery asynchrony)	Cycling/ Termination asynchrony
Ineffective trigger/ Delayed trigger	Related to fixed flow	Premature cycling
Double trigger	Related to high flow	Delayed cycling
Auto trigger (<2%)	Related to inadequate flow	
Common asynchrony	**Patient breath**	**Ventilator breath**
Ineffective trigger	1	0
Double trigger	1	2
Auto trigger	0	1
Delayed cycling	2	1

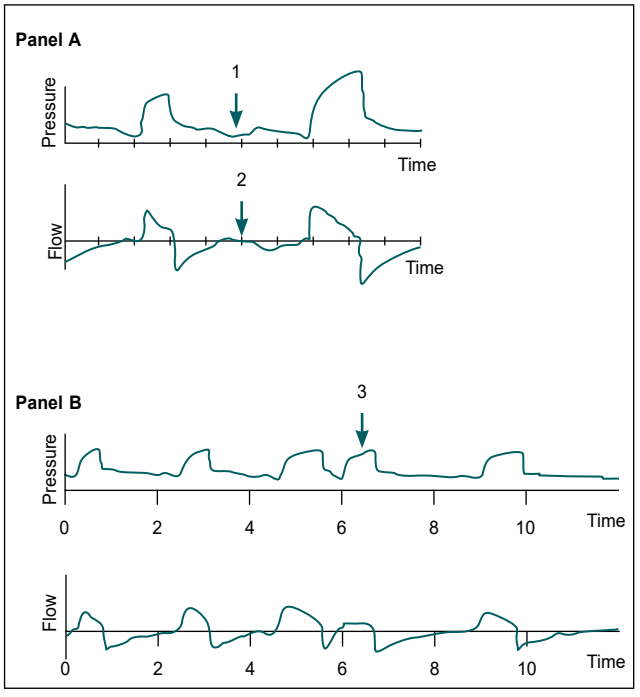

Figure 4. Trigger asynchrony: **Panel A** is showing ineffective triggering which is shown by a decrease in airway pressure (mark 1) and simultaneous increase in airflow (mark 2). **Panel B** shows double triggering (mark 3).

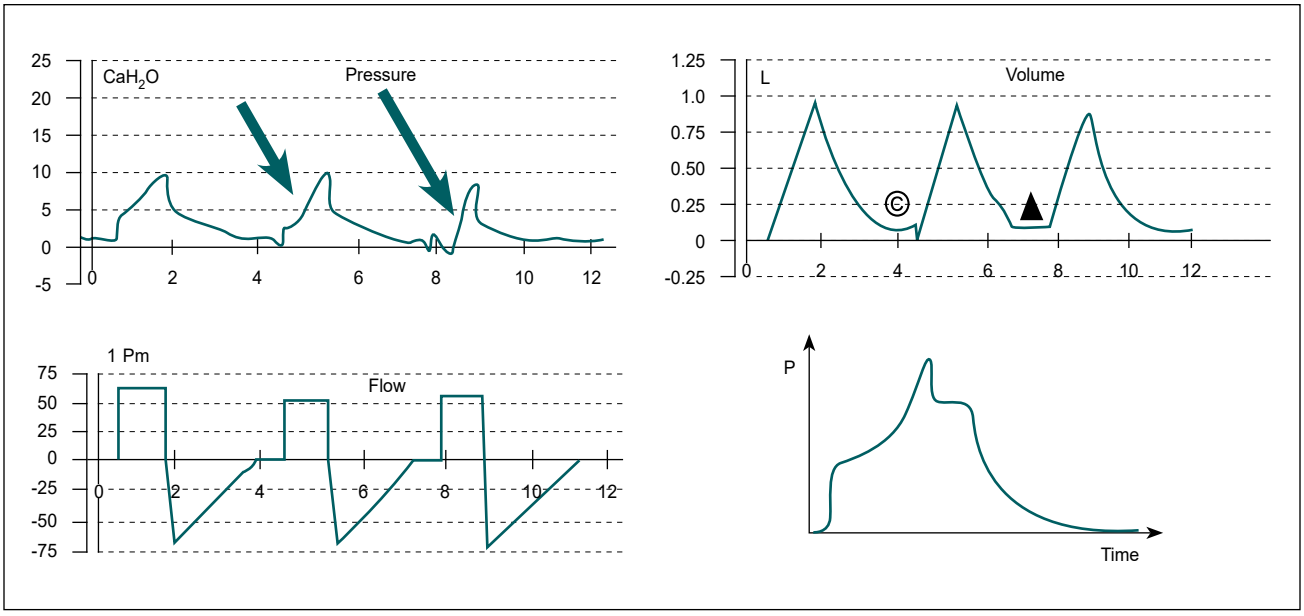

Figure 5. Flow asynchrony: Arrow showing dished out appearance (from convex to concave) due to high flow demand and inadequate flow delivery.

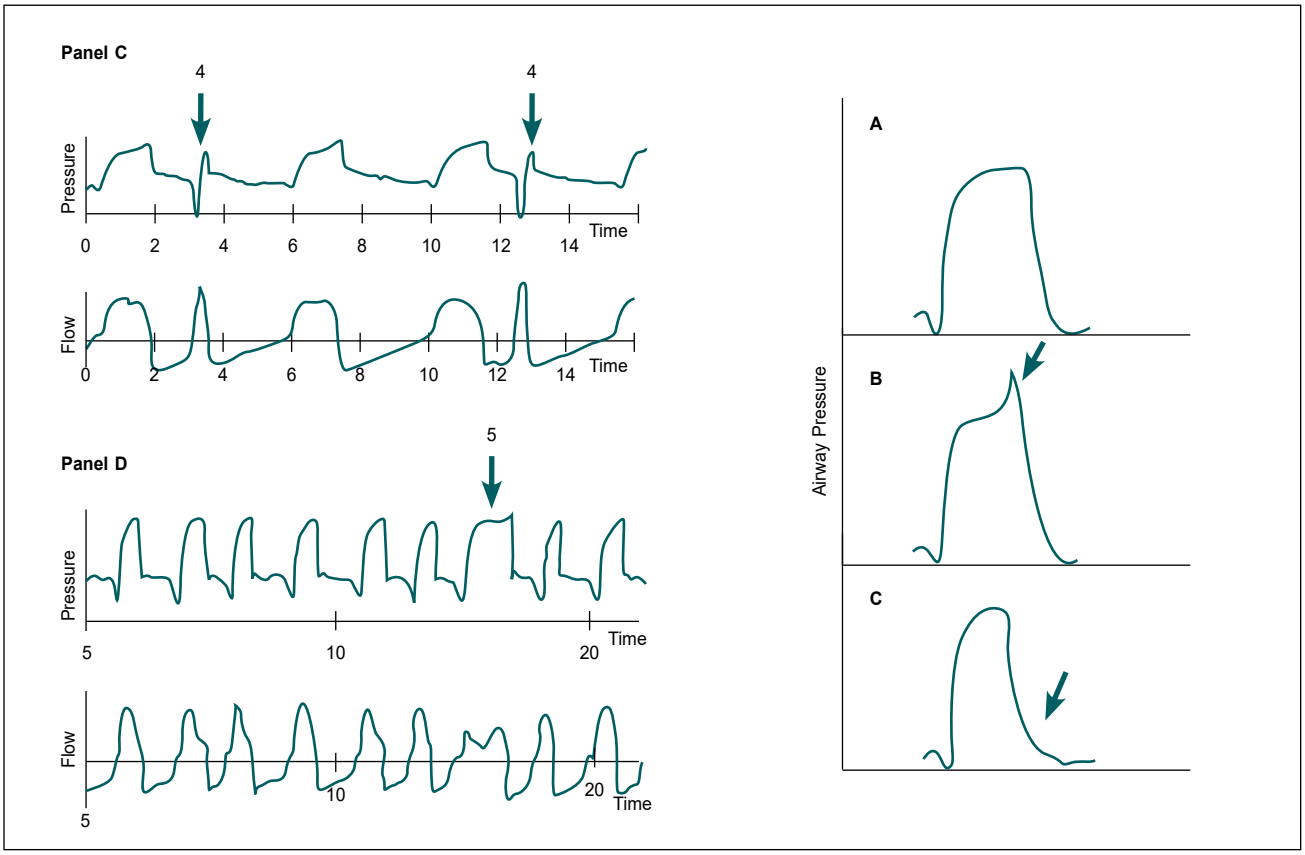

Figure 6. Cycling asynchrony: **Panel C** demonstrates premature cycling (mark 4). **Panel D** demonstrates prolonged cycling (mark 5). Right-sided figure showing pressure-time curves in setting of mismatch with patient and ventilator Ti. ***(A)*** Normal waveform with matching of neural Ti and ventilator Ti. ***(B)*** Sudden rise in airway pressure (*arrow*) indicating that the patient has switched to expiration before completion of mechanical inspiration (Neural Ti < Ventilator Ti). ***(C)*** Sudden fall in airway pressure (*arrow*) indicating that patient inspiratory efforts persist after the end of mechanical inspiration (Neural Ti > Ventilator Ti).

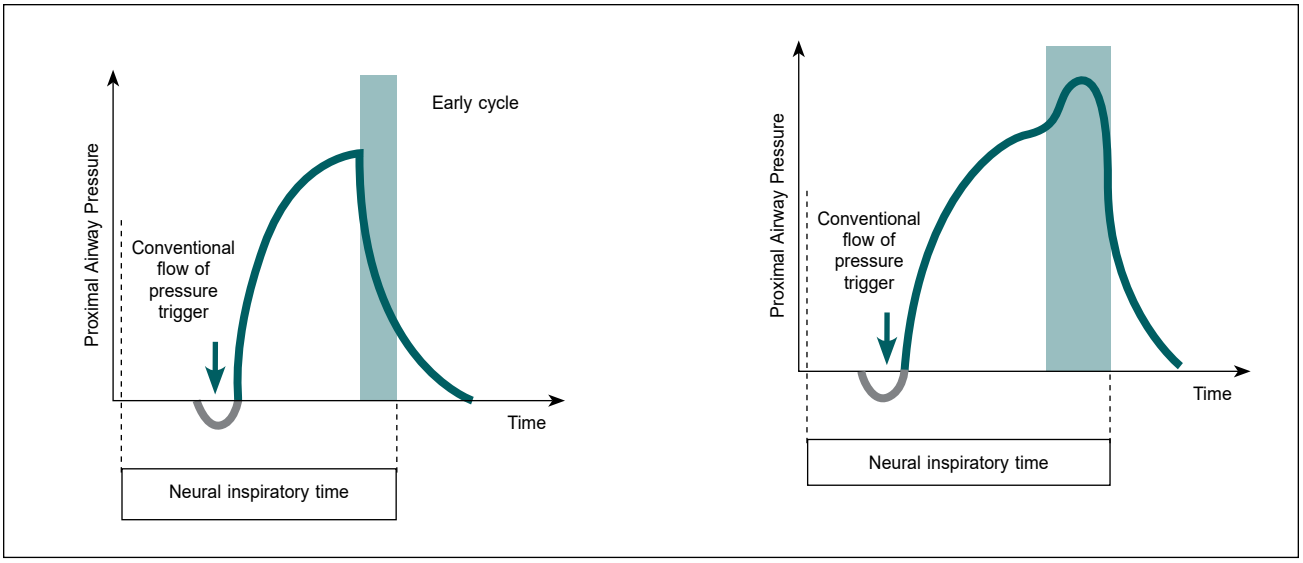

Figure 7. Cycling asynchrony: Figure on the left showing premature cycling while figure on the right showing delayed cycling.

(Flow) which includes rise time and level of pressure support, breath termination (Cycling) and expiration. Problem with any of these phases of respiratory cycle will lead to asynchrony. To minimize patient-ventilator asynchrony, all these phases of breath delivery by ventilator should coincide with patient's breathing pattern.

Triggering

Triggering includes two phases – Trigger phase and post-trigger phase.

Trigger phase is the onset of effort by the patient, to the onset of flow delivery, while the **post-trigger phase** is the onset of flow delivery by the ventilator to the end of inspiration which is significantly longer than the trigger phase.

The main determinants affecting workload associated with triggering are:

- Magnitude of change required to initiate a breath. This can be optimized by increasing trigger sensitivity and appropriate setting of positive end-expiratory pressure (PEEP), particularly, in patients of COPD and bronchial asthma, as air trapping and intrinsic PEEP make it difficult for the patient to trigger inspiration.
- Delay between onset of patient inspiratory effort and the time to ventilator response.

Studies suggest that flow triggering leads to lower work of breathing compared to pressure triggering, but this difference is probably of little clinical significance. Modern

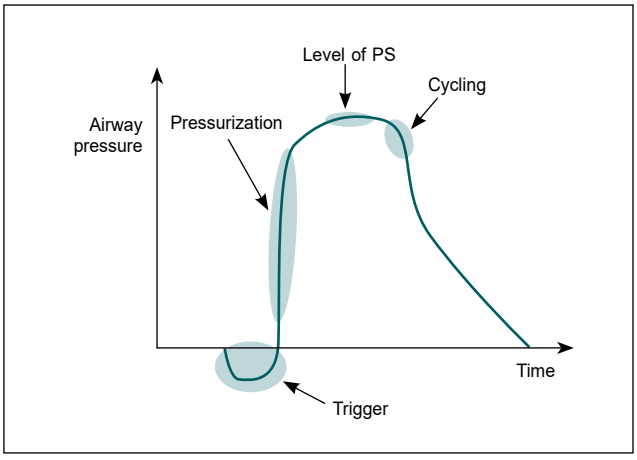

Figure 8. Diagram showing four key phases of pressure support cycle.

ventilators have very sensitive trigger mechanisms, with regards to both the inspiratory effort required to trigger and trigger delay. So triggering adds little to the overall work of breathing. Most difference in work of breathing between pressure and flow trigger is found in the post-trigger phase rather than trigger phase.

Rise-time/Pressurization Slope

During pressure support ventilation (PSV), the slope of pressurization can be adjusted on most modern ventilators. The steeper the slope, the faster the rise of P_{aw} (Airway pressure) to its target value, thus, lower the work of breathing. But, breathing comfort is lowest at both the lowest and highest rise time. Usually, rise time is set between 100 and 200 ms. If a patient exhibits discomfort due to "air hunger", the rise time can be

hastened to 50 ms. A faster rise time helps increase initial inspiratory flow.

Level of Pressure Support

Figure 9 summarizes the adverse effects of both insufficient as well as excessive pressure support on work of breathing.

Cycling

The transition from inspiration to expiration is known as cycling. Cycling can be time cycled, volume cycled or flow cycled. In PSV, it is flow cycled, where cycling occurs when flow decreases to predetermined fraction of peak inspiratory flow (PIF), defined as expiratory trigger (ET). In most ventilators, ET is 0.25, i.e., 25% of PIF. Higher the ET, lesser the magnitude of delayed cycling and the possibility of improved synchrony, particularly in patients with dynamic hyperinflation and air trapping. The higher ET will cut off inspiration at high flow rates (>25% of PIF) and allow more time for exhalation and minimize air trapping.

The problems that arise from too premature a cycling is that the patient is still in the inspiratory phase, but ventilator has switched to expiration. This can lead to double triggering and increased work of breathing. Thus, when Neural Ti > Ventilator Ti, **premature cycling** occurs and when Neural Ti < Ventilator Ti, **delayed cycling** occurs.

Consequences of delayed cycling

Figure 10 depicts the consequences of delayed cycling. Table 3 summarizes trigger asynchrony.

Reverse Trigger

It can be misidentified as double trigger or auto trigger, but it is different from both and under-recognized form of asynchrony. Various mechanisms for reverse trigger are thoracic or diaphragmatic stretch receptors, spinal reflex, etc. It is reported in deeply sedated patients with ARDS, brain death, etc.

Tables 4 and 5 summarize flow asynchrony and cycling asynchrony, respectively.

NONINVASIVE VENTILATION AND ASYNCHRONY

Noninvasive ventilation (NIV) usually has higher levels of leak causing auto triggering and cycling asynchrony. Asynchrony index is >10% in nearly 40-50% of the patients on NIV. So, asynchrony is of greater concern during NIV.

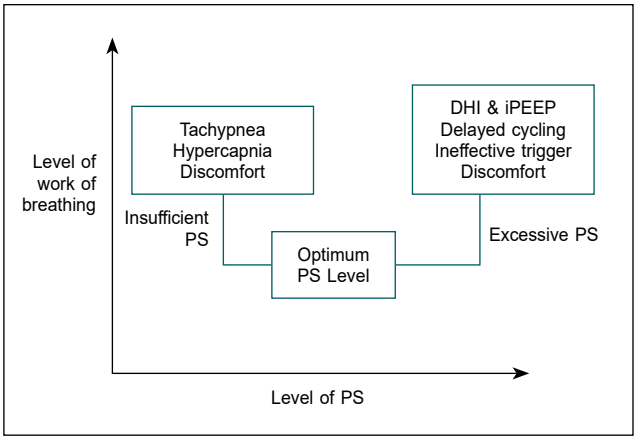

Figure 9. Adverse effects of insufficient as well as excessive pressure support on work of breathing.

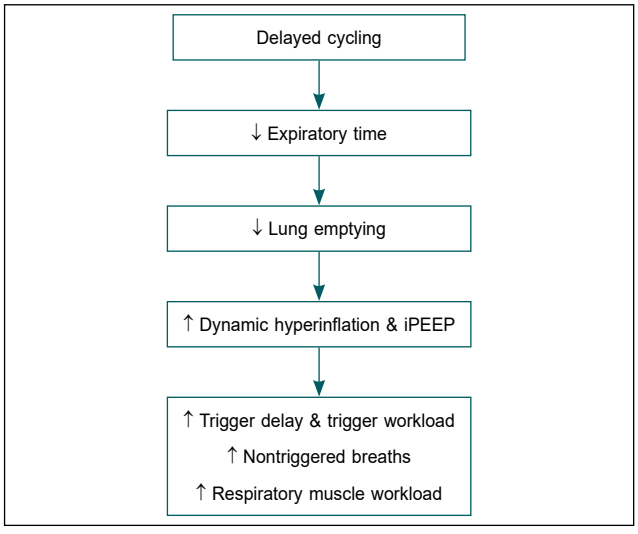

Figure 10. Outcomes of delayed cycling

- Flow cycling during NIV causes more asynchrony than time cycling due to leak (e.g., during pressure assist control).
- Modern ventilators with NIV mode compensate better for leaks (up to 120 L/min) and cause less asynchrony.
- BiPAP machine causes even less asynchrony than mechanical ventilator with NIV modes.

Table 6 represents a technical guide to troubleshooting.

ROLE OF NOVEL MODES OF VENTILATION

Automatic Tube Compensation

Automatic tube compensation (ATC) is not a mode, but, an integration option which can be used in conventional modes in modern ventilators. Endotracheal tube and ventilator tubing may increase

Table 3. Trigger Asynchrony

Type	Causes	Management	Remarks
		Trigger asynchrony (Easy to treat)	
Ineffective trigger (Most common)	• High (insensitive) trigger threshold	• Set appropriate trigger threshold, switch from pressure to flow trigger	• Common in COPD • Marker of severity of diseases as well as increases ventilator days
Delayed trigger	• High auto-PEEP DHI • Decreased respiratory drive (Sedation/neurological cause) • Respiratory muscle weakness • High ET tube resistance	• Increase I:E ratio 1:3 or more, increase flow, decrease MV by decreasing TV & RR, add extrinsic PEEP 50-80% of iPEEP • Stop sedation • Optimize nutrition (Avoid overfeeding and supplement adequate protein) • Correct electrolytes (Potassium, magnesium, phosphate, etc.) • Use ATC (Automatic tube compensation), reduce secretions, kinking of tube, etc.	• Detected by presence of chest/abdominal efforts without flow delivery from ventilator • Ventilator underestimates total RR in this asynchrony, no alarms from ventilator • Flow trigger found to have less WOB, less asynchrony and preferred over pressure trigger • Delayed trigger may be minimized by NAVA (Neurally adjusted ventilatory assist)
Double trigger (Breath stacking, double cycling)	• Small tidal volume, inadequate flow, high respiratory drive • Short inspiratory time, Neural Ti > Ventilator Ti • High flow-cycle threshold • Premature cycling	• Increase ventilator rate/TV to increase minute ventilation or give sedation and decrease air hunger • Shorten rise time • Increase peak flow • Increase Ti • Set appropriate expiratory trigger	• Common in ARDS with protective ventilation • Can occur with cough, sighs • More common with volume targeted ventilation
Auto trigger	• Cardiac oscillation, water in circuit, negative suction through chest drain, etc. • Low (sensitive) trigger threshold • Leak in circuit	• Remove secretions and water condensates from tubing • Set appropriate trigger threshold • Decrease leak	• Switching from flow to pressure trigger might help
High work of breathing due to	• Narrow ET tube • High ventilator tubing resistance	• Use ATC • Remove secretion from ET • Increase pressure support level • Remove secretion from ventilator tubing, prevent kinking, etc.	• *In vivo* resistance is higher, so even ATC may underestimate the resistance

work of breathing, which leads to trigger or flow asynchrony. Placement of esophageal balloon and a tracheal catheter is required for accurate detection of same. ATC is supposedly beneficial over PSV in terms of compensating for excess work of breathing due to this. As *in vivo* resistance is usually higher than *in vitro* resistance, ATC may not completely compensate for it.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is a mode which has been developed to improve synchrony and reduce work of breathing. PAV generates respiratory support as a proportion of the total pressure needed to inflate the respiratory system. In this mode, the total pressure needed to inflate the respiratory system is obtained by

Table 4. Flow Asynchrony

Type	Causes	Management	Remarks
	Flow asynchrony (Breath delivery asynchrony) (More common with volume targeted mode than pressure targeted mode)		
Inadequate flow (More common)	• High (slow) rise time in pressure targeted breath • High demand, e.g., Fever, sepsis, pain, anxiety, etc. • Inadequate MV and TV, inadequate flow • Hypoxia and hypercarbia	• Decrease rise time (Faster rise time) • Treat factors causing high demand like pain, fever, sepsis, anxiety, etc. • Increase MV by increasing TV, increase flow • Correct hypoxia and hypercarbia	• Detected by downward deflection (dip) in pressure-time waveform causing deformation of curve from convex to concave (dished out appearance) • Decelerating flow/pressure targeted ventilation is preferred in flow asynchrony
High flow (Less common)	• Low (faster) rise time in pressure targeted breath • High flow in volume targeted breath	• Increase rise time (Slow rise time) • Decrease flow	• Detected by peaking of pressures at the start of inspiration • Causes active exhalation, coughing, etc. • High pressure support may lead to apnea due to fall in pCO_2, especially in CHF.

Table 5. Cycling Asynchrony

Type	Causes	Management	Remarks
	Cycling asynchrony (Termination asynchrony) (Difficult to treat) (Common during NIV)		
Premature cycling	• Neural Ti > Ventilator Ti	• Decrease flow rate *Or* Increase TV to match Neural Ti	• Can be detected by decrease in pressure in pressure-time waveform while increase in airflow in flow-time waveform after termination of ventilator delivered breath • May lead to double triggering and increase work of breathing
Delayed cycling	• Neural Ti < Ventilator Ti • Usually in dynamic hyperinflation • High resistance and low elastic recoil as in COPD	• Decrease ventilator Ti by decreasing pressure support, faster rise time, high flow rate, raising expiratory trigger >25% up to 40-50% • Switch to pressure-support ventilation in patients with variable inspiratory time • Change to time cycled ventilation and match Neural Ti	• Can lead to large TV and less expiratory time, so air-trapping and ineffective triggering in subsequent breaths • Can be detected by tenting at the end of inspiration which shows end of neural inspiration • Can be detected by zero flow state in flow-time waveform in pressure targeted breath

automatic and repeated calculations of resistance and compliance via short end-inspiratory occlusions. That is the reason why leaks impede proper PAV functioning as it underestimates resistance and leads to inadequate ventilatory assist and increased work of breathing.

Neurally-adjusted Ventilatory Assist

Neurally-adjusted ventilatory assist (NAVA) uses diaphragmatic neural activity to trigger gas delivery. Unlike PAV, the trigger mechanism in NAVA is not

Table 6. Technical Guide to NIV Troubleshooting

Problem	Cause	Solution
Ventilator cycling independent of patient effort (Auto trigger)	• Too sensitive trigger • Excessive mask leak	• Adjust trigger sensitivity • Reduce mask leak
Ventilator not triggering despite patient effort (Ineffective trigger)	• Too high trigger sensitivity • Excessive mask leak	• Adjust trigger sensitivity • Reduce mask leak
Inadequate chest expansion despite triggering	Inadequate Tidal volume/ pressurization	• Increase IPAP • In neuromuscular disease, keep longer Ti
Chest/Abdominal paradox	Upper airway obstruction	• Avoid neck flexion • Increase EPAP
Premature expiratory effort by patient (Delayed cycling)	Excessive Ti/IPAP	• Adjust Ti • Decrease IPAP

affected by leaks or intrinsic positive end-expiratory pressure (iPEEP).

NAVA improves patient-ventilator synchrony by reducing triggering and cycling delays in comparison to PSV. Despite the theoretical benefit of PAV and NAVA, data till date are not sufficient to claim that either mode is superior to conventional modes such as PSV in terms of major clinical outcomes (i.e., duration of MV, length of ICU stay).

Figure 11 illustrates the way NAVA senses the electrical activity of the diaphragm (Edi), which is the earliest respiratory signal that can be detected while conventional technology is limited to sensing patient effort at final stage of respiratory effort. Figure 12 shows trigger delay between onset of diaphragmatic activity and start of ventilator inspiratory cycle which is common in DHI due to COPD. No ventilator settings can overcome this trigger delay except NAVA which works on sensing electrical activity of diaphragm. Cycling off occurs when EAdi falls to 70% of maximum EAdi.

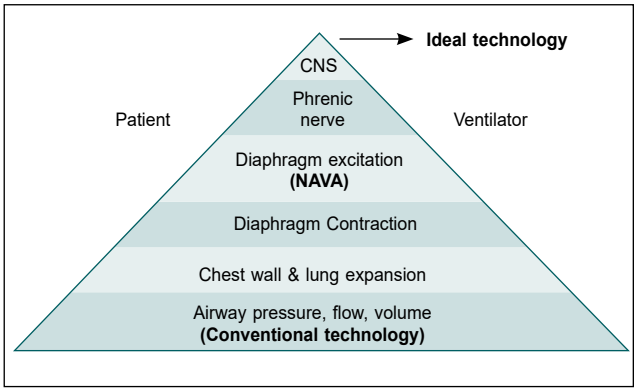

Figure 11. NAVA senses the electrical activity of the diaphragm (Edi).

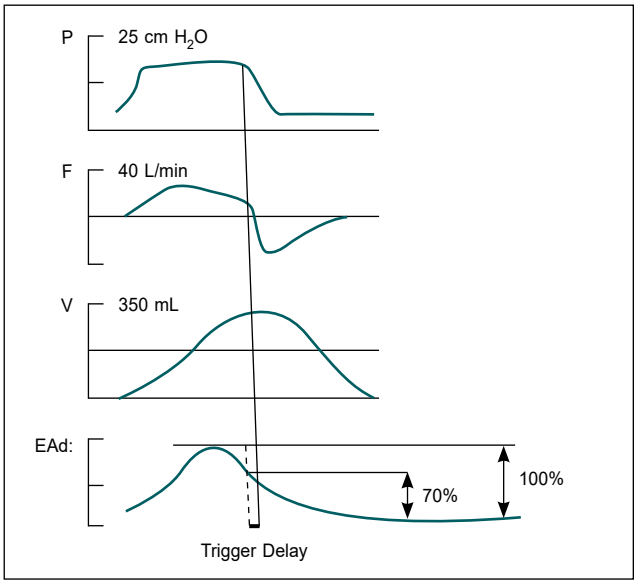

Figure 12. Trigger delay: Trigger delay between onset of diaphragmatic activity and start of ventilator inspiratory cycle which is common in DHI due to COPD.

Other modes

- Volume assured pressure support
- Pressure augmentation
- Automode
- Volume support
- Adaptive support ventilation (ASV)

These are closed loop systems to improve patient ventilator interaction, but at present, major studies show their beneficial efficacy are lacking.

Approach to Patient Ventilator Asynchrony: Summary	
Sedation, analgesia and paralysis	• Give optimum sedation and analgesia during mechanical ventilation, give sedation free interval daily, optimize ventilator settings before increasing sedation. • Treat pain, fever and other treatable factors before increasing sedation. • Use neuromuscular blockers only during intubation, up to 48 hours of intubation in ARDS, routine use after 48 hours not recommended.
Respiratory rate	• Match respiratory rate of ventilator with patient's respiratory rate. • Keep high respiratory rate during low tidal volume ventilation to maintain minute ventilation.
Trigger sensitivity	Optimize trigger sensitivity for each patient while initiating mechanical ventilation and weaning.
PEEP	• Titrate optimum PEEP for each patient. • Use 50-75% of iPEEP as ePEEP to counter auto-PEEP.
Inspiratory flow	Increase flow when high demand, decelerating flow when flow asynchrony.
Inspiratory time	Match neural Ti with Ventilator Ti. Shorter Ti when high flow demand, auto-PEEP, expiratory flow limitation, etc.
Cycling	Use high cycling cut-off when expiratory flow limitation to minimize dynamic hyperinflation (i.e., increase from 25% to up to 50%).
Rise time	Faster rise time when high flow demand; Set as per patient's demand (Usual range – 50-200 ms).
Mode	Pressure targeted mode preferred over volume targeted mode when flow asynchrony is there.

KEY POINTS

- An uncomfortable patient should be evaluated for asynchrony, apart from physical and psychological causes of distress. Asynchrony index >10% or any asynchrony causing patient discomfort is considered significant and should be treated.
- Excessive ventilator support leads to ineffective triggering while insufficient ventilator support leads to increased work of breathing.
- Do not forget to set trigger sensitivity. Always look at the patient as well as ventilator graphics before and after changing any ventilator settings and stay there for a while. Intensivist should look at the ventilator waveforms to assess status of lungs as well as of patient in same way as a cardiologist looks at the ECG for the heart.
- Use modes which you are familiar with. Don't use newer modes, just because they are there and the manufacturer claims certain advantages. Basic modes are sufficient for most situations. It is you and your monitoring which will improve synchrony and outcome, not any mode by itself.
- It should be noted that every patient is different and the same ventilator settings are not suitable for all patients. Clinicians must optimize ventilator settings at the bedside for each patient individually to improve the synchrony between patient and ventilator. Stay and watch the patient for some time after each change of settings.
- Heavy sedation or neuromuscular blockade is not the answer to all ventilator alarms and it should be used as a last resort to improve patient-ventilator interaction.
- Appropriate treatment of contributing factors to asynchrony (e.g., fever, pain, anxiety, iPEEP, bronchospasm, decreased drive due to sedation, electrolyte abnormalities, malnutrition leading to muscle weakness, etc.) is essential to improve asynchrony. Just changing ventilator settings is not going to be of any use.
- Normal arterial blood gas (ABG) analysis doesn't mean optimum ventilator settings; patient can have increased work of breathing despite normal ABG values.
- Mechanical ventilation does not guarantee decreased work of breathing. Many studies have found lower airway pressures during assisted breath, as compared to controlled breaths, which shows continuous inspiratory muscle contraction during mechanical inflation which increases work of breathing.
- Multiple studies demonstrate that pressure targeted ventilation improves flow asynchrony as compared

to volume targeted ventilation. Use pressure targeted/decelerating flow pattern ventilation whenever flow asynchrony is the main problem.

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It is Premature to Change Authorized COVID-19 Vaccines Dosing, Schedules: FDA

The idea of modifying the authorized dosing or schedules of COVID-19 vaccines was premature and was not supported by the available data, stated the US FDA.

The agency said that it had been following discussions and news reports about decreasing the number of doses, increasing the length of time between the doses, reducing the dose in half, or mixing and matching vaccines in a bid to vaccinate more people. While the questions were reasonable to consider, the agency stated that changing the FDA-authorized dosing or schedules of these vaccines at this time is premature and has no robust evidence available. In the absence of appropriate data supporting the changes in vaccine administration, there is a significant risk of placing public health at risk… (*Reuters*)

Covaxin to be Tested on Children as Young as 2 Years

After becoming the first COVID-19 vaccine in the world to be tested on children as young as 12 years, Covaxin is now going to be tested on children as young as 2 years, stated Bharat Biotech chairman and managing director Dr Krishna Ella.

A clinical trial is now being planned on children aged 2-15 years. A proposal will soon be submitted to the subject expert committee. Ella emphasized that Covaxin is an inactivated virus vaccine based on a tried and tested vero cell platform that has been used for several vaccines. Covaxin was the first among the COVID-19 vaccines to initiate testing on children (in September). Covaxin Phase II trials were conducted on 380 volunteers in September 2020 that included participants aged 12-65 years. The Pfizer vaccine started testing on 12-year-olds in October while Moderna started enrolling participants aged 12 years and above in December… (*ET Healthworld – TNN*)

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Indian Journal of Clinical Practice, Vol. 31, No. 8, January 2021

A Study to Evaluate the Efficacy and Safety of a Herbal Preparation for Burn Wounds

MADHURI GORE*, DIPESH WAGHMARE†

ABSTRACT

Background: Burn is a common medico-surgical problem all over the world, most devastating of all wounds, and imposes a serious burden on physical, mental and socioeconomic conditions of the victim. Rapid and effective treatment of burnt skin is vital to hasten wound closure and healing. The process of burn wound healing is divided into four consecutive and overlapping phases: hemostasis, inflammation, proliferation and remodelling. Local treatment of burn wounds includes cleansing, debridement and burn wound dressing, typically incorporating topical antimicrobial agents; however, there is no consensus on which agent or dressing is optimal for burn wound coverage to prevent or control infection or to enhance wound healing. Various silver preparations (monocrystalline and slow release) are the mainstay of many approaches but antimicrobial peptides, topical photodynamic therapy, chitosan preparations, new iodine delivery formulations, phage therapy and natural products, such as honey and essential oils, have all been tested. The continuous increase in antibiotic resistance, besides the high susceptibility of burn wounds to infection, and the difficulty of systemically administered antibiotics to reach the damaged tissue, have all made the development of new topical antimicrobials for burn infections a potential area of innovation for researchers. Use of medicinal plants for dressing wounds has been described by traditional medicine. **Objectives:** The purpose of this study was to evaluate the efficacy and safety of a herbal preparation in patients with burns in a prospective, noncomparative, open-label and single-center study design. The study population comprised of patients aged 18 years and above suffering from superficial and deep burns involving up to 30% total body surface area. **Methods:** After written informed consent and evaluation of inclusion/exclusion criteria, subjects were treated for 14 days. Efficacy assessments included wound epithelialization, wound microbiology, blood leukocyte counts and safety assessments included pain score and adverse events. **Results:** Over a period of 5 months, 26 patients, mainly between 20 and 30 years, and with female predominance, were enrolled in the study. At the end of treatment, almost 74% of the subjects showed more than 50% skin epithelialization. Approximately, 82.6% of patients had fall in blood leukocyte count. Wound colonization showed Klebsiella and Pseudomonas in a decreasing trend from 39.1% on Day 7 to 8.7% on Day 14, remarkably less than historical controls. All patients experienced burning pain after spraying the product which lasted for almost 15 minutes and demonstrated decreasing intensity from Day 1 to 14. No local adverse events were found in the patients, with high patient satisfaction. **Conclusion:** The herbal preparation was a very effective and safe treatment option in patients with superficial and deep partial-thickness burns involving up to 30% total body surface area. It prevented wound infection and significantly improved wound epithelialization.

Keywords: Burn wounds, total body surface area, herbal spray

Burns, one of the most common forms of injury, have devastating consequences. The detrimental outcomes of burns include physical disabilities as well as mental and emotional disorders.[1,2] There are several factors that guide the evaluation and management of burns. First, the type of burn, such as thermal, chemical, electrical or radiation. Second, the extent of the burn, characterized by the percentage of total body surface area (TBSA) involved. Third, the depth of the burn, whether superficial (first-degree), partial (second-degree) or full-thickness (third-degree). Other factors include patient characteristics such as the age of the patient (<10 or >50 years old); other medical conditions; specific locations of the burn (face, eyes,

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ears, nose, hands, feet and perineum) and presence of any associated injuries, such as smoke inhalation and other traumatic injuries.[3-6]

Despite the discovery of an array of topical antiseptic agents, healing of burns remains a challenge to modern medicine.[7] Topical antiseptic agents and disinfectants often cause allergic reactions, skin irritations and damage to healthy skin tissues, which decreases the rate of skin repair and increases the rehabilitation period.[2] Bacterial colonization versus infection is an area that needs to be appropriately understood by treating clinicians, in order to use antimicrobials and adjunct therapies effectively. While all wounds contain bacteria, colonization refers to a condition where bacteria are multiplying but their actions do not elicit an immune response.[8]

Local treatment of burn wounds involves cleansing, debridement and wound dressing, particularly using topical antimicrobial agents; however, there is a lack of consensus on the optimal agent or dressing for burn wound coverage in order to prevent or control infection or to hasten wound healing. Commonly used topical agents include combination antimicrobials, silver sulfadiazine, bismuth-impregnated petroleum gauze, mafenide and chlorhexidine. Other agents such as honey, povidone-iodine are less commonly used. Combinations of antimicrobials and topical antifungals have also been found to be effective for the local treatment of burns.

Many of the plants used in the herbal preparation used in this study have been shown to have very good antibacterial, anti-inflammatory, antioxidant, cell proliferative and angiogenic activities. The herbal oil is prepared from Chameli (*Jasminum grandiflorum*), Neem (*Azadirachta indica*), Mom (Wax), Daruharidra (*Berberis aristata*), Tutiya (Copper sulfate), Haridra (*Curcuma longa*), Yashtimadhu (*Glycyrrhiza glabra*), Sariva (*Hemidesmus indicus*), Nilofer (*Nymphaea alba*), Kutki (*Picrorhiza kurroa*), Karanj (*Pongamia glabra*), Padmakh (*Prunus cerasoides*), Manjistha (*Rubia cordifolia*), Lodhra (*Symplocos racemosa*), Haritaki (*Terminalia chebula*), Patola (*Trichosanthes dioica*), Kumari Oil (*Aloe barbadensis*) and Chandan oil (*Santalum album*).

This manuscript will highlight the current evidence on pharmacological and nonpharmacological therapeutic options for mixed depth thickness burns up to 30% TBSA. In Ayurveda, the Indian traditional system of medicine, the use of herb extracts or polyherbal formulations to treat various burns wounds have been mentioned. The herbal preparation in this study has shown to be effective in the treatment of patients with burns wounds.

OBJECTIVES

The purpose of this study was to investigate the efficacy and safety of herbal preparation for adult patients diagnosed with superficial and deep partial-thickness burns.

METHODS

This was a single-center, open-labelled, prospective clinical study. Patients aged 18 years or above were included in the study. Main inclusion criteria included patients diagnosed with superficial and deep partial-thickness burns up to 30% TBSA with the maximum extent of deep/full-thickness burn less than 10% TBSA. Major exclusion criteria included pregnant females and patients with comorbidities such as diabetes, hypertension, renal or hepatic dysfunction. Patients were treated for 14 days with the herbal preparation as a topical application.

A total of 26 subjects were enrolled in the study. All patients were clinically examined for height, body weight, vital signs, symptoms and adverse events at every visit. Patients were examined clinically, laboratory evaluations (white blood cell [WBC] count, biochemical and hematological parameters), wound epithelialization, wound microbiology and pain score evaluation at their follow-up visit accordingly at Day 1, 7 and 14. The primary and secondary efficacy and safety assessment were done before treatment (Day 0) and after the end of treatment (Day 14).

STATISTICAL ANALYSIS

Continuous data were described as mean ± SD (standard deviation) in case of normally distributed data and with median (minimum-maximum) otherwise. Categorical data were described by counts and percentages. A nonparametric Friedman test was used to detect changes over time for blocked continuous variables (local infection, pain and wound size).

RESULTS

A total of 26 subjects were enrolled in the study. Out of 26 subjects, 3 subjects could not complete the study due to various reasons (discharge without permission, leave without permission, etc.). Hence, these 3 subjects had not been included for further data analysis. The age of the patients ranged from 18 to 65 years with the maximum

number (n = 16) of patients in the age group 21-30 years as mentioned in Figure 1. With female predominance, 19 patients were female and 7 patients were male.

Out of a total of 26 enrolled patients, cause of burns was sustained accidental burns in 22 patients and suicidal attempt in 4 patients. The extent of burn ranged from 8% to 30% TBSA which is mentioned in Figure 2, with 12 (46%) patients having more than 20% TBSA burns. Ten patients had only partial-thickness burn while 16 patients had mixed depth burns with deep partial and full-thickness burn extent ranging from 4% to 10% TBSA.

WBC Counts

There was a decrease in the number of patients with clinically significant WBC count, which indicates the absence of invasive sepsis, as mentioned in Table 1. The number of patients with WBC count <10,000/mm^3 was significantly lower at Day 14 compared to baseline.

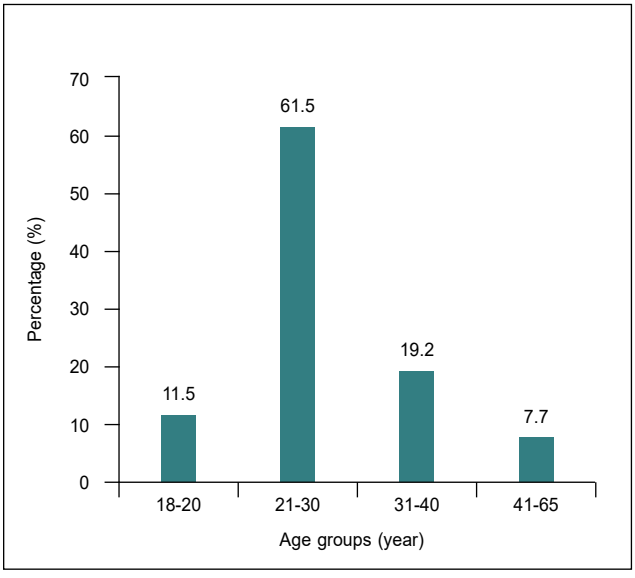

Figure 1. Age distribution of subjects.

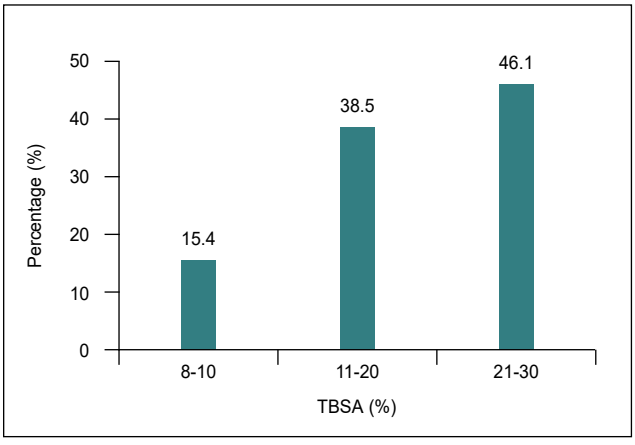

Figure 2. Burn extent.

Wound Epithelialization

The status of wound epithelialization in terms of percentage epithelialization of wound on the end of treatment (EOT) on Day 14 is mentioned in Figure 3.

In 11 patients out of 23 evaluable patients (48%), more than 75% of the wound had epithelialized at Day 14 and 10 patients of these did not need split skin grafting (SSG) for wound closure. Thirteen patients with the variable extent of deep partial and full-thickness burns required SSG for obtaining wound closure; the area receiving SSG ranged from 4% to 10% TBSA.

Wound Microbiology

On Day 7, wounds of 39.1% of patients grew various organisms such as Klebsiella, Pseudomonas Acinetobacter, methicillin-resistant *Staphylococcus aureus* (MRSA). *Pseudomonas aeruginosa* was the most common organism isolated in about 21.7% of patients. On Day 14, only 8.7% of patients were detected to grow organism from wound swab cultures and these were MRSA. The wounds appeared clean and while on Day 7, the colonization was detected in 39.1%,

Table 1. WBC Counts Indications

	WBC count <10,000/mm^3 (N)%	WBC count >10,000/mm^3 (N)%
Day 1	4 (17.4)	19 (82.6)
Day 14	16 (69.6)	7 (30.4)

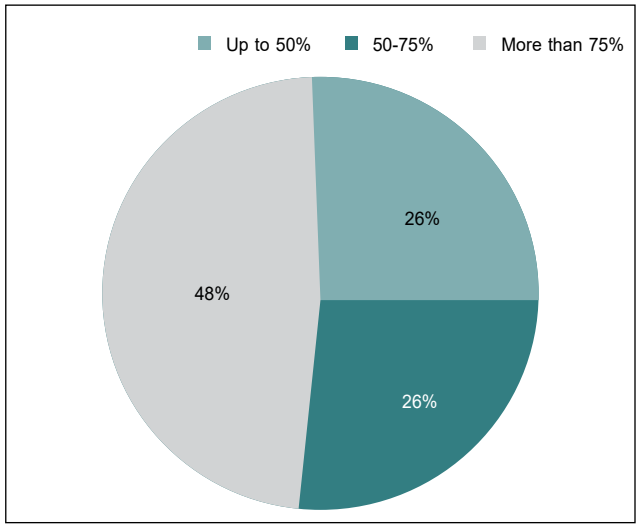

Figure 3. Wound epithelialization at end of treatment.

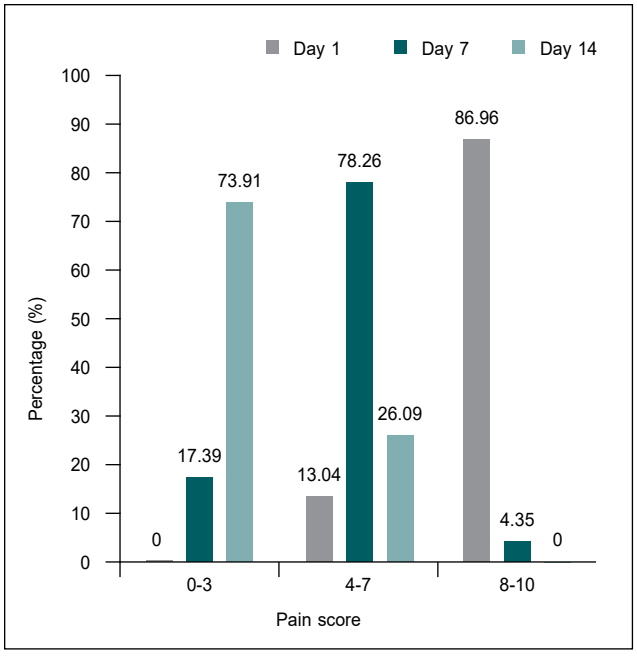

Figure 4. Pain score evaluation on the application of the investigational product .

it was controlled and decreased to 8.7% by Day 14. This difference was statistically significant. This was remarkably different from the usual observation of almost 95% wound colonization on 7th post-burn day.

Pain Score Evaluation

All patients experienced burning pain for about 10-15 minutes after spraying the investigational product on the burn wound. The pain score assigned by patients on Day 1, 7 and 14 is depicted in Figure 4. On Day 1, 87% patients experienced severe pain (score 8-10), which decreased to moderate pain (score 4-7) in 78% by Day 7 and to mild pain (score 0-3) in 74% by Day 14, which was the most significant difference observed during pain score evaluation.

Adverse Reaction and Patient Evaluation

None of the patients had suffered from any adverse effects due to investigational product and no subject had evidence of skin irritation, rash, itching or additional inflammatory changes around the wound. None of the patients expressed dissatisfaction with the treatment and no one requested discontinuation of the therapy.

Images of some selected patients are shown in Figure 5.

DISCUSSION

Despite several topical applications available for the management of burn wounds, there is a necessity to develop safer and more effective treatment options. The aim of the present study was to evaluate the efficacy and safety of a herbal preparation for burn wound management.

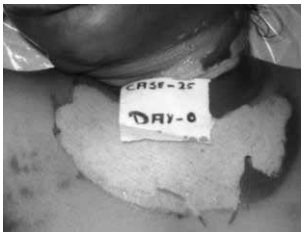

Figure 5 (A). Burn case no. 25 on Day 0.

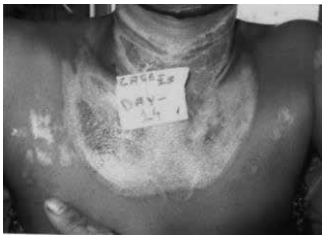

Figure 5 (B). Burn case no. 25 on Day 14.

Figure 5 (C). Burn case no. 17 on Day 7.

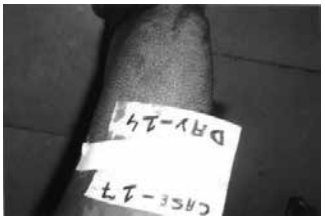

Figure 5 (D). Burn case no. 17 on Day 14.

A total of 26 patients with less than 30% of TBSA burns were enrolled in this open-labelled study over 5 months. There was female predominance and 16, i.e., 61.5%, patients were in the age group 21-30 years, with 12 (46%) patients having burn extent between 20 and 30% TBSA. From Day 1 to Day 14, the WBC count showed a significant reduction with 82.6% of patients having >10,000/mm^3 counts on Day 1 to 69.6% having <10,000/mm^3 counts on Day 14. More than 50% of the wound was epithelialized in 74% of patients on Day 14 of the study. A total of 43.4% of patients had complete epithelialization and did not require SSG for wound closure. A total of 56.5% of patients needed SSG for wound closure of 4-10% of TBSA burns.

Wound microbiology revealed positive swab cultures in 39.1% patients on Day 7 and in 8.7% patients on Day 14. This was significantly different from the usual observation of wound colonization in about 95% of patients on Day 7.

Wound infection adversely impacts wound healing. The diagnosis and management of wound infection are arguable and vary from clinician to clinician. Understanding the factors that affect the progression from colonization to infection can help clinicians with the interpretation of clinical findings and microbiological investigations in patients with chronic wounds. In the present study, the burn wounds appeared clean with progressive wound healing.

The wound colonization with bacteria was controlled effectively and was better than historical controls. This aided wound epithelialization. None of the superficial or deep thickness wounds got converted to full-thickness depth. This can be attributed to the inhibition of bacterial infection of wounds. The same has been supported by the increased number of patients with lower WBC counts.

The pain score decreased significantly in the majority of the patients from Day 1 to Day 7 to Day 14. No adverse effects or reactions were observed and the product was well accepted by all the patients.

The investigator experienced no difficulty in the use of the product. The investigator perceived the efficacy of the product as better than routinely used local agents (silver preparations).

CONCLUSION

The herbal preparation used in this study is an effective and safe topical treatment for mixed depth burn wounds involving up to 30% of TBSA. The burn wounds appeared clean with progressive wound healing. The wound colonization with bacteria was controlled effectively and better than historical controls.

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Disclosures: Dipesh Waghmare is the Medical Advisor Executive of Millennium Herbal Care Limited. All other authors have nothing to disclose and no relationship with the related industry.

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Laparoscopic Lavage is Safe in Perforated Diverticulitis

Long-term severe complications appeared to be similar with laparoscopic lavage and primary resection in perforated purulent diverticulitis patients, reported researchers in a study published in *JAMA Surgery*. However, recurrence was more frequent following lavage.

At a median follow-up of just below 5 years, results from the ongoing SCANDIV trial suggested no difference in severe complications (primary outcome) or in mortality, quality of life (QoL) and functional outcomes (secondary outcomes) between the treatment groups. Severe complications were noted in 36% (n = 26/73) in the laparoscopic lavage group compared to 35% (n = 24/69) in the resection group (p = 0.92). Recurrence of diverticulitis was more frequent following lavage, often resulting in sigmoid resection (30% in the lavage group proceeded to sigmoid resection), but with a lower stoma prevalence; stoma prevalence was 8% (n = 4) in the lavage group compared to 33% (n = 17, p = 0.002) in the resection group… (*Medpage Today*)

- Allergic Cough
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Grilinctus®-LS Syrup

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*Laryngopharyngeal/ Gastro-oesophageal reflux Disease
RTI : Respiratory Tract Infection

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Study of *Pseudomonas aeruginosa* Growth in Hospitalized Patients

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ABSTRACT

Pseudomonas aeruginosa is a leading cause of nosocomial infections, ranking second among the Gram-negative pathogens. Hence, this study was required to enhance the knowledge about this particular organism. A total of 100 isolates of *P. aeruginosa* isolated from various clinical specimens like urine, pus, blood, body fluids, sputum, collected from patients, irrespective of age and sex, were identified by standard microbiological procedures. A total of 100 culture positive samples were taken and it was found that *P. aeruginosa* was predominantly present in urine samples of males aged between 21 and 30 years.

Keywords: *Pseudomonas aeruginosa*, National Nosocomial Infections Surveillance system, intensive care unit

Pseudomonas aeruginosa is the perfect example of an opportunistic pathogen of humans. Infection due to *P. aeruginosa* is seldom encountered in healthy adults. Now the organism has become increasingly recognized as the etiological agent in a variety of serious infections in hospitalized patients with impaired immune defenses. It causes infections particularly in burns patients as the skin host defenses are destroyed, orthopedic-related infections, respiratory diseases, immunosuppressed and catheterized patients. It may be the cause of the chronic debilitating pulmonary infections, which is one major cause of death in patients with cystic fibrosis. Generally, it contributes substantially to wound-related morbidity and mortality worldwide. *P. aeruginosa* is a leading cause of nosocomial infections, ranking second among the Gram-negative pathogens reported to the National Nosocomial Infections Surveillance (NNIS) system. Hence, this study is required to observe the growth of *P. aeruginosa* in various samples according to parameters related to hospitalized patients, to enhance the knowledge about this particular organism.

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MATERIAL AND METHODS

This study was conducted in the Dept. of Microbiology, Pt. BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, over a period of 1 year.

A total of 100 isolates of *P. aeruginosa* isolated from various clinical specimens like urine, pus, blood, body fluids, sputum, etc., were collected from patients, irrespective of age and sex, and were identified by standard microbiological procedures.

Collection of specimen

1. Urine: clean catch midstream urine samples were collected.
2. Pus: aspirated samples of pus or swabs were collected.
3. Blood: blood samples were collected by aseptic venipuncture.
4. Body fluids: body fluids were aspirated under aseptic conditions.
5. Sputum: expectorated sputum samples were collected.

Processing and Culture of Organism

Microscopy and culture of all the above mentioned samples were done. Cultures were performed on blood agar and MacConkey agar. Inoculated media were examined for growth after overnight incubation at 37^0C. Blood samples were cultured in glucose broth and subcultured on blood agar and MacConkey agar after incubation at 37^0C for 24 hours, 48 hours, 72 hours and

on 7th day. The evaluation of colony morphology on the plating media was done and the subsequent identification procedures were carried on the isolated bacteria, using standard procedures.

Blood agar and MacConkey agar were inoculated within half an hour of collection with the specimen. Inoculation of samples on culture medium was done using an ordinary reusable inoculating loop.

IDENTIFICATION AND SCREENING OF *P. AERUGINOSA*

Gram Staining

The smear was prepared on clean, grease free slide, air dried and heat fixed. Crystal violet was poured on the slide, allowed to remain for 1 minute and rinsed with tap water. Gram's iodine was then poured on the slide, retained for 1 minute and then rinsed with tap water. The smear was decolorized with acetone and rinsed immediately with tap water. The slide was counter stained with carbol fuchsin for 30 seconds and rinsed with tap water and air dried. The slide was finally examined under an oil immersion lens for presence of Gram-negative bacilli.

Detection of Motility Using Hanging Drop Preparation

A part of colony was passed into peptone water and incubated at 37°C for 2 hours. After 2 hours, hanging drop was prepared by taking a loopful of growth from peptone water. It was kept on a cover slip and was inverted on a slide with a plasticine ring over it. First, the edge of the drop was focused under 10X of microscope and then it was examined under 40X. Gliding type of motility was seen in maximum number of isolates.

Biochemical Reactions

The various biochemical reactions used were oxidase test, catalase test, motility, growth at 42°C, oxidative/fermentative medium (Glucose, Maltose, Lactose), nitrate reduction test, MR/VP, mannitol motility medium, triple sugar iron agar, indole production, urea hydrolysis, citrate utilization.

RESULTS

A total of 100 isolates of *P. aeruginosa* isolated from various clinical specimens like urine, pus, blood, body fluids, sputum, etc., collected from patients, irrespective of age and sex, were included in the present study. *P. aeruginosa* isolates were identified on the basis of Gram staining, motility and biochemical reactions.

Out of 48,218 clinical samples received in the laboratory during the study period, 12,854 (26.66%) showed bacterial growth, while rest 35,364 samples (73.34%) were either culture sterile, or showed the growth of bacterial contaminants or fungal isolates. The overall isolation rate of *P. aeruginosa* was 12.21%.

Table 1 shows the sex distribution of patients with *P. aeruginosa* infection among different age groups. The male-to-female ratio among patients with *P. aeruginosa* was 1.27:1. Majority of the patients from whom *P. aeruginosa* was isolated belonged to age group 21-30 years (40%), followed by age group 31-40 years (17%) and age group 41-50 years (16%).

Table 2 shows the distribution of *P. aeruginosa* isolates among a total of 100 clinical isolates. The maximum number of *P. aeruginosa* isolates were from urine samples (49%), followed by pus samples (20%), blood samples (19%), sputum (11%) and body fluids (1%).

Table 1. Age and Sex-wise Distribution of Patients from whom 100 Isolates of *P. aeruginosa* were Taken

Age groups (years)	Male		Female		Total	
	n	%	n	%	n	%
0-10	2	3.57	5	11.36	7	7.0
11-20	9	16.07	5	11.36	14	14.0
21-30	17	30.36	23	52.27	40	40.0
31-40	11	19.64	6	13.64	17	17.0
41-50	12	21.43	4	9.09	16	16.0
51-60	3	5.36	1	2.27	4	4.0
>60	2	3.57	0	0.0	2	2.0
Total	**56**	**56.0**	**44**	**44.0**	**100**	**100.0**

Table 2. Distribution of *P. aeruginosa* Isolates Among Various Clinical Samples

Name of sample	Number of *P. aeruginosa* isolates (n)	Percentage (%) of *P. aeruginosa* isolates
Urine	49	49
Pus	20	20
Blood	19	19
Sputum	11	11
Body fluids	1	1
Total	**100**	**100**

DISCUSSION

The purpose of this study was to enhance the knowledge about this organism according to various patient-related parameters.

Nosocomial infections caused by *P. aeruginosa* are frequently life-threatening and often challenging to treat. In the current study, the rate of isolation of *P. aeruginosa* isolates from culture positive samples was 12.21%, which was lower than studies by other authors who have reported an isolation rate of 19-31.71% from all culture positive samples. This discordance may be due to implementation of better infection control measures in our hospital, like barrier precautions, frequent hand washing by hospital staff, removal of catheters at frequent intervals, regular environmental sampling from ICUs, operation theaters and wards. However, Sherertz et al have reported an isolation rate of 12.5% which was similar to current study. Gales et al and Khan et al have reported an isolation rate of 9.46% and 6.67%, respectively from culture positive samples, which was low as compared to this study. This may be due to different prevalence rates of *P. aeruginosa* isolates in different geographical areas. In addition, prevalence rate may also vary from hospital to hospital.

The present study showed maximum rate of isolation of *P. aeruginosa* isolates from urine samples (49%), followed by pus samples (20%), blood samples (19%), sputum (11%) and body fluids (1%). The results of current study were in accordance with those of a study by Pitout et al who have also reported maximum rate of isolation of *P. aeruginosa* isolates from urine samples (43%), followed by pus samples (21%) and respiratory tract samples (20%) and blood samples (7%). However, Khan et al reported maximum rate of isolation of *P. aeruginosa* isolates from pus samples (57.64%), followed by urine (24.2%) samples. The difference in rates of isolation may be due to difference in type of samples received in different laboratories.

The male-to-female ratio among the patients with *P. aeruginosa* infections in the present study was 1.27:1, which was in accordance with the study done by Sherertz et al who also reported the male-to-female ratio in patients with *P. aeruginosa* infection to be 1.3:1. Khan et al reported the male-to-female ratio among patients with *P. aeruginosa* infection to be 1.6:1. Higher incidence of infection among males in the present study was in accordance with these studies.

In the present study, the majority of patients from which *P. aeruginosa* was isolated belonged to age group 21-30 years (40%), followed by age group 31-40 years (17%) and age group 41-50 years (16%). Another study by Ruhil et al revealed the occurrence of *P. aeruginosa* infection was highest in patients aged 16-40 years. However, Mahmoud et al reported more *P. aeruginosa* infections in patients in the age group >45 years (mean) and Sherertz et al reported majority of *P. aeruginosa* infections in patients in age group 50-80 years.

CONCLUSION

This study concluded that *P. aeruginosa* was grown predominantly in urine samples, especially in young adult hospitalized patients. Hence, suspicion of *P. aeruginosa* should not be avoided, especially in northern part of India.

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New Coronavirus Variant Raises R Number by up to 0.7

The new variant of coronavirus is more transmissible than the virus's previous version, reported a study by the Imperial College, London. It further stated that the new variant increases the Reproduction or R number by 0.4 to 0.7.

The UK's latest R number is estimated at between 1.1 and 1.3, and should be below 1.0 for the number of cases to start falling. Prof Axel Gandy of London's Imperial College has stated that the differences between the virus types were quite extreme. The study suggests that the transmission of the new variant tripled during England's November lockdown while the previous version was reduced by one-third… (*BBC*)

CRC Risk in Young Adults Not as High as Previously Estimated

The risk for colorectal cancer (CRC) in young adults appears to be lower than what has been previously estimated, as previous studies did not differentiate between colorectal adenocarcinoma and carcinoid tumors, which are incidental findings, suggest experts.

New estimates for the risk of CRC in young adults, which differentiate colorectal adenocarcinoma from other types, appear in a study published in the *Annals of Internal Medicine*. The new analysis revealed that 4-20% of the lesions previously described as CRC were not adenocarcinoma but carcinoid tumors.

Investigators determined the incidence rates of early colorectal cancer, using Surveillance, Epidemiology and End Results (SEER) data from 2000 to 2016, and stratified the data by histologic subtype (primarily adenocarcinoma and carcinoid tumors), age group (20-29, 30-39, 40-49 and 50-54 years) and subsite. The absolute incidence rate in the age groups of 20-29 and 30-39 years was very low compared to 40-49 and 50-54 years age groups. The greatest changes in adenocarcinoma 3-year average annual incident rates (2000 to 2002 vs. 2014 to 2016) were for rectal-only cases in those aged 20-29 years (+39%), as well as rectal-only cases in the 30-39 years (+39%), and colon-only cases in the age group of 30-39 years (+20%)… (*Medscape*)

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Effectiveness of Home-based Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Pulmonary rehabilitation (PR) is an effective intervention for chronic obstructive pulmonary disease (COPD). However, uptake of PR is low due to patient frailty, transportation issues and access. Home-based rehabilitation has been introduced in recent years to palliate the lack of feasibility for many patients to attend traditional center-based PR programs. Hence, this study was conducted to evaluate COPD patients in home-based PR. A total of 56 patients were evaluated for 6 months' period in 4 different occasions. It was concluded that home-based PR was effective as improvement occurred in all parameters.

Keywords: Pulmonary rehabilitation, chronic obstructive pulmonary disease, noninvasive ventilation

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide. COPD is a chronic condition for which patients are using various pharmacological and nonpharmacological therapies. Pulmonary rehabilitation (PR) is one of the nonpharmacological therapies.[1] PR program can be conducted either in facility-based settings or in home-based settings. PR is an effective intervention for COPD. However, uptake of PR is low due to patient frailty, transportation issues and access.[2,3] Home-based PR program is mainly offered in severe COPD and to increase the participation rate of patients. A home-based PR program is more feasible and convenient, especially for patients with severe COPD.[4] Home-based rehabilitation has been introduced in recent years to palliate the lack of feasibility for many patients to attend traditional center-based PR programs.[5,6] Owing to its physiological and functional effects, PR has been considered unsuitable for older people with COPD, especially for those at risk of chronic respiratory failure.[4] Few studies have evaluated the effectiveness of PR in people with COPD over the age of 70, in comparison to their younger counterparts. Thus, the main aim of this study was to evaluate effectiveness of PR in patients who are either older or younger than 70 years.

MATERIAL AND METHODS

This was an observational study conducted in a private setup offering home-based PR for people with chronic respiratory disease living in central India, from September 2019 to August 2020 (6-month enrolment followed by 6 month follow-up assessment). Participants were referred to the home-based PR by their pulmonologist who diagnosed COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification system.[1] Patients who had cardiovascular disease, any contraindication to exercise training, e.g., neurological sequelae and bone and joint diseases, dementia and poorly controlled psychiatric illness, were excluded from study.[7] Participants were divided into two groups: one group included individuals aged ≤70 years, and the other one, people >70 years. The cut-off of 70 years to define the older group was chosen in accordance with the World Health Organization (WHO) report on aging and health.[8] All participants signed a written informed consent prior to the start of the program, which included their approval to use the collected data for research purposes.

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The rehabilitation team was composed of one nurse, one physiotherapist, one adapted physical activity instructor, and a weekly supervised 90-minute home session, for 8 weeks was conducted. The program included an initial educational needs assessment, endurance physical exercise training, specific daily living functional task training, strengthening and balance exercises, lower limb electrostimulation, therapeutic education, psychosocial support and motivational communication. Exercise intensity was progressively adjusted to dyspnea symptoms in order to maintain a score between 3 and 5 on the Borg 0-10 scale. Apart from the weekly visit of the team member who supervised the sessions, participants were expected to perform, on their own, personalized daily physical activities and endurance exercises training the rest of the week. Patients and team members were instructed to announce all adverse events, including study withdrawal for any reasons, hospitalization or death during PR at the 6-month follow-up.

Patients were evaluated at home at the beginning (M0), at the end of the 2 months PR program (M2) and at 4 months (M4) and 6 months (M6). The 6-minute walk test (6MWT) and the timed up-and-go (TUG) test were used to evaluate exercise tolerance and functional capacity, respectively. The psychological status and the health-related quality of life were assessed with the Hospital Anxiety and Depression (HAD) scale and the Visual Simplified Respiratory Questionnaire (VSRQ), respectively.

RESULTS

Table 1 is showing baseline characteristics of patients. From September 2019 to August 2020, total 86 patients were enrolled and referred for home PR. Among them, 14 patients refused to participate and 16 patients left the study in between the process and out of these 16 patients, 12 were aged >70 years. Thus, a total of 56 patients completed the study; out of them, 52 were male and 4 were females. Majority of patients (47) were aged <70 years and remaining (9) were >70 years. Out of 56 patients, 29 patients had comorbidities and 37 patients were categorized as severe and very severe COPD according to GOLD guidelines 2019. Among them, 25 patients were current smoker. Out of total patients, 6 patients were on long-term oxygen therapy (LTOT) and 3 patients were using noninvasive ventilation (NIV), and all of them were aged <70 years.

At baseline, the younger group had lower mean HAD total score (14.00) as compared to older group (14.56), but it was statistically nonsignificant ($p > 0.05$). Anxiety and depression scores were also lower in younger group than older group, but it was also statistically nonsignificant ($p > 0.05$). This means anxiety and

Table 1. Baseline Characteristics of Participants

Characteristics	Total group (n = 56)	≤70 years (n = 47)	>70 years (n = 9)	P value
Age (years)	63.55 ± 7.9	61.28 ± 6.35	75.44 ± 2.92	0.001
Male	52 (92.9)	43 (91.5)	9 (100.0)	0.364
Female	4 (7.1)	4 (8.5)	0 (0.0)	
Current smokers	25 (44.6)	21 (44.7)	4 (44.4)	0.353
Ex-smokers	23 (41.1)	18 (38.3)	5 (55.6)	
Nonsmokers	8 (14.3)	8 (17.0)	0 (0.0)	
LTOT	6 (10.7)	6 (12.8)	0 (0.0)	0.257
NIV	3 (5.4)	3 (6.4)	0 (0.0)	0.436
Gold stage				
Mild	4 (7.1)	3 (6.4)	1 (11.1)	0.693
Moderate	15 (26.8)	14 (29.8)	1 (11.1)	
Severe	27 (48.2)	22 (46.8)	5 (55.6)	
Very severe	10 (17.9)	8 (17.0)	2 (22.2)	
Comorbidities	29 (51.8)	21 (44.6)	8 (88.8)	0.227

depression do not depend on age of the patient and occur according to the mental condition of the patient. Similarly, VSRQ and TUG were also better in younger group than older group, but it was also statistically nonsignificant. This means VSRQ and TUG depend upon patient's lung condition and not on the age of the patient. Six-minute step test (6MST) performance, reflected by mean strokes performed was significantly better in younger group as compared to older group (337 and 285, respectively) (Table 2).

Table 3 is showing the changes in outcome of PR from baseline to end of 6 months. Both groups showed improvements in all outcomes between baseline and M2, M4 and M6. Some of patients (4) from both groups showed no improvement or even deterioration in M4 and M6 in all parameters.

Figure 1 is showing decreasing mean of total HAD score in both age groups at 2, 4 and end of 6 months and fall of HAD score was more in >70 age group ($p > 0.05$). Figures 2 and 3 are showing improvement in

Table 2. Assessments at Baseline

Baseline	Total group (n = 56)	≤70 years (n = 47)	>70 years (n = 9)	T value	P value
HAD	14.09 ± 3.53	14.00 ± 3.52	14.56 ± 3.78	0.02	0.670
Anxiety	6.41 ± 2.19	6.38 ± 2.11	6.56 ± 2.74	0.51	0.831
Depression	7.68 ± 2.29	7.62 ± 2.25	8.00 ± 2.65	1.76	0.651
VSRQ	43.86 ± 12.48	44.38 ± 12.32	41.11 ± 13.67	0.42	0.476
6MST	311 ± 53	337 ± 56	285 ± 50	2.59	0.01
TUG	20.43 ± 5.54	20.32 ± 5.58	21.00 ± 5.64	0.39	0.739

Table 3. Changes of the Outcomes in M2, M4, M6, after PR According to Age

	≤70 years			>70 years		
	M2	M4	M6	M2	M4	M6
HAD	13.28 ± 3.31	12.34 ± 3.01	11.62 ± 3.02	13.67 ± 3.35	12.89 ± 3.41	11.56 ± 2.96
Anxiety	5.89 ± 1.51	5.81 ± 1.47	5.47 ± 1.54	5.89 ± 1.54	5.44 ± 1.34	5.33 ± 1.58
Depression	7.38 ± 2.41	6.53 ± 1.96	6.15 ± 1.67	7.78 ± 2.64	7.44 ± 2.51	6.00 ± 1.50
VSRQ	51.21 ± 9.89	57.89 ± 7.23	64.89 ± 4.65	50.67 ± 11.49	57.67 ± 8.81	64.11 ± 5.28
6MST	406 ± 65	409 ± 86	448 ± 88	302 ± 56	309 ± 74	328 ± 98
TUG	17.91 ± 5.07	14.45 ± 3.65	11.55 ± 2.61	18.56 ± 4.91	15.22 ± 4.05	12.22 ± 3.15

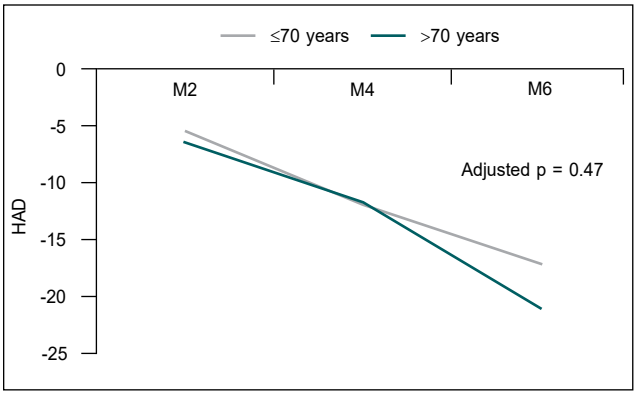

Figure 1. Mean total HAD score in both age groups at M2, M4 and M6.

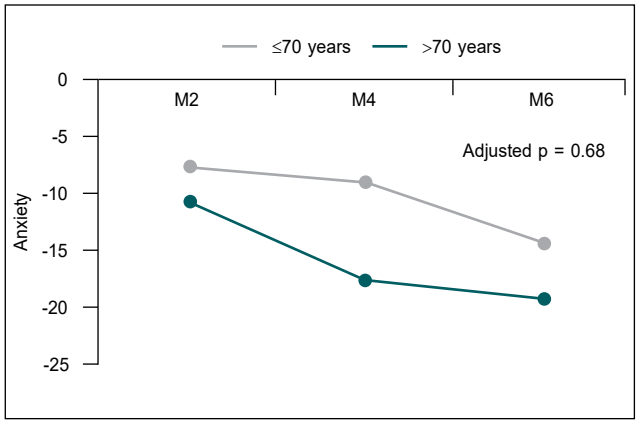

Figure 2. Change in anxiety score at M2, M4 and M6.

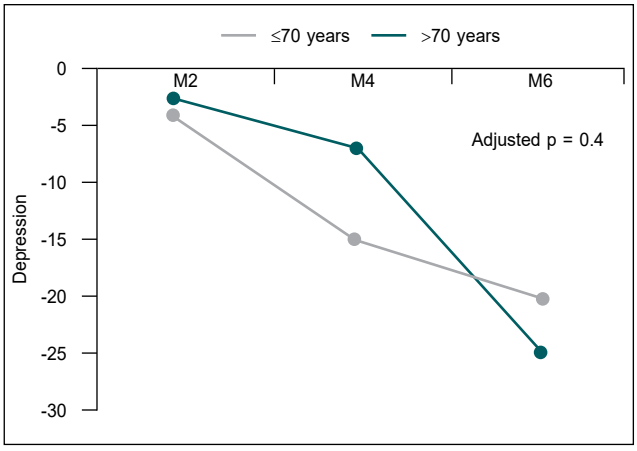

Figure 3. Change in depression score at M2, M4 and M6.

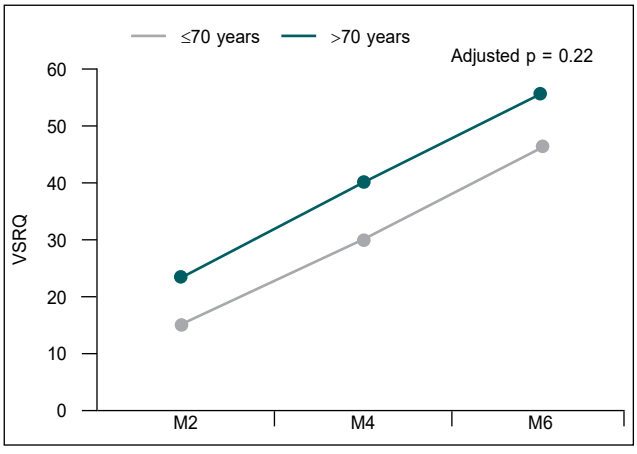

Figure 4. Change in VSRQ at M2, M4 and M6.

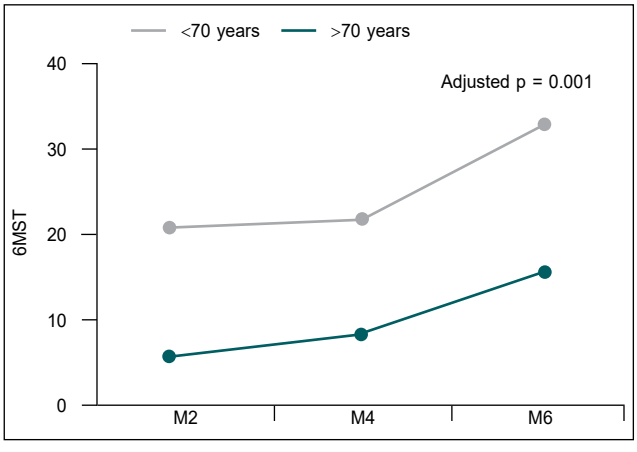

Figure 5. Change in 6MST at M2, M4 and M6.

anxiety and depression scores individually at 2, 4 and end of 6 months of PR. More improvement in anxiety was seen in older age group than younger age group ($p > 0.05$). Similarly, more improvement in depression was seen in older age group than younger age group ($p > 0.05$).

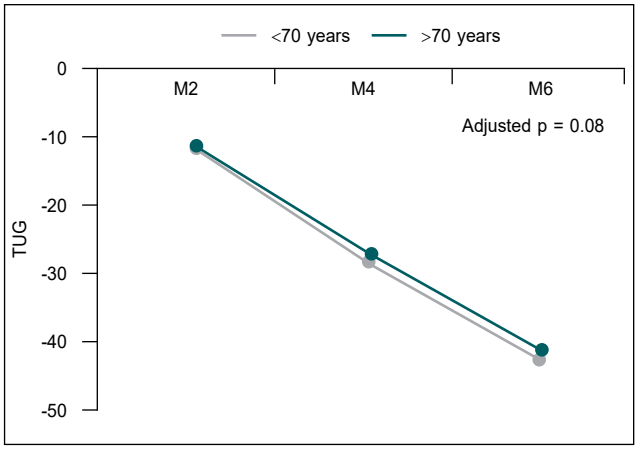

Figure 6. Change in TUG at M2, M4 and M6.

Figure 4 is showing increasing mean of VSRQ scale in both age groups, which means improvement in respiratory conditions of patients occurred in both groups ($p > 0.05$).

Figure 5 is showing increase of 6MST in both groups which indicates the mean number of strokes increased in both age groups and increment was more in younger age group than older age group ($p > 0.05$).

Figure 6 is showing decrease of TUG in both groups, which means the mean time of patient performing TUG became less from baseline to 6 months ($p > 0.05$).

DISCUSSION

The purpose of this study was to observe the effectiveness of home-based PR program at 2, 4 and end of 6 months.

Patients were categorized in two groups: age ≤70 years (younger) and >70 years (older). Out of 56 patients, 47 were in younger and remaining 9 patients were in older group. Dropouts and failure to program are common problems in older patients. In this study, less number of patients were there in older group. This was one of the drawbacks of this study. Out of 16 patients who left the study in between, 12 patients were from older group. Out of total patients, 25 (44.6%) patients were current smoker, 21 patients were from younger group and 4 patients were from older group. Smoking cessation was also prescribed before and during program as smoking can reduce fitness and the ability to perform exercises.[9] In this study, almost half (48.2%) of patients had severe COPD and remaining patients had mild (7.1%), moderate (26.8%) and very severe (17.9%) COPD. Korkmaz Ekren et al did a study and found benefits from PR for mild-to-moderate COPD and suggested that these patients should be included in PR.[10]

At baseline all scores were towards better side in younger group than older group, but they were not comparable, p value was not significant except 6MST parameter, which means younger patients attained more number of strokes than older patients. Anxiety and depression were also less in younger group than older group. A study was conducted by Gephine et al and they observed that anxiety component was high in younger group and depression component was same in both groups. Similarly, VSRQ was also comparable in both groups and TUG was higher in older group.[4] In our study, the number of patients was very less in older group. This may explain the above differences.

In our study, from baseline to end of program, improvement occurred in all parameters in both groups and more improvement occurred in total HAD score, anxiety and depression in older group. According to the study of Gephine et al, improvement was seen in all parameters in younger group but in older group improvement was present in all parameters up to initial 2 months from baseline and thereafter improvement was seen only in total HAD score, anxiety component and depression.[4] In our study, improvement in all parameters was comparable in both groups except 6MST strokes, which was lesser in older group. This difference could be due to higher age as exercise tolerance and fitness are reduced in elder persons as compared to younger individuals.

CONCLUSION

This study concluded that home-based PR was effective as improvement occurred in all parameters and improvement was significant in 6MST strokes from baseline to end of 6-month of program.

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Correlation Between Nasal Mucociliary Clearance and Peak Expiratory Flow Rate During Various Phases of Menstrual Cycle

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ABSTRACT

Nasal mucociliary clearance (NMC) time and peak expiratory flow rate (PEFR) were tested in 30 Indian healthy female volunteer medical students, 18-24 years of age, having regular menstrual cycles. NMC time was assessed by Andersen's saccharin technique. The mean values of NMC of two menstrual cycles were 10.81 ± 2.143, 8.233 ± 1.942 and 11.12 ± 2.118 in menstrual, proliferative and luteal phase, respectively. On comparing proliferative phase with menstrual and luteal phases, NMC time difference was highly significant ($p < 0.001$) and when luteal and menstrual phases were compared, results were not significant ($p > 0.05$). NMC time was significantly less in proliferative phase when compared with other two phases of menstrual cycles. Thus, various phases of menstrual cycle do have effect on nasal mucosa. This may be related to change in hormonal levels in different phases of menstrual cycle. PEFR and NMC time were measured during menstrual (2nd-4th day), proliferative (9th-12th day) and luteal phase (19th-21st day) of menstrual cycles. PEFR was measured by Wright's peak flow meter in standing position during various phases of two menstrual cycles. The mean of PEFR of two menstrual cycles was considered. On comparison of luteal and menstrual phases, the PEFR difference was found highly significant ($p < 0.001$). Similarly on comparing proliferative and luteal phases, the PEFR difference was found highly significant ($p < 0.001$). But on comparing menstrual and proliferative phases, the PEFR difference was not found significant ($p > 0.05$). When NMC and PEFR were correlated by Pearson's equation in all the three phases of menstrual cycle 1, then the correlation coefficient was found not significant in menstrual ($r = 0.330$, $p > 0.05$), proliferative ($r = 0.2499$, $p > 0.05$) and in luteal phase ($r = 0.3433$, $p > 0.05$), which showed that any increase or decrease in one parameter (NMC) is not significantly affecting other parameter (PEFR) in any phase of menstrual cycle. Similar results were found in menstrual cycle 2 and even when mean of both cycles was considered. The correlation coefficient of cycle 2 was $r = 0.3361$, $p > 0.05$ in menstrual, $r = 0.3375$, $p > 0.05$ in proliferative and $r = 0.3514$, $p > 0.05$ in luteal phase, which was not significant. The correlation coefficient of NMC and PEFR of both cycles was $r = 0.343$, $p > 0.05$ in menstrual, $r = 0.2903$, $p > 0.05$ in proliferative and $r = 0.3570$, $p > 0.05$ in luteal phase, which was also not significant.

Keywords: Menstrual cycle, menstrual phase, proliferative phase, luteal phase, NMC, PEFR

There is increased nasal obstruction in women at times of high blood estrogen levels, compared with controls, as measured by acoustic rhinometry and anterior rhinomanometry. Nasal congestion occurs along with the rise in serum estrogen levels seen at ovulation in the normal menstrual cycle. Haeggström et al found a connection between high blood estrogen levels and nasal mucosal reactivity. The study revealed that the nasal mucosa became hyperreactive to histamine in connection with ovulation, when the estrogen level in the blood reached its peak, thus suggesting some role of estrogen on nasal mucosa. Several factors and diseases like aging, smoking, lung diseases, rhinitis, irradiation, diabetes mellitus and various phases of menstrual cycle affect nasal mucociliary clearance (NMC).

Peak expiratory flow rate (PEFR) is a highly sensitive and accurate index of airway obstruction and is very useful in the diagnosis, management and follow-up of bronchial asthma and predicts the status of ventilatory lung function. PEFR can also be used as treatment scheme of asthma. PEFR is influenced by various phases of menstrual cycle. The variations in functional

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parameters of respiratory system may be related to fluctuations in the hormonal levels during various phases of menstrual cycle. PEFR is usually measured for the assessment of pulmonary functions. PEFR is maximal expiratory flow rate sustained by a subject for at least 10 msec expressed in liter per minute. PEFR has been used as measurement of ventilatory functions since long, as it is a much simpler and less exhaustive procedure compared to maximum voluntary ventilation (MVV).

MATERIAL AND METHODS

NMC time and PEFR were tested in 30 Indian healthy unmarried female volunteer medical students aged 18-24 years having regular menstrual cycles. NMC time on both sides was recorded during various phases of menstrual cycle, i.e., menstruation (2nd-4th day), follicular (9th-12th day) and luteal phase (19th-21st day), in 30 girls during two menstrual cycles. The mean of both menstrual cycles was taken as mean for calculations. Persons having anemia, common cold, nasal polyps, deviated nasal septum, chronic sinusitis, allergic rhinitis, atrophic rhinitis, chronic smokers and patients with recent nasal packings/surgery, cardiovascular and respiratory system diseases and on hormone therapy were excluded from study. Subjects were instructed to come to the laboratory on 2nd-4th day, 9th-12th day and 19th-21st day of menstrual cycles. NMC assessment was carried out during two menstrual cycles. If NMC assessment in any phase of a cycle was missed due to holiday or some other reason, then all the phases of next regular menstrual cycle were considered. NMC was assessed by Andersen's saccharin method in the present study. Saccharin test can be used for serial measurements during treatment, although it should be repeated only after the sweet taste has completely disappeared. A 1 mm particle of saccharin was placed on the floor of the nose approximately 1 cm behind the anterior end of inferior turbinate under direct vision with the subject in sitting position. They were asked to swallow at about every 30 seconds and to report the first change in their sensation of taste. The test was carried out in both the nostrils and the mean of the two was taken as mucociliary clearance time. This was done to obviate the effect, if any, of nasal cycle on the mucociliary clearance time. The time taken by the subjects from placement of particle to perception of sweet taste was recorded as the NMC time in minutes. All subjects were tested in similar environmental conditions and were instructed not to inhale or exhale forcefully, sniff, eat or drink and avoid coughing and sneezing during that time. Whenever there was coughing or sneezing, then the test was repeated.

The same subjects on which NMC was tested were instructed to come to the laboratory on 2nd-4th day, 9th-12th day and 19th-21st day of menstrual cycles to record PEFR. Recordings were carried out during two menstrual cycles. When recording during any phase of a cycle was missed due to holiday or some other reason, then all the phases of next menstrual cycle were considered. Wright's peak flow meter is widely used to measure the PEFR values. PEFR was recorded by Wright's peak flow meter by connecting subject with the help of mouthpiece. The recording scale was up to 1,000 L/min. The subject performed the test in standing position by holding peak flow meter properly. The subject was asked to take a deep breath and then to exhale it by forceful expiration as fast as possible after maintaining air tight seal between lips and mouthpiece of instrument. Maximum of three readings of PEFR was considered. PEFR was recorded in all phases of two menstrual cycles.

Data were analyzed by repetitive ANOVAs for comparison between all three phases of menstrual cycle and results were expressed in mean ± SD (standard deviation) and correlation between NMC and PEFR was done by Pearson's equation.

OBSERVATIONS AND RESULTS

Nasal Mucociliary Clearance

The mean values of NMC time in minutes in cycle 1 were 10.63 ± 2.23 , 8.258 ± 2.116 and 10.94 ± 2.208 in menstrual, proliferative and luteal phases, respectively while the mean values of NMC time in cycle 2 were 10.98 ± 2.107, 8.209 ± 1.795 and 11.3 ± 2.101 in menstrual, proliferative and luteal phases, respectively. When both cycles were considered, the mean values of NMC time were 10.81 ± 2.143, 8.233 ± 1.942 and 11.12 ± 2.118 in menstrual, proliferative and luteal phases, respectively (Table 1). It was found that there was significant decrease in NMC time in proliferative phase as compared to luteal and menstrual phases. On comparing menstrual with proliferative phase and proliferative with luteal phases, the NMC time difference was found highly significant ($p < 0.001$) in the two individual menstrual cycles as well as the mean of two cycles. But on comparing luteal with menstrual phases, the NMC time difference was found not significant ($p > 0.05$) in the two individual menstrual cycles as well as the mean of two cycles (Table 2).

Table 1. NMC Time Values (Minutes) among Various Phases of Menstrual Cycles

Cycles	Menstrual phase (2nd-4th day)	Proliferative phase (9th-12th day)	Luteal phase (19th-21st day)
Cycle 1	10.63 ± 2.23	8.258 ± 2.116	10.94 ± 2.208
Cycle 2	10.98 ± 2.107	8.209 ± 1.795	11.3 ± 2.101
Both cycles	10.81 ± 2.143	8.233 ± 1.942	11.12 ± 2.118

Mean ± SD

Table 2. Comparison of NMC Time among Various Phases of Menstrual Cycles

Cycles	Menstrual vs. proliferative	Proliferative vs. luteal	Luteal vs. menstrual
Cycle 1	P < 0.001	P < 0.001	P > 0.05
Cycle 2	P < 0.001	P < 0.001	P > 0.05
Both cycles	P < 0.001	P < 0.001	P > 0.05

P < 0.001= Highly significant, p > 0.05 = Not significant.

Table 3. PEFR (Liters/Min) in Various Phases of Menstrual Cycles

Cycles	Menstrual phase (2nd-4th day)	Proliferative phase (9th-12th day)	Luteal phase (19th-21st day)
Cycle 1	335.0 ± 32.88	342.2 ± 32.53	381.2 ± 26.51
Cycle 2	336.7 ± 29.63	338.7 ± 28.74	387.0 ± 26.80
Both cycles	335.8 ± 30.85	340.4 ± 29.73	384.1 ± 26.41

Mean ± SD

Table 4. Comparison of PEFR among Various Phases of Menstrual Cycles

Cycles	Menstrual vs. proliferative	Proliferative vs. luteal	Luteal vs. menstrual
Cycle 1	P > 0.05	P < 0.001	P < 0.001
Cycle 2	P > 0.05	P < 0.001	P < 0.001
Both cycles	P > 0.05	P < 0.001	P < 0.001

P < 0.001= Highly significant, p > 0.05 = Not significant.

Peak Expiratory Flow Rate

The mean values of PEFR in cycle 1 were 335.0 ± 32.88, 342.2 ± 32.53 and 381.2 ± 26.51 in menstrual, proliferative and luteal phases, respectively while mean values of PEFR in cycle 2 were 336.7 ± 29.63, 338.7 ± 28.74 and 387.0 ± 26.80 in menstrual, proliferative and luteal phases, respectively. When both cycles were considered the mean PEFR values were 335.8 ± 30.85, 340.4 ± 29.73 and 384.1 ± 26.41 in menstrual, proliferative and luteal phases, respectively (Table 3). PEFR was found significantly increased in luteal phase as compared to menstrual and proliferative phase in the two individual menstrual cycles as well as the mean of two cycles. On comparison of luteal and menstrual phases, the PEFR difference was found highly significant ($p < 0.001$) in the two individual menstrual cycles as well as the mean of two cycles. Similarly on comparing proliferative and luteal phases, the PEFR difference was found highly significant ($p < 0.001$) in the two individual menstrual cycles as well as the mean of two cycles. But on comparing menstrual and proliferative phases, the PEFR difference was not found significant ($p > 0.05$) in the two individual menstrual cycles as well as the mean of two cycles (Table 4).

Correlation of NMC and PEFR in Various Phases of Menstrual Cycles

When NMC and PEFR were correlated in all the three phases of menstrual cycle 1, the correlation coefficient was not significant in menstrual ($r = 0.330$, $p > 0.05$),

Table 5. Correlation of NMC and PEFR in Various Phases of Menstrual Cycles

Cycle	Menstrual phase	Proliferative phase	Luteal phase
Cycle 1	r = 0.3307	r = 0.2499	r = 0.3433
	r^2 = 0.1094	r^2 = 0.06243	r^2 = 0.1178
	P = 0.0743	P = 0.183	P = 0.0633
Cycle 2	r = 0.3361	r = 0.3375	r = 0.3514
	r^2 = 0.113	r^2 = 0.1139	r^2 = 0.1235
	P = 0.0694	P = 0.0682	P = 0.0569
Both cycles	r = 0.3437	r = 0.2903	r = 0.3570
	r^2 = 0.1181	r^2 = 0.08425	r^2 = 0.1274
	P = 0.0630	P = 0.1197	P = 0.0528

R = Pearson's r, p > 0.05 = Not significant.

proliferative (r = 0.2499, p > 0.05) and in luteal phase (r = 0.3433, p > 0.05), which showed that any increase or decrease in one parameter (NMC) is not significantly affecting the other parameter (PEFR) in any phase of menstrual cycle. Similar results were found in cycle 2 and even when mean of both cycles were considered. The correlation coefficient of cycle 2 was r = 0.3361, p > 0.05 in menstrual, r = 0.3375, p > 0.05 in proliferative and r = 0.3514, p > 0.05 in luteal phase, which was not significant. The correlation coefficient of NMC and PEFR of both cycles was r = 0.343, p > 0.05 in menstrual, r = 0.2903, p > 0.05 in proliferative and r = 0.3570, p > 0.05 in luteal phase which was also not significant (Table 5).

DISCUSSION

Menstrual cycle is an integral part of female reproductive system which reflects a complex interplay between brain, pituitary gland and ovary. Menstrual cycle occurs in three phases, i.e., menstrual, follicular and luteal. The mean menstrual cycle is of 28 days. Levels of hormones in the three phases of menstrual cycle are fluctuating. This fluctuation in sex hormones plays a major role in virtually all physiological processes and hence affects various systems of human body. In our study, we studied the effect of different phases of menstrual cycle on NMC and PEFR and their correlation. There is a connection between symptoms such as nasal stuffiness and coryza and hormonal variations in pregnancy, use of contraceptives and menstrual cycle phases. Andersen et al described saccharin test, which is a simple and reproducible clinical test for determining abnormal NMC. Deborah et al also emphasized that saccharin test is a simple, inexpensive and noninvasive method, while methods using radiolabeled particles are time consuming, inconvenient and expensive.

The mechanism of action of sex steroid hormones is via their own unique receptors: estrogen receptor (ER-α and ER-β), progesterone receptor (PR-A and PR-B) and an androgen receptor. Estradiol binds with a higher affinity to ER than its metabolic products such as estrone and estriol. It is known that estrogen and progesterone receptors have a role in sexual development. However, their effect beyond the reproductive system is becoming increasingly recognized. The ER-α, ER-β, PR-A and PR-B receptors are expressed in rats, mice and humans. Androgen receptors are expressed primarily in mammalian reproductive tissues. ER-α, ER-β, PR-A and PR-B expression have been found not only in the mammalian female and male reproductive tracts, but also in the female mammary glands, bone, cardiovascular tissues, lung, brain and nasal mucosa.

Among the factors influencing NMC, the most important is acetylcholine (Ach), a vasodilator neurohumoral transmitter secreted at somatic and autonomic sites under normal and physiological conditions. Most of the Ach is present in the ionic solution within the synaptic vessels but some is also found in free form in the cytoplasm of cholinergic nerve endings. It is destroyed by enzyme acetylcholinesterase. Muscarinic receptors are believed to play an important role in modulation of ciliary action in respiratory system's activity. The cryostimulation by methacholine in human upper airway mucosa involves M1- and M3-muscarinic receptor subtypes, but not the M2-receptor subtype. Aerosolized methacholine stimulated the ciliary beat frequency (CBF) from the baseline of 5.8 ± 0.7 to 9.4 ± 3.0 Hz. The hypothalamic

stimulus that leads to release of female hormones also releases Ach in nasal mucosa. The hormones are selectively concentrated in nasal mucosa almost 1,000-fold and inhibit acetylcholinesterase, hence increasing local concentration of acetylcholine that leads to increase in vasomotor reaction and thus mucociliary clearance. Acetylcholine itself increases CBF while atropine causes the reduction in the secretion of the nose and hence depresses the CBF. A study was done on dogs to find stimulation of CBF by autonomic agonists *in vivo*. It was assumed that increase in autonomic activity would result in increase in CBF *in vivo*. It was found that CBF in the lower respiratory tract is regulated by autonomic agonists. This was perhaps due to effect of estrogen on autonomic system.

Toppozada et al, through their studies on humans, demonstrated that the morphological and histochemical changes occurring in the nasal mucosa were associated with estrogen in healthy fertile women during the menstrual cycle. Navarrete-Palacios et al did cytological analysis in different phases of the menstrual cycle which revealed that both nasal and vaginal smear showed the same characteristics, suggesting that cell turnover in the nasal epithelium is influenced by hormonal state during the menstrual cycle. Serra et al studied 88 women with ovulatory menstrual cycle, who underwent nasal sampling with a cytobrush of the middle and inferior nasal turbinates under direct vision during the follicular, periovular and luteal phases of the menstrual cycle. Hematoxylin-eosin staining revealed the cytological characteristics of the nasal respiratory epithelium and of vaginal smears correlated according to the three different phases of the menstrual cycle, suggesting that the vaginal cells as well as the nasal respiratory epithelium is an ovarian steroid target. Millas et al evaluated the presence of specific estrogen receptors (α and β) in the inferior turbinate of asymptomatic patients, in order to characterize the influence of hormones on physiology and pathological nasal processes and showed the presence of α and β receptors, with higher β expression and higher intensity in the anterior portion of the inferior turbinate.

Shirasaki et al studied nasal mucosa by using immunohistochemistry and observed antibodies to glucocorticoid receptor (GR) that showed the presence of GR within all cells of nasal mucosa, with the highest quantities of GR being localized in epithelial cells, submucosal glands and inflammatory leukocytes. Immunohistochemical analysis of sex steroid receptor demonstrated anti-ERα antibody labeled mast cells and anti-ERβ antibody labeled submucosal glands, showing the presence of ERα and ERβ but no progesterone receptor or androgen receptors.

Armnostone et al studied nasal mucociliary transport time using the vegetable charcoal powder technique. Three measurements were made at different points of the cycle, i.e., during the early follicular phase, periovulatory phase and luteal phase. Transit was found to be significantly accelerated during the periovulatory phase ($p < 0.01$), when the serum estrogens are at their highest. In our study, we found almost same results by using saccharin method. Transit was significantly accelerated during the proliferative phase ($p < 0.01$).

Littlejohn et al studied NMC in both the congested and decongested phases of the cycle. The results were statistically significant and suggested a difference in NMC between the two phases of cycle, with the congested phase having more rapid clearance.

Stübner et al reported that for influencing the neurogenic nasal symptoms, higher hormone concentrations seem to be necessary than those achieved after administration of oral contraceptives.

Haeggström et al found a connection between high blood estrogen levels and nasal mucosal reactivity. They found that the nasal mucosa became hyperreactive to histamine during ovulation, when the blood level of estrogen reached its peak suggesting some role of estrogen on nasal mucosa. Philpott et al also found some association between nasal symptoms and blood estrogen levels. It was observed that there was increased nasal obstruction in women at times of high blood estrogen levels when compared with a control group by using acoustic rhinometry, anterior rhinomanometry and measurements of peak inspiratory nasal flow. It was due to nasal congestion at the periovulatory stage of the cycle, of which anterior rhinomanometry and mucociliary time were decreased significantly ($p < 0.05$). Nasal congestion thus occurs in association with the rise in serum estrogens occurring at ovulation in the normal menstrual cycle. So, it was suggested that pharmacological antagonism of estrogens may alleviate nasal congestion and should be further explored.

Nappi et al found that both intranasal and transdermal hormonal therapy (HT) with 17-β estradiol improved nasal symptomatology and nasal mucosa appearance and reduced mean mucociliary transport time.

Soylu et al studied, in premenopausal and postmenopausal women, the mean NMC time and found that in postmenopausal women, the mean NMC time was significantly longer than in premenopausal women ($p < 0.0001$). There was a positive correlation

between menopause duration and NMC time in postmenopausal women ($p < 0.0001$).

These studies are at par with our study which showed that there was significant decrease in NMC time in proliferative phase as compared to luteal and menstrual phases. On comparing menstrual and proliferative phases, the NMC time difference was found highly significant ($p < 0.001$). Similarly on comparing luteal and proliferative phases, the NMC time difference was found highly significant ($p < 0.001$). But on comparing menstrual and luteal phases, the NMC time difference was not found significant ($p > 0.05$).

Changes in lung function have been reported in different phases of menstrual cycle owing to action of hormone progesterone. Some studies showed that phases of menstrual cycle and individual cycles had no significant effect on spirometry variables except for peak expiratory flow and respiratory static pressures. The correlations observed between sex hormones and respiratory control variables hint at a positive influence of female sex hormones controlling the thoracic pump muscles in luteal phase. According to a study, the pulmonary functions qualified as lung volumes and capacities were better during luteal phase of the menstrual cycle, pointing to a possible beneficial role of progesterone in management of premenstrual asthma.

PEFR and forced expiratory volume in 1 second (FEV_1) have been reported to be increased in luteal phase ($p < 0.05$) and this increase in PEFR and FEV_1 is suggestive of decreased airway resistance. Lower PEFR and slow vital capacity (SVC) in postmenopausal women in comparison to premenopausal women during follicular and luteal phase are most likely due to decreased level of progesterone and estrogen. Reduced levels of estrogen and progesterone would increase compression of thoracic spine, decrease the relaxation of bronchial smooth muscle and decrease muscular strength, thus resulting in decreased level of forced expiratory flow (FEF_{25-75}), PEFR and SVC.

Another study showed significantly higher serum progesterone and forced vital capacity (FVC), FEV_1 and PEFR during secretory phase and a strong positive correlation of serum progesterone in secretory phase with FVC and negative correlation with FEV_1%. The improvement of pulmonary function during secretory phase was related with increase in serum progesterone levels which have a dual effect of overall smooth muscle relaxation and hyperventilation. But some other studies showed that although there was increase in FEV_1 and FVC in secretory phase which may be due to domination of estrogen in follicular phase which in turn increases the resting minute volume in secretory phase, but, there was no significant difference when PEFR was compared in different phases of menstrual cycle.

A study was conducted to ascertain the effect of normal physiological fluctuation of serum progesterone on PEFR. PEFR% was higher in luteal phase as compared to follicular phase of premenopausal women, and the relationship was significant ($p < 0.01$, $r = 0.995$). Thus, it was suggested that the normal cyclical progesterone hormone level should be considered while interpreting PEFR%.

Similarly, in our study also, PEFR was significantly higher in luteal phase than proliferative phase. Both exogenous progesterone and estradiol administration have been reported to improve asthma in women. In a few patients, intramuscular supplementary progesterone eliminated the premenstrual fall in PEFR and allowed better control of asthma as lower concentration of progesterone in premenopausal phase may be a possible mechanism for premenstrual asthma.

In our study, PEFR was found significantly increased in luteal phase as compared to menstrual and proliferative phase in the two individual menstrual cycles as well as the mean of two cycles ($p < 0.001$).

In our study, no correlation was observed between NMC and PEFR in three phases of menstrual cycle. Review of English literature on NMC and PEFR did not reveal any reported study on correlation of NMC and PEFR. It needs to be elucidated by further studies.

CONCLUSION

NMC time was found significantly decreased in proliferative phase while PEFR was significantly increased in luteal phase of normal menstrual cycle in young healthy females. There was no correlation between NMC and PEFR during various phases of normal menstrual cycles.

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■■■■

WHO Issues Its First Emergency Use Validation for a Vaccine Against COVID-19

The WHO has listed the Pfizer-BioNTech COVID-19 mRNA vaccine for emergency use, thus making it the first one to be given emergency validation by the agency.

This Emergency Use Listing (EUL) will enable countries to speed up their own regulatory approval processes for import and administration of the vaccine. It will also allow UNICEF and the Pan-American Health Organization to procure the vaccine for distribution to countries in need. Dr Mariângela Simão, WHO Assistant-Director General for Access to Medicines and Health Products, called it a positive move towards ensuring global access to COVID-19 vaccines and emphasized on the need for greater effort to attain enough vaccine supply to meet the demands of priority populations across the globe… (*WHO*)

Microvascular Injury of Brain, Olfactory Bulbs Noted in COVID-19

Multifocal microvascular injury in the brain and olfactory bulbs appears to be a possible adverse outcome from COVID-19, suggests new research published online December 30 as a "correspondence" in the *New England Journal of Medicine*.

Postmortem magnetic resonance imaging (MRI) brain scans of 13 patients who died from COVID-19 exhibited abnormalities in 10 participants. Nine of these had punctate hyperintensities, representing areas of microvascular injury and fibrinogen leakage, suggested the investigators. Immunostaining demonstrated thinning of the basal lamina in 5 of these patients. Additional evaluation revealed punctate hypointensities linked to congested blood vessels in 10 patients. These areas were interpreted as microhemorrhages. There was no evidence of viral infection, including SARS-CoV-2… (*Medscape*)

Gabapentinoids *plus* Opioids Increase Overdose Risk After Surgery

Gabapentinoids, gabapentin or pregabalin, added to opioids the day of surgery appeared to heighten the risk of opioid overdose and other adverse events, though absolute risks appeared to be low, reported an observational study.

In the study of nearly 5.5 million surgical admissions, including around 9,00,000 patients who received gabapentinoids with opioids, 441 overdose events were recorded. Absolute risk of overdose was 1.4 per 10,000 patients with gabapentinoid exposure and 0.7 per 10,000 patients with opioids only, reported researchers in *JAMA Network Open*. After propensity score trimming, adjusted HR for opioid overdose was 1.95 (95% CI 1.49-2.55) and the number needed to treat for an additional overdose to occur was 16,914 patients (95% CI 11,556-31,537)… (*Medpage Today*)

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
Geeta Anand
Dr Uday Kakroo
Harish Malik
Aarti Upadhyay
Raj Kumar Daga
Shalin Kataria
Anisha Kataria
Vishnu Sureka
Rishab Soni

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

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

http://heartcarefoundationfund.heartcarefoundation.org

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A Demographic and Etiological Study of Dyspepsia Patients Presenting to a Rural Hospital in South-West Rajasthan

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ABSTRACT

Introduction: Dyspepsia is one of the most common complaints of patients coming to a hospital causing great economic and social burden over a society. A proper understanding of its causes in a specific region can greatly help in reducing the cost of healthcare and in increasing productivity. **Material and methods:** A total of 128 patients were included in the study. Proper history-taking, physical examination and relevant investigations including upper gastrointestinal endoscopy (UGIE) + rapid urease test (RUT) and ultrasound abdomen were done to evaluate the causes of dyspepsia. Rome III diagnostic criteria-based questionnaire was used to find out functional dyspepsia. **Results:** Amongst the various causes of dyspepsia, gastroduodenitis was the most common cause of dyspepsia (89%), out of which 77.2% were *Helicobacter pylori* positive, and as many as 22.8% were *H. pylori* negative. On the other hand, of all the patients who were *H. pylori* positive (total 91 patients, i.e., 71.1%), 96.7% (88 out of 91) patients had gastroduodenitis and/or peptic ulcer disease. Functional dyspepsia was found only in 8.6% patients. Majority of patients (60.2%) consumed drinking water from reverse osmosis supply. UGIE could lead to a definitive diagnosis in as many as 91.5% cases. **Conclusion:** In the South-West Rajasthan region, *H. pylori* infection has a strong correlation with gastroduodenitis and peptic ulcer disease although all gastroduodenitis patients may not be *H. pylori* positive. Functional dyspepsia is not a very common entity in this region. In our study, reverse osmosis water seems to provide no protection from dyspepsia.

Keywords: Dyspepsia, *Helicobacter pylori*, South-West Rajasthan, UGIE, RUT

Dyspepsia is one of the most common complaints of patients coming to a hospital. Dyspepsia is derived from the Greek words *dys* and *pepse* and literally means "Difficult Digestion". It is broadly defined as pain or discomfort centered in the upper abdomen with symptoms such as epigastric pain, postprandial fullness, early satiety, anorexia, belching, nausea and vomiting, upper abdominal bloating and even heartburn and regurgitation. Prevalence of dyspepsia is about 20-40% worldwide. A study from India reported the prevalence of dyspepsia to be 30.4%. In another multicentric study from India, prevalence of dyspeptic symptoms was found to be as high as 49%. Dyspepsia is caused by a wide variety of etiologies, ranging from organic to functional. Functional dyspepsia is a more challenging problem and difficult to diagnose and manage. Rome diagnostic criteria are useful to identify functional dyspepsia. To reach correct diagnosis, one needs to choose appropriate diagnostic modality on the basis of symptoms and clinical examination of the patient. Ultrasound examination of the abdomen and upper gastrointestinal endoscopy (UGIE) with rapid urease test (RUT) for *Helicobacter pylori* are important diagnostic tools used to evaluate the causes of dyspepsia. It has been shown that gastric *H. pylori* infection is associated with dyspeptic symptoms. Eighty percent of Indian adults have antibodies against *H. pylori* in their sera.

No Indian study is available to show the health-related quality of life in relation to dyspepsia. Studies from other countries showed that functional dyspepsia is associated with substantial impairment of quality of life, work absenteeism, reduced productivity and use of

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healthcare resources with consequent economic burden. Considering high prevalence of dyspepsia in Indian population, socioeconomic burden of this disease in Indian population is expected to be enormous. Studies are needed on this issue in Indian population.

Dyspepsia may be costing society £1 billion each year in the UK. Thus, dyspepsia is a huge clinical and economic burden and cost-effective management strategies and treatments are urgently required. Overall, dyspepsia is costing society £21 per person per year.

MATERIAL AND METHODS

Ethics

The study was approved by the Ethical Committee of JW Global Hospital and Research Centre. Informed consent from all the participants was taken.

Study Design

This is a prospective, cross-sectional, observational study of dyspepsia in terms of its demographic and etiological distribution amongst the patients presenting to a rural hospital in South-West Rajasthan. The sample size for this study was calculated taking 50% prevalence from a multicentric study from India with 10% precision level and 95% confidence level; the sample size derived was 96. We included all patients coming to JW Global Hospital and Research Centre, Mount Abu, Rajasthan with complaint of dyspepsia during 18 months period between September 2016 and March 2018. A total of 128 patients were registered with their due informed consent; thorough physical examination with basic investigations (complete blood count [CBC], urine examination, stool examination, abdomen ultrasound, UGIE and RUT for *H. pylori*) were done to evaluate causes of dyspepsia.

Rome III diagnostic criteria-based questionnaire was used to make a diagnosis of functional dyspepsia in cases where no organic pathology was found.

Statistics

Data analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program.

RESULTS

A total of 128 adults were registered in the study. The socio-demographic profile has been presented in Table 1. Dyspepsia was more common in young patients between the age group of 18-45 years (59.4%). Minor female predominance in patients presenting with dyspepsia (54.7%) was observed. In our study, most of the patients (47.7%) were in the body mass index (BMI) range of 18.5-24.9. Dyspepsia was equally distributed in primary educated (35.2%) and graduates (33.6%). No significant relation was observed between dyspepsia and the household income. Majority of patients (64.1%) in our study population gave positive family history of dyspepsia. Majority of patients (60.2%) consumed drinking water from reverse osmosis supply. In our study, epigastric burning was the commonest chief complaint of patients (82.8% patients). Majority of patients (57%) from our study population gave anxiety/depressive disorder as history of past illness.

Gastritis and duodenitis together accounted for the highest number of cases with dyspepsia (114 out of 128, i.e., 89%). Gastritis was the most common cause of dyspepsia in 88.3% patients, gastroesophageal reflux

Table 1. Socio-demographic Profile of Participants

Age	Frequency	Percent
18-30	34	26.6
31-45	42	32.8
46-60	30	23.4
>60	22	17.2
Mean ± SD	43.406 ± 16.13	
Gender		
F	70	54.7
M	58	45.3
Educational qualification		
Illiterate	15	11.7
Primary education	45	35.2
Secondary education	22	17.2
Graduation/PG	43	33.6
Professional	3	2.3
Drinking water source		
Village well	6	4.7
Government supply	27	21.1
Hand pump	4	3.1
Borewell	14	10.9
Reverse osmosis	77	60.2
Consumed/Nonconsumed	Mean ± SD	55.92 ± 72.58

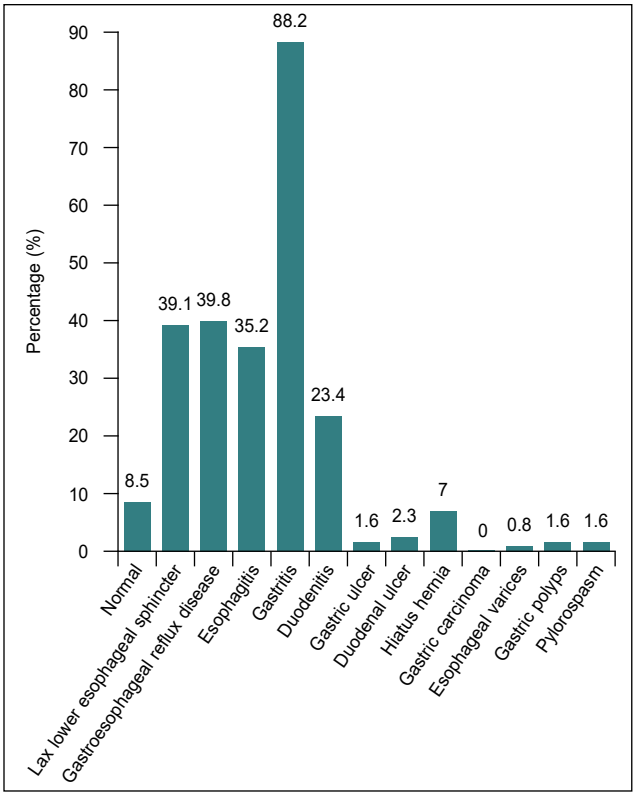

Figure 1. Upper GI Endoscopy findings in our study population.

disease (GERD) in 39.8% patients, esophagitis in 35.2%, duodenitis in 23.4%, urolithiasis in 13.3%, functional dyspepsia in 8.6%, hiatus hernia in 7%, duodenal ulcer in 2.3%, anemia in 2.3%, gastric ulcer in 1.6%, intestinal parasites in 1.6%, cholelithiasis in 1.6%, gastric polyps in 1.6%, irritable bowel syndrome in 0.8%, cholelithiasis with cholecystitis in 0.8%. Functional dyspepsia was found in 8.6% patients only (Figs. 1 and 2).

About 71.1% of total dyspepsia patients were *H. pylori* positive; while 28.9% patients were *H. pylori* negative (Fig. 3). Amongst gastroduodenitis and peptic ulcer patients 77.2% were *H. pylori* positive and 22.8% were *H. pylori* negative (Table 2). About 77.2% (88 out of 114) of total dyspepsia patients with a positive UGIE findings for gastroduodenitis and peptic ulcer were also positive for *H. pylori* ($p < 0.001$), stressing upon a positive correlation between the two; but, at the same time, indicating towards the varied etiology of the disease. Amongst *H. pylori* positive dyspepsia patients, 96.7% developed gastroduodenitis and peptic ulcer, and 3.3% did not develop gastroduodenitis and peptic ulcer (Table 3). There is statistically significant correlation between the *H. pylori* infection and development of gastroduodenitis and peptic ulcer as 96.7% (88 out of 91) of *H. pylori* positive patients developed gastroduodenitis and peptic

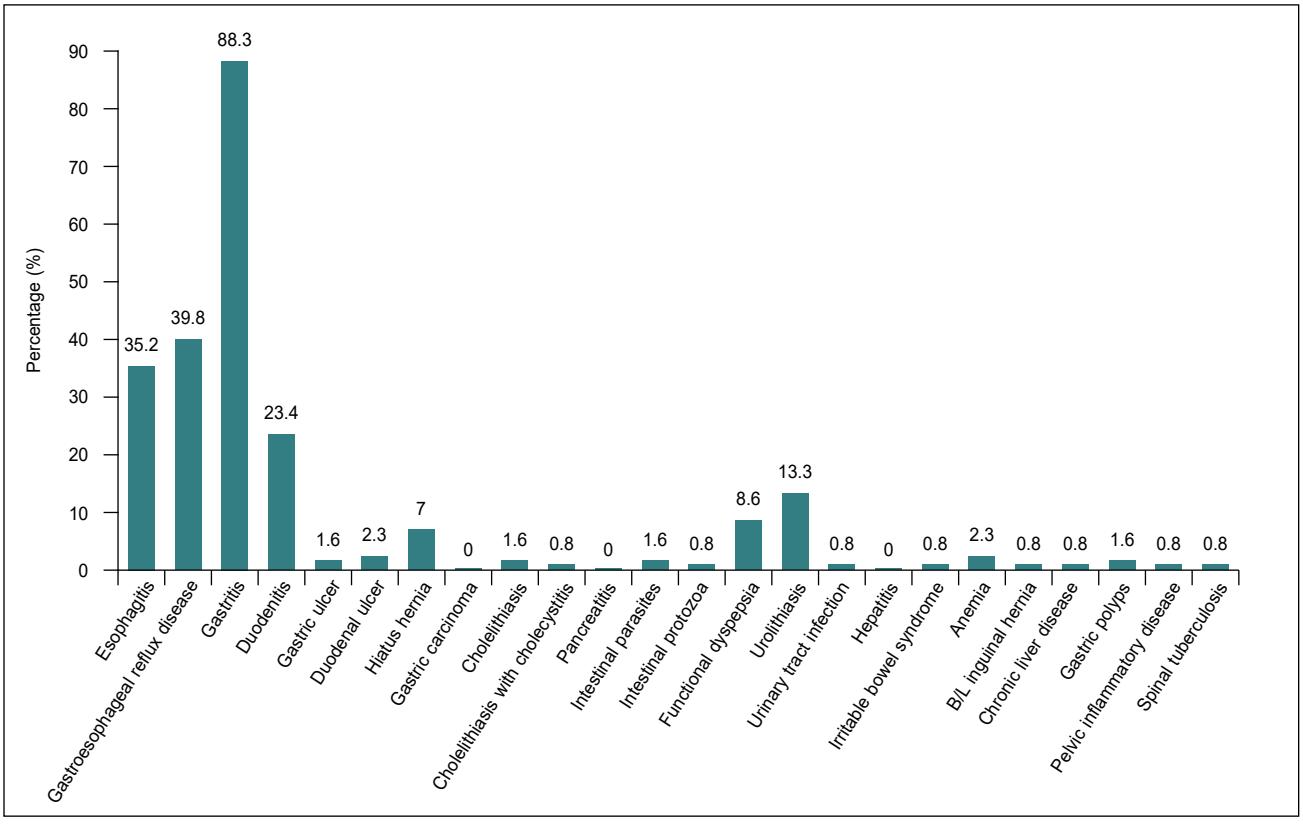

Figure 2. Various causes of dyspepsia in our study population.

ulcer ($p < 0.001$). The remaining 3.3%, although did not have frank gastroduodenitis and peptic ulcer, but had esophagitis and GERD. In other words, 100% *H. pylori* positive patients had some positive UGIE findings.

DISCUSSION

In our study, we observed that in all dyspepsia patients, the most common UGIE finding was gastritis in 88.2% patients. Ayana and colleagues also found gastritis as the most common endoscopic finding in 61.10% patients.

Amongst the various causes of dyspepsia, in our study, gastroduodenitis was found to be the most common cause of dyspepsia, i.e., 89%; out of which, 77.2% of our patients were *H. pylori* positive, and as many as 22.8% were *H. pylori* negative. On the other hand, of all the patients who were *H. pylori* positive (total 91 patients, i.e., 71.1%), 96.7% (88 out of 91) patients had gastrodudenitis and/or peptic ulcer disease. This illustrates that although majority of *H. pylori*-infected patients would have gastroduodenitis, but all patients with gastroduodenitis may not be *H. pylori* positive.

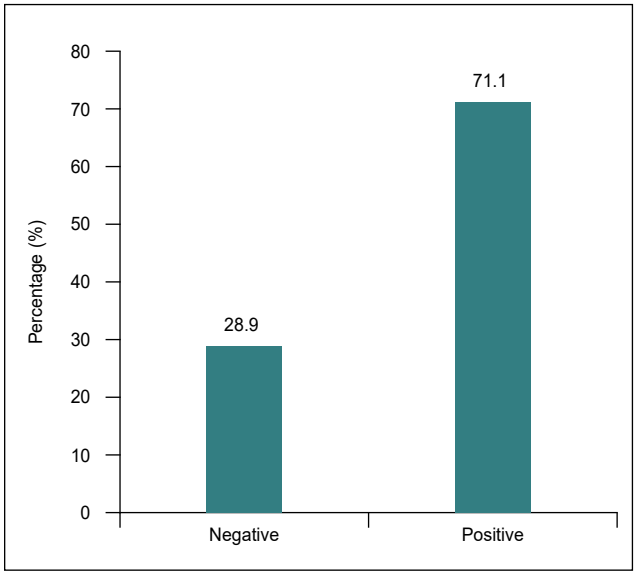

Figure 3. RUT for *H. pylori* results in our study population.

In a study by Adlekha et al, RUT for *H. pylori* was positive in 57.7% cases, the commonest identifiable lesion at endoscopy was gastritis (69%). The correlation of endoscopic abnormality with *H. pylori* infection was statistically highly significant ($p < 0.01$). In a study by Srinivasan and colleagues also, there was a high prevalence of *H. pylori* infection (51.7%). Studies from India show that the prevalence of *H. pylori* is as high as 80%. In the study by Ayana et al, *H. pylori* infection was detected in 65% of patients. Gastritis and duodenal ulcer were statistically significantly associated with *H. pylori* ($p < 0.001$).

In our study, majority of patients (60.2%) consumed drinking water from reverse osmosis supply. This seems confusing as, on one hand, several studies relate *H. pylori* infection to be directly related to the quality of drinking water, while some others prove a correlation of gastroduodenitis and peptic ulcer with reverse osmosis water. Klein and coworkers first suggested water as a source of *H. pylori* infection, who observed that Peruvian children with an external source of drinking water were more likely to be infected with *H. pylori* than children

Table 2. Relation of Gastroduodenitis and Peptic Ulcer with RUT for *H. pylori* in Our Study Population

		RUT for *H. pylori*		Total	P value
		Negative	Positive		
Gastritis/Duodenitis/Gastric ulcer/ Duodenal ulcer	Absent	11 (78.6)	3 (21.4)	14 (100)	<0.001 (S)
	Present	26 (22.8)	88 (77.2)	114 (100)	
Total		**37 (28.9)**	**91 (71.1)**	**128 (100)**	

Table 3. Relation of RUT for *H. pylori* with Gastroduodenitis and Peptic Ulcer in Our Study Population

		Gastritis/Duodenitis/Gastric ulcer/Duodenal ulcer		Total	P value
		Absent	Present		
RUT for *H. pylori*	Negative	11 (29.7)	26 (70.3)	37 (100)	<0.001 (S)
	Positive	3 (3.3)	88 (96.7)	91 (100)	
Total		**14 (10.9)**	**114 (89.1)**	**128 (100)**	

with an internal source. A study conducted in India indicated that sewage and sanitary workers experience a high risk of *H. pylori* infection. A study conducted by Lutai in Russian population found the area supplied with water lower in minerals, like RO water, was associated with gastric and duodenal ulcers, chronic gastritis and cholecystitis.

May be clean drinking water is preferable to RO water as far as protection against dyspepsia is concerned. So we recommend using clean drinking water (boiled/filtered/obtained from reliable clean source) instead of reverse osmosis water. For a proper diagnosis of the cause of dyspepsia, UGIE with RUT seems to be the most efficient tool to rule out organic causes, and Rome III criteria for functional dyspepsia.

The limitation of this study is that it is confined to only one hospital of the South-West Rajasthan region. For a more accurate sampling, a multicenter study would be required which can cover a larger area and population sample. This study was restricted only to the profiling of the various causes of dyspepsia. Treatment and outcome were not followed. The study could be extended in future to encompass larger samples from other districts of Rajasthan.

CONCLUSION

In the South-West Rajasthan region, *H. pylori* infection has a strong correlation with gastroduodenitis and peptic ulcer disease, although all gastroduodenitis patients may not be *H. pylori* positive. Functional dyspepsia is not a very common entity in this region. UGIE could lead to a definitive diagnosis in as many as 91.5% cases, proving its utility as an excellent reliable diagnostic tool in cases of dyspepsia. Clean drinking water is preferable to RO water as far as protection against dyspepsia is concerned.

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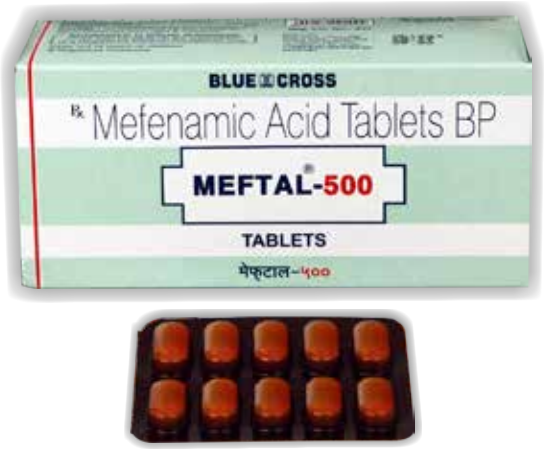

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Indian Journal of Clinical Practice, Vol. 31, No. 8, January 2021

Mefenamic Acid as Steroid-sparing Anti-inflammatory Drug During Viral Phase of COVID-19: 5 Case Reports

KK AGGARWAL

ABSTRACT

The diverse disease manifestations in coronavirus disease 2019 (COVID-19) patients are an enigma since some cases display little to no symptoms, whereas others develop severe fever and pneumonia, leading to acute respiratory distress syndrome and eventually death. Given the excessive inflammatory activity, there is a need to target a regulator of cellular inflammation while leaving the antiviral pathways intact. Corticosteroids are used as potent anti-inflammatory agents; however, it may also be linked with attenuation of viral clearance leading to nonuniform benefits across the disease spectrum. Mefenamic acid can be used as a steroid-sparing, long-term drug in the management of COVID-19 and post-COVID inflammation. In this article, the management of 5 mild-to-moderate COVID-19 cases using steroid-sparing anti-inflammatory agents is described.

Keywords: Mefenamic acid, steroid-sparing anti-inflammatory drugs, COVID-19, fenamates, NLRP3 inflammasome

One of the greatest enigmas around COVID-19 is the varied disease trajectories among COVID-19 patients. While some of the patients may develop little to no symptoms, others develop severe fever and pneumonia, resulting in acute respiratory distress syndrome and eventually death. The key to overcoming excessive inflammatory activity is to target a critical regulator of cellular inflammation while the antiviral pathways are left intact.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the lung cell damage triggers a local immune response, utilizing macrophages and monocytes responding to infection that release cytokines and prime adaptive T- and B-cell immune responses. In a dysfunctional immune response, hyperinflammation and cytokine storm occur, eventually leading to severe lung injury and even systemic pathologies. It is equally significant to control the inflammatory response as well as targeting the virus. Therapies inhibiting viral infection and regulating dysfunctional immune response may act in synergy to block pathologies at different steps.[2] The available evidence has shown that the anti-inflammatory effects of nonsteroidal anti-inflammatory drugs (NSAIDs) like mefenamic acid reduce acute symptoms such as fever.[3] Mefenamic acid can be used along with the different antiviral drugs being currently tried for the treatment of COVID-19.[4]

In this retrospective case study, 5 COVID-19 patients were managed with steroid-sparing anti-inflammatory therapy. The article discusses the role of treating COVID-19 with an anti-inflammatory approach using mefenamic acid with or without colchicine.

CASE PRESENTATIONS

Participants and Sources of Data

All patients treated at Heart Care Foundation of India (HCFI) OPD between November 01 and December 01, 2020, diagnosed with COVID-19 and treated with mefenamic acid were considered, and of these cases, 5 patients treated with mefenamic acid were randomly selected. The indication criteria for mefenamic acid use was a mild-to-moderate symptomatic case of COVID-19 with C-reactive protein (CRP) levels above 10 mg/L. Mefenamic acid was given along with the other standard of care treatment as recommended by the Ministry of Health and Family Welfare, Government of India. The Institutional Review Board of HCFI approved this report and waived the need for informed consent from individual patients due to the absence of identifying images or personal or clinical details that could

President, CMAAO and HCFI

compromise anonymity. Table 1 provides details of all the patients included in the study.

Procedures

All 5 patients in the study received mefenamic acid 500 mg thrice a day for a maximum duration of 14 days. COVID-19 diagnosis was confirmed through the reverse transcription polymerase chain reaction (RT-PCR) test. All the required tests were done at the baseline, and blood hemogram and CRP were repeated after the intervention. CRP values served as an important biomarker for the measurement of the inflammatory response of the patients. Vital statistics were assessed at the time of examining the patients.

RESULTS

Case 1

A 43-year-old male presented with moderate grade fever and body pain. His vitals were normal, CRP 13.55 mg/L. His chest X-ray was done, and the results were normal. On examination, he confessed to being a chain smoker and an alcoholic. The chest X-ray did not reveal any abnormalities. The patient was started on mefenamic acid 500 mg, thrice a day, ivermectin 12 mg, twice a day for 3 days, doxycycline 100 mg twice a day for 5 days, and multivitamin capsules. Symptomatic relief was seen in 8 days. His CRP levels reduced to 8.07 mg/L in 8 days, and the treatment was discontinued. The patient has not come back with any post-COVID syndrome.

Case 2

A 27-year-old female with a mild fever and runny nose presented to the clinic. She had traveled to Mumbai for an official meeting. She had no other comorbidities and was not on any other prior medications. There were no abnormalities seen in the chest X-ray. Her CRP was 12.43 mg/L. She was started on mefenamic acid 500 mg thrice a day for 10 days, doxycycline 100 mg twice a day for 5 days. Her CRP was reduced to 10.16 mg/L on the 11th day. Symptoms were relieved after 3 days of treatment.

Table 1. Details of Patients Included in the Study

Patient	Patient characteristics	Symptoms	Baseline assessment	Treatment approach	Post-treatment assessment	Patient outcome	Post-COVID symptoms
1	43 years, male	Moderate grade fever and body pain	Vitals normal, CRP: 13.55 mg/L; chest X-ray normal without abnormalities	Mefenamic acid 500 mg thrice a day; ivermectin 12 mg twice a day; doxycycline 100 mg twice a day; multivitamins	CRP: 8.07 mg/L	CRP reduced in 8 days	None
2	27 years, female	Mild fever and runny nose	CRP: 12.43 mg/L. No abnormalities in chest X-ray	Mefenamic acid 500 mg thrice a day; doxycycline 100 mg twice a day	CRP: 10.16 mg/L	Symptom relief in 3 days	None
3	43 years, female	Fever, cough and body aches	Normal vitals CRP: 4.78 mg/L Chest X-ray clear without any abnormality	Mefenamic acid 500 mg thrice a day Multivitamins	CRP: 2.47 mg/L	CRP reduced after 6 days of treatment	Fatigue and persistent cough after 10-12 days
4	25 years, male	Loss of taste and smell	CRP: 6.78 mg/L; Chest X-ray: normal	Mefenamic acid 500 mg, thrice a day	CRP: 3 mg/L	Regained his sense of taste and smell CRP reduced in 5 days	None
5	35 years, female	Headache, nose block, lethargy, cough, shortness of breath and loose motions	Normal vitals CRP: 12.56 mg/L Chest X-ray score 2	Mefenamic acid 500 mg thrice a day; ivermectin 12 mg twice a day; doxycycline 100 mg twice a day for 5 days; oral multivitamins	CRP: 9.47 mg/L	Symptom relief in 6 days CRP reduced in 7 days of treatment	None

Case 3

A 43-year-old female presented with fever, cough and body aches. Her vitals were normal, and her CRP levels were 4.78 mg/L. The chest X-ray was clear without any abnormalities. She was given mefenamic acid 500 mg thrice a day and multivitamins. Her CRP was reduced to 2.47 mg/L after 6 days. However, she complained of fatigue and persistent cough after 10-12 days. Her CRP values rose again, and she was given colchicine along with mefenamic acid and ivermectin.

Case 4

A 25-year-old male complained of loss of taste and smell. He had no other debilitating symptoms. Otherwise, a healthy male, he did not smoke or drink. He had been given favipiravir previously. His CRP level was tested to be 6.78 mg/L. The chest X-ray score was normal. He was given mefenamic acid 500 mg thrice a day for 5 days. His CRP was reduced to 3 mg/L after 3 days. He regained his sense of taste and smell. He has not reported back with any post-COVID symptoms.

Case 5

A 35-year-old female complained of headache, nose block, lethargy, cough, shortness of breath and loose motions. Her vitals were normal; she had suffered from allergic rhinitis 3 months back. Her CRP at the time of presentation was 12.56 mg/L. Her chest X-ray score was 2. She was immediately started on mefenamic acid 500 mg thrice a day, ivermectin 12 mg twice a day, doxycycline 100 mg twice a day for 5 days and oral multivitamins. Her CRP was reduced to 9.47 mg/L after 7 days of treatment; treatment was discontinued after 10 days. Symptoms were relieved in 6 days.

DISCUSSION

Early monitoring of crucial indicators forms a critical basis to make decisions on treatment approaches. Early evaluation of the severity of the patient's condition has great significance.[5]

CRP levels are correlated with the level of inflammation, and its concentration level remains unaffected by factors including age, sex and physical condition. At the early stage of COVID-19, CRP levels are positively correlated with lung lesions, hence reflect disease severity, and should be employed as a key indicator for disease monitoring.[5]

Serum CRP has been found to be an important marker that alters significantly in severe patients with COVID-19. It serves as an early marker of infection and inflammation. CRP preferably binds to phosphocholine expressed highly on the surface of damaged cells.[6]

This binding leads to the activation of the classical complement pathway of the immune system and modulates the phagocytic activity to clear microbes and damaged cells from the organism. With the resolution of the inflammation or tissue damage, CRP concentration reduces, making it a useful marker for monitoring the severity of COVID-19.[7]

It has also been suggested that interleukin (IL)-6 acts as the primary inducer of CRP gene expression, with IL-1β augmenting the effect. On the other hand, growing evidence has shown that CRP plays an important role in the inflammatory process and host responses to infection, including the complement pathway, apoptosis, phagocytosis, nitric oxide release and the production of cytokines, especially IL-6 and tumor necrosis factor (TNF)-α.[8]

In COVID-19 disease, the initial viral infection and subsequent host inflammatory response may lead to the excessive release of pro-inflammatory cytokines, IL-6 and IL-8, as well as TNF-α, eventually leading to hypercytokinemia. In order to address this hyperimmune-inflammatory pathogenesis, anti-inflammatory medicines targeting specific cytokines are a useful treatment approach.[9]

NLRP3 inflammasome has been implicated in a plethora of diseases. It is also involved in antiviral responses and virus-associated illnesses. As a mechanism to intensify disease pathogenesis, inflammasome activation can trigger cellular pyroptosis, which is a kind of programmed cell death. Pyroptosis of macrophages that have phagocytosed viruses rapidly releases multiple alarmins, including viral particles, cytokines, chemokines, lactate dehydrogenase (LDH), ATP and reactive oxygen species (ROS) prompting an immediate reaction from surrounding immune cells and thus inducing a pyroptic chain reaction. Besides, pyroptosis may lead to the generation of immune complex and circulation and deposition of viral antigens and RNA in target organs to initiate inflammatory cascade.[1]

SARS-CoV-2-induced inflammasome activation and pyroptosis in alveolar macrophages and recruited monocyte-derived macrophages, could drastically aggravate pneumonia symptoms, including acute respiratory distress syndrome and fever. Widespread and uncontrolled pyroptosis could lead to excessive tissue inflammation, organ failure and even death.[1]

The use of NLRP3 suppressors offers a viable solution to the treatment of hyperinflammatory responses in

virus infections. The benefits of NLRP3 inflammasome inhibitors like fenamates reduce local inflammation and ameliorate comorbidities associated with COVID-19, including hypertension, chronic obstructive pulmonary disease, type 2 diabetes mellitus and cardiovascular diseases as NLRP3 inflammasome activation is implicated in these diseases. In the management of COVID-19, there are two anti-inflammatory approaches: steroids and steroid-sparing agents like mefenamic acid with or without colchicine. However, early initiation of steroids is associated with a risk of increasing viral load.[1]

Corticosteroids are potent anti-inflammatory agents suggested to check the deleterious effects of cytokine storm in COVID-19.[10] Initial reports from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed that dexamethasone improved 28-day mortality compared to placebo in patients needing invasive mechanical ventilation (IMV) and those requiring oxygen therapy.[11] It strengthened the recommendation to use corticosteroids in hospitalized COVID-19 patients. However, it is essential to understand here that steroids in viral infection can behave like a double-edged sword, where the corticosteroid therapy may lead to attenuation of viral clearance as seen in the case of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) influenza and hence worsen clinical outcomes. It may also increase the probability of bacterial infections and mortality. Hence, the risk:benefit ratio of corticosteroid use may not be consistent across the varying disease severity of COVID-19, thereby leading to more harm than benefits. Hence, it becomes necessary to look for nonsteroid agents that exhibit much-needed anti-inflammatory properties to reduce cytokine storm and improve patient outcomes. In this context, mefenamic acid is an essential NSAID acting via selective NLRP3 inflammasome inhibition.[10]

The management of mild-to-moderate cases currently comprises antiviral agents, symptomatic treatment, and anti-inflammatory drugs. Doxycycline and ivermectin combination is given to symptomatic and asymptomatic COVID-19 patients for symptomatic relief and viral clearance.[12] Studies have shown that ivermectin is effective for the treatment of early-onset mild COVID-19 in adult patients causing early viral clearance of SARS-CoV-2 in treated patients; however, remission of fever, cough and sore throat is not attributed to the use of ivermectin.[13] Nonsteroidal anti-inflammatory agents have well-known anti-inflammatory activity and are suggested to be beneficial for both the early control of inflammation and prevention of thromboembolism, thereby theoretically restricting COVID-19 progression.[14] Mefenamic acid is one such NSAID that is known to provide significant protection against increased levels of TNF-α and IL-1β in radiation-induced genotoxicity of human lymphocytes.[15,16] Mefenamic acid has also been reported to be beneficial in patients who do not respond to paracetamol. Besides, paracetamol is a particular NSAID with no or almost negligible anti-inflammatory and antiplatelet activity and there are evident concerns about paracetamol-induced toxicty.[14,17]

In the cases presented above, early initiation of treatment with mefenamic acid provided symptomatic relief to the patients, who were not hypoxic, in reducing fever. The use of mefenamic acid alone led to the lowering of the CRP levels, which can also prevent cytokine storm, reflecting the significant anti-inflammatory activity of mefenamic acid in COVID-19 patients. The anti-inflammatory activity of mefenamic acid is very well-established, and it inhibits cyclooxygenase enzymes in the synthesis of prostaglandins and has been widely used to treat pain and inflammation. It is also a selective inhibitor of NLRP3 inflammasome and IL-1β release.[4]

As seen in one of the cases, in patients with cough, it is advisable to prescribe mefenamic acid along with other anti-inflammatory agents such as colchicine, as the cough could be due to viral pneumonia. In all mild-to-moderate cases of COVID-19 (CRP levels between 10 and 14 mg/L), mefenamic acid can be prescribed as an effective anti-inflammatory and antipyretic agent with careful monitoring and regular assessment of CRP values. Besides, nonsteroidal anti-inflammatory agents like mefenamic acid may be given in the case of post-COVID myalgia till the CRP level reduces below 1. Mefenamic acid is continued until two consecutive CRP readings <1 is achieved in an interval of 3-7 days.

CLINICAL PEARLS

- Mefenamic acid with or without colchicine can be used early to manage mild and moderate COVID-19 cases for combating cytokine inflammation (rising CRP) as a steroid-sparing potent anti-inflammatory drug during the early high viral load state of the disease.
- Mefenamic acid may also be used as a steroid-sparing long-term drug in post-COVID inflammation till CRP levels below 1 mg/L are achieved.

Mefenamic acid is a repurposed antipyretic and anti-inflammatory agent (selective NLRP3 inflammasome inhibitor) in treating mild-to-moderate COVID-19 patients.

CONCLUSION

Considering the clinical effect of mefenamic acid in mild-to-moderate COVID patients, it can be repurposed as an antipyretic and anti-inflammatory agent in treating COVID-19. Owing to its role as an antipyretic and anti-inflammatory drug, mefenamic acid plays a significant role in reducing fever and inflammation and can be used as a steroid-sparing medicine in treating COVID-19. Even though these case studies determine the potential usefulness of mefenamic acid in COVID-19 patients, larger clinical trials are needed to corroborate further the evidence seen in the cases mentioned above.

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Multiple Causes Leading to Massive Splenomegaly in an Elderly Female

MUHAMMAD UWAIS ASHRAF*, SHEHZAD FAIZUL HAQUE†, MOHD. JAVED‡

ABSTRACT

Splenomegaly is defined as enlargement of the spleen measured by size or weight. The spleen is an essential site for hematopoiesis and immunosurveillance. Splenomegaly may be diagnosed clinically or radiographically using ultrasound, CT imaging or MRI. Splenomegaly may be a transient condition or may be due to serious underlying acute or chronic condition. A combination of clinical examination, serology and imaging may diagnose splenomegaly and the underlying cause. Derangement in the complete blood (cell) counts and morphology including WBC, RBC and platelets will vary based on underlying disease. Abnormalities in liver function tests, lipase, rheumatologic panels and disease-specific infectious testing help in ascertaining the cause of splenomegaly. We present here a rare case of massive splenomegaly which had multiple causes within the same patient contributing to a massive spleen and a diagnostic enigma.

Keywords: Splenomegaly, autoimmune hepatitis, autoimmune hemolytic anemia

Splenomegaly is the enlargement of the spleen as measured by size or weight. The spleen is an essential site for hematopoiesis and immunosurveillance. The major functions performed by the spleen include clearance of abnormal erythrocytes, removal of microorganisms and antigens as well as the synthesis of immunoglobulin G (IgG). Apart from that, one-third of circulating platelets are stored in the spleen. Spleen usually measures up to 11 cm in craniocaudal length. Splenomegaly may be diagnosed clinically or radiographically using ultrasound, computed tomography (CT) imaging or magnetic resonance imaging (MRI). Splenomegaly may be a transient condition or may be due to serious underlying acute or chronic condition.

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A combination of clinical examination, serology and imaging may diagnose splenomegaly and the underlying cause. Derangement in the complete blood (cell) counts and morphology including white blood cell (WBC), red blood cell (RBC) and platelets will vary based on underlying disease. Abnormalities in liver function tests, lipase, rheumatologic panels and disease-specific infectious testing help in ascertaining the cause of splenomegaly.

Imaging is useful in deciphering the underlying cause of splenomegaly. The spleen has a similar attenuation as the liver when measured on CT scan. Ultrasound is a useful imaging modality in measuring the spleen and spares the patient radiation from CT imaging. MRI, positron emission tomography (PET) scans, liver-spleen colloid scanning and splenectomy and splenic biopsy may be indicated in certain cases.

We present here a rare case of massive splenomegaly which had multiple causes of splenomegaly within the same patient, contributing to a massive spleen and a diagnostic enigma.

CASE SUMMARY

A 60-year-old female presented with fatigue for 6 months, dragging sensation in abdomen for 2 months and melena for 2 days. There was no history of shortness of breath, palpitation, high grade fever, rashes over the body, epigastric discomfort or hematemesis.

There was no previous evidence of trauma to abdomen, pain abdomen, diarrhea, hematochezia and constipation. There was a past history of yellowish discoloration of eyes 2 years back. On general examination, pulse rate was 92/min, blood pressure was 112/76 mmHg, severe pallor was present, icterus was absent; there was no lymphadenopathy or rashes. Jugular venous pressure (JVP) was not raised and there was no pedal edema.

Abdomen was soft and nontender. There was no fluid thrill or shifting dullness. Liver span was 11 cm. There was massive splenomegaly, 10 cm below the costal margin. The other systems were within normal limits.

The hemoglobin was 4.7 g%, total leukocyte count (TLC) was 4,400/mm^3, differential leukocyte count (DLC) was $P_{79}L_{19}E_{01}$, mean corpuscular volume (MCV) was 76.3 fl and platelet count was 64,000/μL. Blood urea was 22 mg/dL, serum creatinine was 0.79 mg/dL, blood sugar was 136 mg/dL. Serum aspartate aminotransferase (AST) was 17 IU/L, serum alanine aminotransferase (ALT) was 20 IU/L, total bilirubin was 4.5 mg/dL, direct bilirubin was 0.8 mg/dL and indirect bilirubin was 3.7 mg/dL. Reticulocyte count was 6%, serum albumin was 3 g/dL, serum globulin was 2.5 g/dL, A:G ratio was 0.7:1, prothrombin time was 18.6 seconds and INR was 1.7.

Ultrasound abdomen revealed massive splenomegaly with normal liver echotexture and normal portal vein. There was no ascites on ultrasonography. The general blood picture (GBP) was suggestive of moderate anisocytosis with few microspherocytes, polychromatophils, target cells, tear drop cells and nucleated RBCs (Figs. 1 and 2).

Based on the GBP findings, the following diagnosis was proposed: Hemolytic anemia with associated microcytic hypochromic anemia. An extensive work-up was done to find out the cause of hemolytic anemia. Serum lactate dehydrogenase (LDH) was normal, there was no evidence of hemoglobinuria, the hemoglobin electrophoresis was normal. However, indirect Coombs test was positive. Thus, a diagnosis of autoimmune hemolytic anemia (AIHA) was made. The cause of splenomegaly was proposed to be extravascular hemolysis as evidenced by a positive Coombs test. This explained all the findings in the patient and practically seemed the end of the case. However, there was something which needed further evaluation.

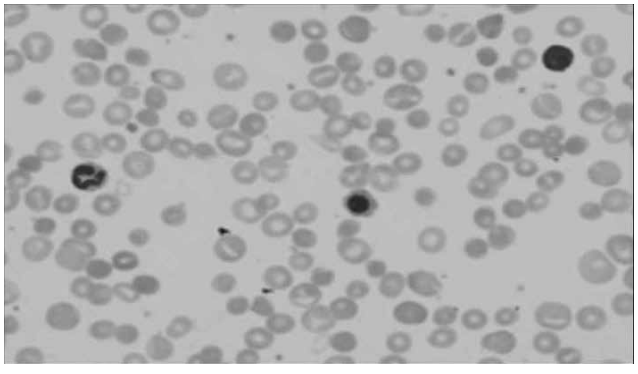

Figure 1. The general blood picture showing features of hemolysis.

The Unexplained Findings in this Case

Although severe anemia and splenomegaly could be explained with hemolysis in this patient, the cause of melena was not understood. Although, it was thought that thrombocytopenia due to hypersplenism or associated immune thrombocytopenic purpura (ITP) could be contributing to upper gastrointestinal bleeding and melena. However, to know the exact cause of melena, an esophagogastroduodenoscopy (EGD) was done. The EGD was suggestive of Grade II esophageal varices with portal hypertensive gastropathy (Fig. 3).

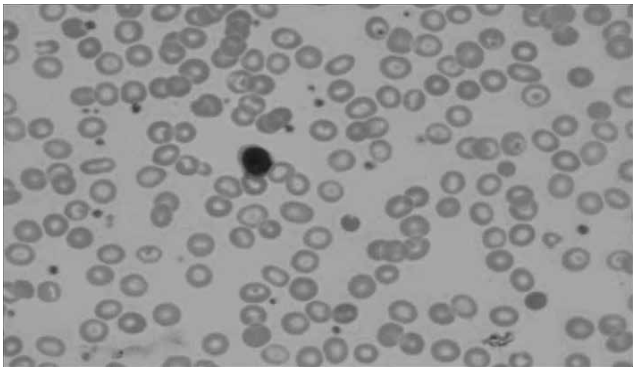

Figure 2. Peripheral smear showing target cells and nucleated RBCs.

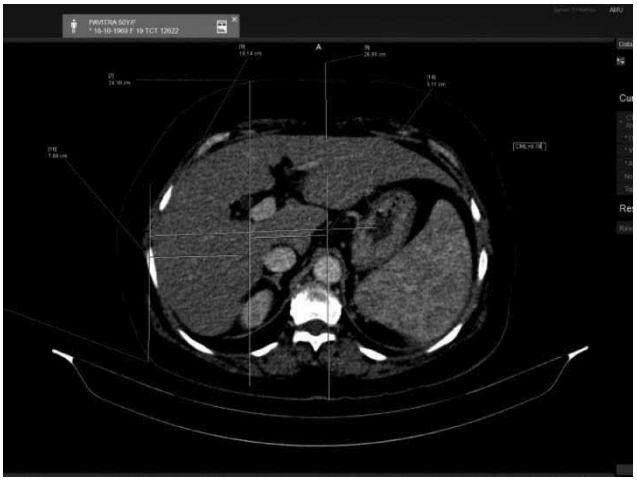

Figure 3. Endoscopy showing esophageal varices.

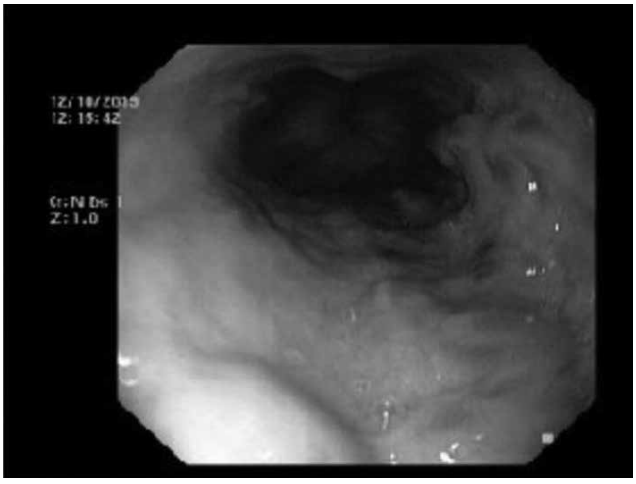

Figure 4. CECT showing caudate–right lobe ratio (C:RL ratio) of 0.78.

Since, the liver span was normal on clinical examination as well as on ultrasonography and there was no evidence of chronic liver disease or a dilated portal vein, a contrast-enhanced CT (CECT) scan of the abdomen was planned. While going for CECT, extrahepatic portal vein obstruction (EHPVO) or noncirrhotic portal fibrosis (NCPF) were suspected.

The CECT was suggestive of multiple gallbladder calculi (cholelithiasis); the caudate-right lobe ratio (C:RL ratio) was 0.78 with normal portal vein diameter (13 mm) and borderline increased splenic vein (~10.7 mm) and there were early esophageal varices noted, which confirmed the endoscopy findings (Fig. 4).

The C:RL ratio being >0.65 suggested cirrhosis of liver. To further confirm cirrhosis, transient elastography (fibroscan) was done which revealed a median stiffness of 23.11 KPa, confirming cirrhosis of liver. Thus, a final diagnosis of AIHA with cirrhosis of liver was made.

The next step in this patient was to find out the cause of cirrhosis of liver. Hepatitis B surface antigen (HBsAg) and anti-HCV (hepatitis C virus) were negative, ruling out viral hepatitis as the cause of cirrhosis. Serum ceruloplasmin, serum ferritin were normal. Total IgG was raised and antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA) and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) were positive. Anti-liver/kidney microsomal antibodies type 1 (anti-LKM-1) was negative.

Thus, a final diagnosis was made: AIHA with chronic liver disease (Type 1 AIH-related) Child-Pugh Class A with portal hypertension with Grade II esophageal varices with massive splenomegaly.

DISCUSSION

Our case is unusual because there were multiple contributing factors for massive splenomegaly in the same patient. Patient had AIHA which could explain all the findings on GBP and imaging and could explain splenomegaly in the patient. There was persistent thrombocytopenia which could be explained by hypersplenism (which is known to present with pancytopenia). However, the history of melena could only partially be explained by thrombocytopenia and a work-up was required. Melena itself can lead to iron deficiency which can lead to extramedullary erythropoiesis and give rise to splenomegaly. Apart from that, the presence of esophageal varices led to a search for noncirrhotic causes of portal hypertension. It is important to remember that in this patient, the ultrasound was not suggestive of chronic liver disease or portal hypertension. In a subset of patients, there may be no evidence of cirrhosis clinically and yet there may be advanced fibrosis. The ideal investigation for such situations is to go for a liver biopsy but now a large number of noninvasive tests have evolved, which include transient elastography, aspartate transaminase-to-platelet ratio index (APRI), acoustic radiation force impulse (ARFI), MR elastography, etc. It is imperative to note that in the absence of clinical or imaging evidence of cirrhosis, the patient was further taken up for evaluation of cirrhosis, otherwise an important diagnosis could have been missed as there was sufficient evidence to explain all the findings by AIHA.

Another important tool which initially suggested cirrhosis was the C:RL ratio, which is an important index in such occult cases of cirrhosis of liver. It has been reported that C:RL ratio is useful for diagnosis of liver cirrhosis by noninvasive imaging modalities such as CT and ultrasonography. The right-to-left (R/L) hepatic lobe ratio has been shown to be highly specific (100%) and very sensitive (85.7%) for cirrhosis. Except for liver biopsy and elastography, no other combination of tests has this degree of specificity and sensitivity.

Thus, in our patient, there were multiple causes leading to massive splenomegaly:

- AIHA, leading to extravascular hemolysis in spleen
- Severe anemia leading to extramedullary hematopoiesis in spleen
- Portal hypertension, secondary to AIH-related cirrhosis of liver.

Autoimmune hepatitis is a disease of unknown cause which is characterized by interface hepatitis,

lymphoplasmacytic infiltration, hypergammaglobulinemia and autoantibodies. It has a global distribution and affects all ages and both genders. Men have an earlier age of onset. Peak incidence in men is during teenage and in women, peak incidence is after menopause. It is associated with genetic predispositions, especially human leukocyte antigen (HLA)-DRB1*03 and HLA-DRB1*04.

Patients more than 60 years of age are more likely to have autoimmune thyroid disease and rheumatologic disorders. Patients younger than 30 are more likely to have ulcerative colitis and AIHA. Celiac disease may be seen in up to 2-4% patients. About 10-15% patients of APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia) have autoimmune hepatitis.

Diagnosis depends upon liver biopsy and presence of autoantibodies. Immunofluorescence and enzyme immunoassays are available for the following autoantibodies in serum, which are helpful in making a diagnosis: ANA, ASMA, anti-LKM-1, p-ANCA, IgA anti-tTG, SLA (soluble liver antigen), ASGPR (asialoglycoprotein receptor), anti-LC1 (liver cytosol type 1). The most commonly used initial treatment options are immunosuppressive therapy with either a combination of prednisone and azathioprine, a combination of budesonide and azathioprine or high-dose prednisone monotherapy. The two most studied treatment regimens are high-dose prednisone monotherapy or combination therapy of prednisone *plus* azathioprine.

CONCLUSION

We have presented here, a case of massive splenomegaly due to AIHA, which on further evaluation came out to be associated with autoimmune hepatitis. This case is interesting for many reasons. First, once the diagnosis of AIHA was confirmed, there seemed no reason to evaluate further, but once evaluated, a diagnosis as grave as cirrhosis was confirmed. This outlines the need for cautious interpretation of imaging modalities and high index of suspicion. In our case, the ultrasound was normal, and an important indicator was the C:R/L ratio on CECT abdomen, thus highlighting the role of C:R/L in such cases of borderline imaging results and no concrete initial evidence of cirrhosis.

Secondly, once cirrhosis was confirmed using transient elastography, the diagnosis of autoimmune hepatitis leading to cirrhosis was kept as a first differential because of the strong association between AIH and AIHA. Thirdly, this case is rare as there were three causes of splenomegaly and each could have masked the diagnosis of the other: hemolysis, portal hypertension and severe anemia with extramedullary hematopoiesis.

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Uterine Didelphys with Pregnancy and Obstructed Labor: Intrapartum Course Complicated by a Rare Uterine Anomaly

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ABSTRACT

Mullerian duct anomalies (MDAs) are congenital anatomic abnormalities of the female genital tract that arise from non-development or non-fusion of the mullerian ducts or failed resorption of the uterine septum, with a reported incidence of 0.1-10.0%. MDAs are clinically important because they are associated with an increased incidence of impaired fertility, menstrual disorders and obstetric complications. We hereby report a case of a primigravida with full-term pregnancy with obstructed labor referred from a primary health center. During the course of examination, she was found to have congenital abnormality of uterus and vagina. She underwent an emergency cesarean section with good perinatal outcome. Women with uterus didelphys belong to a high-risk group, although pregnancy outcome is comparatively good.

Keywords: Mullerian duct anomalies, congenital anatomic abnormalities, obstructed labor, uterus didelphys

The true incidence of congenital uterine anomalies in the general population and among women with recurrent pregnancy loss is not known accurately. Although incidences of 0.1-10% have been reported, the overall data suggest an incidence of 1% in the general population and 3% in women with recurrent pregnancy loss and poor reproductive outcome. Female genital tract develops from 3 sites, ovaries from the germ cells that migrate from the yolk sac into the mesenchyme of the peritoneal cavity and develop into ova and supporting cells; lower third of vagina develops from the ascending sinovaginal bulb; and uterus, fallopian tubes and upper two-thirds of vagina develop from the fusion of two mullerian ducts. Incomplete fusion of the mullerian or paramesonephric ducts results in the most common types of uterine malformation: uterus didelphys, uterus bicornis bicollis, uterus bicornis unicollis, uterus subseptate, uterus arcuatus and uterus unicornis. Uterus bicornis bicollis is characterized by double or single vagina, double cervix and two single-horned uterus which show partial fusing of their muscular walls with duplication running right down to the uterine orifice. Congenital anomaly of the mullerian duct system can result in various urogenital anomalies including uterus didelphys with blind hemivagina and ipsilateral renal agenesis.[1]

The diagnosis of this condition is usually made after menarche, but its rarity and variable clinical features may contribute to a diagnostic delay for years after menarche.[2] With timely and accurate diagnosis, appropriate management is likely to provide the best possible outcome for all such patients.

CASE REPORT

A 20-year-old primigravida, wife of a farmer, who was referred from a primary health care center, reported to labor room on 31st May 2009 at 09:13 pm with a history of 9 months of amenorrhea and leak per vagina since 3 days and pain abdomen since 3 days. She was married for 1 year.

General examination was unremarkable. On abdominal examination, uterus was term size and cephalic presentation and there was an unusual contour of abdomen on right side. Fetal heart sound was localized

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Figure 1. Per speculum examination showing right and left hemi vagina with complete vertical vaginal septum.

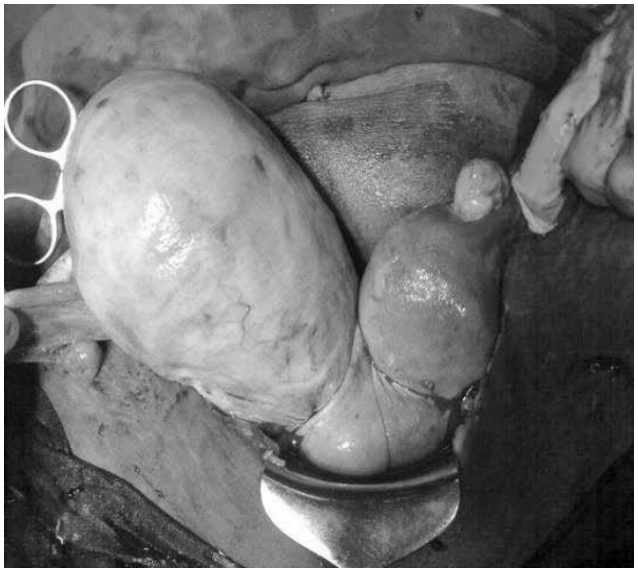

Figure 2. Anterior view of gravid right hemi-uterus with incision on the lower segment and nongravid left hemi-uterus.

in the right iliac fossa and was 146 bt/min. Per speculum examination revealed complete vertical vaginal septum (Fig. 1) and bulging of vaginal fornices in right hemivagina, active clear liquor leak demonstrated on the blade of speculum in right hemivagina. Internal examination revealed right cervix was partially effaced and 2 cm dilated and presenting part at minus three station, and in left hemivagina cervix was uneffaced and os closed.

On clinical examination, the pelvis was found to be grossly contracted. A decision for emergency cesarean

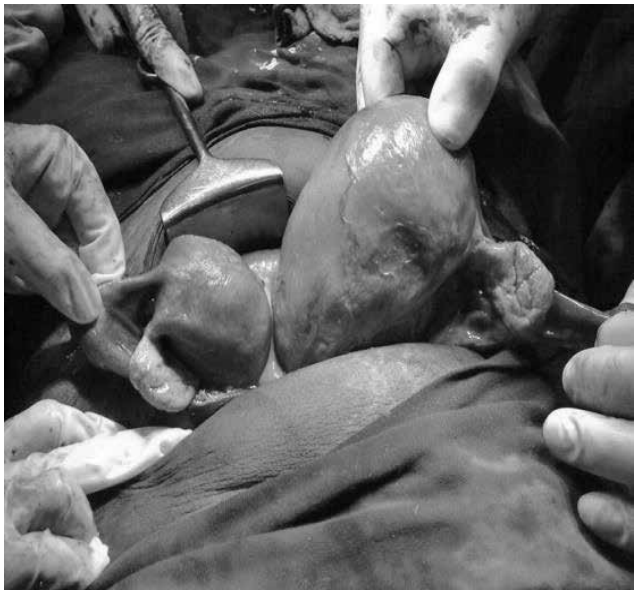

Figure 3. Posterior view of didelphic gravid hemi-uterus.

section was made. She underwent an emergency cesarean section on 01/06/09 at 12:30 am; a full-term male baby of weight 3.2 kg was extracted who cried after delivery. Uterus was found to be bicornis bicollis and pregnancy was found in the right hemi-uterus (Figs. 2 and 3). Postoperative stay was uneventful and sutures were removed on 7th postoperative day and the patient was discharged the same day.

DISCUSSION

Mullerian anomaly rate is reported between 0.1-1% in general population with significantly higher rates associated with infertility and reproductive wastage. Uterus didelphys is one of the least common anomalies, representing approximately 5-7% of müllerian defects. The reproductive outcomes are slightly better than those of women with unicornuate uterus. Acién reported that poorest viability results were found in the bicornuate (40%), arcuate (45%) and septate uterus groups (59%) and rates of children surviving for more than 7 days were around 70% in the bicornis bicollis, didelphys, unicornuate and subseptus uterus groups.[3] Maneschi et al reported live birth rate of 81% and suggested that reproductive and gestational performances of women with uterus didelphys are preserved. In patients with infertility complaints, associated causes must be ruled out before surgical correction. If these are present, their correction must be attempted as first therapeutic step, and term pregnancy with live baby is the rule.[4] Interestingly, pregnancy has been observed consistently in right horn.[5]

In case of single pregnancy, it is in the right uterus in uterus didelphys. Even in this present case, pregnancy has been found in the right hemi-uterus. Heinonen and colleagues observed a cesarean section rate of 82% and fetal survival rate of 67.5% and premature delivery of 21%.[6] All the patients also had a longitudinal vaginal septum.

Three-dimensional sonography has contributed the most and has become the investigation of choice in units where available. Raga et al and Wu et al reported that three-dimensional sonography offered a 100% specificity and is reproducible and reliable noninvasive diagnostic procedure for the exclusion of uterine anomalies and was able to differentiate between the different anomalies.[7,8] Magnetic resonance imaging (MRI) is the most sensitive imaging modality for congenital anomalies.

CONCLUSION

Congenital uterovaginal anomalies can have adverse effects on pregnancy outcome. Early diagnosis and an aggressive evaluation of any patient presenting with mid-trimester abortion, premature labor, malpresentation, prevent additional pregnancy wastage and maternal morbidity and are likely to provide the best possible outcome for all such patients.

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Deficiency of Trace Elements in Patients with Alcoholic Hepatitis

Malnutrition is normally seen in patients with alcohol-related liver disease. Trace elements such as cobalt, copper, iron, selenium and zinc are crucial for several cellular processes including antioxidant pathways. The prevalence and significance of trace element deficiency in alcoholic hepatitis is not clearly understood.

A study was therefore designed to ascertain the prevalence of trace element deficiency and its association with clinical outcomes among alcoholic hepatitis patients.

Serum was obtained from patients with alcoholic hepatitis, alcohol-related cirrhosis and healthy volunteers. Investigators quantified the trace element concentration using inductively coupled plasma mass spectrometry. The link between trace element levels and development of infection within 90 days and mortality within 28 and 90 days was determined.

Sera were obtained from 302 patients with alcoholic hepatitis, 46 with alcohol-related cirrhosis and 15 healthy controls and were subjected to an evaluation for trace element levels. The prevalence of zinc deficiency was 85% and that of selenium deficiency was 67% in alcoholic hepatitis patients. It was found to be higher in patients with alcoholic hepatitis as compared to patients with alcohol-related cirrhosis (72% and 37%, respectively). Zinc, chromium, copper and selenium were shown to be significantly different between the groups. Iron deficiency predicted infection within 90 days while zinc deficiency appeared to predict mortality within 28 and 90 days.

Trace element deficiency was found to have a high prevalence in patients with alcoholic hepatitis and was associated with infection and mortality. Supplementation with certain trace elements could possibly enhance clinical outcomes in these patients.

(*Source: Aliment Pharmacol Ther. 2020;52(3):537-44.*)

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Information Technology and Healthcare Education: Scope and Opportunities

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

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

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

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

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US Dietary Advisory Committee Recommends No Added Sugar Until Two Years of Age

A US government advisory group has issued its first-ever set of dietary guidelines for infants and toddlers. The plan from the 2020 Dietary Guidelines Advisory Committee recommends that children under 2 years of age should not be given any added sugar.

It further states that infants should be fed only breast milk for the first 6 months, where possible. The report stresses on breast milk as the best option for babies and states that it can help reduce the risk of obesity later on. However, if it is not available, infants should be given iron-fortified formula. Supplemental vitamin D should also be started soon after birth. The guidelines recommend that all Americans must limit added sugar to less than 10% of daily food intake… (*BBC*)

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Professional Indemnity Insurance for Medical Professionals

KK AGGARWAL

Doctors in India, since Vedic time, have been equated to God. No other profession, whether it is priest, lawyers, judges or politicians, occupies the same status as that of the medical doctors. Medical profession is the noblest profession.

However, doctors are also human beings and "**to err is human**". Medical error or injury has been known since the time of Hippocrates as principle of non-maleficence, derived from the doctrine of "*primum non-cere*", which means "first do no harm" and its natural corollary, beneficence or "do good", which means doing the right thing for the patient.

With the modern advancement in medical profession, the doctor-patient relationship has also changed from "paternalism", where doctors were "parent figures" taking medical decisions on behalf of their patients to the current "patient-centric" where the patient is an "equal partner". Thus, the type of patients has also changed from ignorant to enlightened.

With the advent of Consumer Protection Act, 1986 and various judgments by the Hon'ble Apex Court of the country and other courts and commissions, patients have started questioning the doctors and their treatment. Numerous cases are being filed against the doctors, hospitals, medical staff, etc., under consumer law, criminal law, civil law, etc. Compensation in lakhs and crores of money is being awarded in favor of the patient or his/her relative, which is to be paid by the doctor from his own pocket.

With increasing litigations against the doctors in the country, it has become very important and vital for the doctors to obtain insurance cover against all such litigations and compensation to be paid, if any. Accordingly, in the year 1991, the **Professional Indemnity Insurance** was introduced for the doctors and hospitals in the country.

Group Editor-in-Chief, IJCP Group

MEANING OF THE TERM "INDEMNITY"

The term "indemnity" means "to compensate" or reimburse. The principle of indemnity is strictly followed in liability insurances.

Indemnity means a legal obligation to cover the liability of another. "To indemnify" does not merely mean to reimburse in respect of money paid but to save from loss in respect of the liability against which indemnity has been given.

"To indemnify" means to make good a loss suffered by a person in consequence of the act or default of another.

Indemnity is a contract, express or implied, "to keep a person who has entered, or is about to enter, into a contract of liability indemnified against the liability independently of the question whether a third party makes default or not."

PROFESSIONAL INDEMNITY INSURANCE

Professional indemnity insurances are designed to provide the insured person protection against the financial consequences of legal liability. This policy is meant for professionals to cover liability falling on them as a result of errors and omissions committed by them whilst rendering professional service. If the insured is legally liable to pay damages or compensation to others, the policy will indemnify him subject to the terms and conditions and limitations of the contract.

Indemnity is also available in respect of legal costs awarded against the insured as well as legal costs and expenses incurred by the insured with the written consent of the insurers in the defense or settlement of claims.

IMPORTANCE OF PROFESSIONAL INDEMNITY INSURANCE IN MEDICAL PROFESSION

The medical professional is expected to bring a reasonable degree of skill and knowledge and must exercise a reasonable degree of care.

The medical professionals are entitled to get protection so long as they perform their duties with reasonable skill and competence and in the interest of the patients. The interest and welfare of the patients have to be paramount for the medical professionals.

The Hon'ble Apex Court in the matter titled as **"Kusum Sharma & Others versus Batra Hospital & Medical Research Centre, 2010 (3) SCC 480** has held that-

> *"94. On scrutiny of the leading cases of medical negligence both in our country and other countries specially United Kingdom, some basic principles emerge in dealing with the cases of medical negligence. While deciding whether the medical professional is guilty of medical negligence following well known principles must be kept in view:*
>
> *i. Negligence is the breach of a duty exercised by omission to do something which a reasonable man, guided by those considerations which ordinarily regulate the conduct of human affairs, would do, or doing something which a prudent and reasonable man would not do.*
>
> *ii. Negligence is an essential ingredient of the offence. The negligence to be established by the prosecution must be culpable or gross and not the negligence merely based upon an error of judgment…."*

Gross negligence is intentional failure to perform a manifest duty in reckless disregard of the consequences. Ordinary negligence is based on the fact that one ought to have known results of his acts, while gross negligence rests on the assumption that one knew results of his acts, but was recklessly or wantonly indifferent to the results.

If there is gross medical mistake, then the doctor will be liable for the negligene committed by him. In such case, doctor would be liable to pay huge compensation to the patient or his/her relatives.

To protect oneself from such huge compensation to be paid, if any, it is important and vital to obtain professional indemnity insurance.

SALIENT FEATURES OF PROFESSIONAL INDEMNITY INSURANCE

Indemnity

The professional indemnity insurance is meant for professionals to cover liability falling on them as a result of errors and omissions committed by them whilst rendering professional service. The indemnity applies only to the claim arising out of bodily injury and/or death of any patient caused by or alleged to have been caused by error, omission or negligence in professional service rendered or which should have been rendered by the insured or the assistants or the team of people employed by the insured.

Policy Period

Period commencing from the effective date and hour as mentioned in the policy and terminating at the midnight on the expiry date as mentioned in the policy.

Period of Insurance

Period of insurance means period commencing from the retroactive date and terminating on the expiry date as mentioned in the policy.

Commission of Act

The Act (medical negligence by doctor or hospital) has to be committed during the period of insurance commencing from retroactive date.

Retroactive Date

Retroactive date is the date when the risk is just incepted under "claims made" policy and thereafter renewed without any break in the period of insurance.

Limit of Indemnity

Irrespective of the number of persons or entities named in the insurance policy or added by endorsement, the total liability of the insurance company for damages inclusive of defense costs shall not exceed the limit of indemnity as mentioned in the policy.

Defence Cost

The insurance company pays all costs, fees and expenses incurred with their prior consent in the investigation, defense or settlement of any claim made against the doctor or hospital and the costs of representation at any inquest, inquiry or other proceedings in respect of matters which have a direct nexus to any claim made or which might be made against the insured. Such costs, fees and expenses are called defence cost.

Claims Series Clauses

Where series of losses and/or bodily injuries and/or deaths are attributable directly or indirectly to the same cause or error or commission relating to discharge of professional services all such losses and/or bodily injuries and/or deaths claims shall be added together and all such losses and/or bodily injuries and/or deaths

shall be treated as one claim and such claim shall be deemed to have been made when the first claim was made in writing.

Registration

- **Doctor:** The doctor should be duly registered with his/her respective medical council.
- **Hospital/Medical establishment:** The Hospital/Medical establishment should be registered with competent authority as per local law and rules. In territories where there is no registration facility, then following minimum norms have to be complied with for considering the indemnity insurance policy:
  - At least 10 in-patient facility
  - Fully equipped operation theater of its own
  - Fully qualified nursing staff in its employment round the clock, unless indicated to the contrary and additional premium paid
  - Fully qualified doctor/doctors should be in charge round the clock
  - The insured shall comply with registration formalities as and when official regulations or laws are enforced.

Short Period Policy

Short period policies are not permitted. However, in case of cancellation of the policy by the insured, short period scale rates as provided for will be applicable.

Compromise/Settlement

In normal course, all claims for compensation have to be legally established in court of law. However, insurers can arrive at compromise or settlement if *prima facie* liability exists under the policy.

Jurisdiction

Jurisdiction applicable will be of Indian courts only.

Exclusions

- Liability assumed under the agreement
- Cosmetic surgery (cosmesis)
- Liability arising out of:
  - Deliberate, willful or intentional non-compliance of statutory provisions
  - Loss of goodwill, libel, slander, false arrest, defamation, etc.
  - Fines, penalties, punitive or exemplary damages
  - Genetic injuries caused by X-ray treatment or diagnosis with radioactive substances
  - Professional services rendered by the insured prior to retroactive date
  - War and warlike perils
  - Nuclear fuel/ionizing radiation/radioactive contamination.

Premium Rate of Insurance

Separate rates of insurance are applicable to doctors, medical establishments, medical professionals, etc. Group discounts are available with the insurance companies for a group of doctors. Additional premium is applicable in case doctors want to cover qualified staff working with them. Whenever multiple specializations are involved, then the rate of insurance shall be of the specialization which attracts higher rate of insurance.

List of Eligible Medical Establishments

- Laboratories and diagnostic centers
- Hospitals
- Mental homes
- Nursing/convalescent homes
- Homes for physically disabled
- Clinics
- Dispensing pharmacies
- Veterinary hospitals and/or clinics and the like.

BENEFITS OF PROFESSIONAL INDEMNITY INSURANCE

- It is beneficial not only to the doctors or hospital but also to the patients and their dependents because the insurance company takes care of the compensation.
- Retroactive benefit: This means that the insured will be covered for any professional act or omission occurring during the period of insurance.
- It would take care of the amount of damages against third party.
- Scheme will also compensate on the principle of "no fault liability" to give some relief in the case of death or permanent disablement of the patient.
- The company will also pay the defense costs, which have a direct relevance to the claim.

LIMITATIONS OF PROFESSIONAL INDEMNITY INSURANCE

The only limitation that this policy has is that the amount of compensation is restricted by the limit of indemnity as mentioned in the policy.

CONCLUSION

Professional indemnity insurance is a tool, which not only meets the claim of compensation awarded against doctor/hospital but also gives a sense of mental security that even if some negligence is proved, the insurance company will take care of it.

Professional indemnity insurance covers all sums, which the insured professional becomes legally liable to pay as damages to third party in respect of any error and/or omission on his/her part committed whilst rendering professional service.

The insurance companies not only pay the compensation to other party but also arrange for the legal help from advocates because they sometimes join hand with other party for monetary gains with an excuse that it's the insurance not the doctor who is to pay the compensation.

However, one must never forget that the security is only monetary. The person's reputation and goodwill is not insured. So, all doctors should use their reasonable standard of care while treating and operating on their patients.

SUGGESTED READING

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■■■■

Abnormal Clotting Common in More Severe COVID-19

Endothelial damage and subsequent clotting appear to be common in severe and critical COVID-19, which may have implications for treatment. Clots in the small vessels of all organs, not only the lungs but also the heart, the liver and the kidney, have been described by Bin Cao, MD, of the National Clinical Research Center for Respiratory Diseases in Beijing. The investigators had reported March 11 in *The Lancet* that D-dimer levels >1 μg/L at admission were predictive of 18-fold increased odds of dying before discharge among 191 COVID-19 patients seen at two hospitals in Wuhan. D-dimer can exceed 70 or 80 μg/L.

Acute cardiac injury was reported in 12% of COVID-19 cases in a small case series in *The Lancet* which was cited by Cao. Another study reported a rate of 7.2% among 138 patients from another hospital in Wuhan.

Comorbid CVD is a distinct risk factor for COVID-19, associated with a mortality rate of up to 10.5% among over 70,000 patients in one study. The virus can potentially bind to the endothelial cells and damage the blood vessels, especially the microcirculation of the small blood vessels, leading to platelet aggregation. It is not a myocardial infection, not a stroke, but it is the clots all over the body. Hence, the high D-dimer. It is because of the wide spread of abnormal coagulation all over the body.

Besides endothelial shedding and thrombosis in vessels, autopsies have shown inflammatory changes in the heart with fine interstitial mononuclear inflammatory infiltrates, but no viral inclusions in the heart. Other potential mechanisms for cardiac damage include hypoxia-induced myocardial injury, cardiac microvascular damage and systemic inflammatory response syndrome. In the majority of mild and moderate cases, the only cardiac impact was some tachycardia and slightly higher troponin.

Investigators highlighted the case of a COVID-19-infected man with apparent ST-elevation myocardial infarction (STEMI) by ECG, troponin T >10,000 ng/L and creatine kinase muscle and brain (CK-MB) 113 ng/L, but coronary angiography showing no stenosis. After treatment with steroids, immunoglobulin, norepinephrine, diuretic, a vasodilator and antibiotics, the man's ejection fraction recovered from 27% to 66% and his enlarged heart normalized. (*Medpage Today*)

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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Why Certain COVID Patients Die?

- Advancing age and underlying medical problems explain only part of the phenomenon.
- Some people, especially men, succumb because their immune systems are hit by friendly fire.
- A study in *Science* revealed that 10% of around 1,000 COVID patients who developed life-threatening pneumonia had antibodies that disable interferons. These autoantibodies were not found in 663 people with mild or asymptomatic COVID infections. Only four of 1,227 healthy individuals were found to have the autoantibodies.
- In a second study by the same team, it was noted that an additional 3.5% of critically ill patients had mutations in genes that control the interferons involved in fighting viruses. The body has 500-600 of these genes, therefore, it seems possible that researchers will find more mutations, said lead author of the second study.
- Interferons are the body's first-line of defense against infection.
- They are a fire alarm and a sprinkler system all in one.
- Laboratory studies suggest that interferons are suppressed in some people with COVID-19, probably by the virus itself.
- Interferons are vital for protecting the body against new viruses, such as the coronavirus, which the body has never encountered.
- When infected with the novel coronavirus, the body should have alarms ringing. If the alarm doesn't get out, you could have viruses everywhere in large numbers.
- Patients didn't make autoantibodies in response to the virus. It appeared that they had them before the pandemic began. These autoantibodies never caused a problem until patients were infected with COVID-19. Somehow, the novel coronavirus, or the immune response it triggered, seems to have set them in motion.
- It is not known whether autoantibodies against interferon also increase the risk from other viruses, such as influenza.
- Furthermore, 94% of patients in the study with these autoantibodies were men. About 12.5% of men with life-threatening COVID pneumonia had autoantibodies against interferon, compared to 2.6% of women.

(*Source: Medscape*)

Why Viruses Spread More Easily in Winter?

- In winters, people tend to spend more time indoors, where ventilation is poor and we're in closer proximity to other people.
- The Air Outside is Less Humid: Viruses stay stable and linger for longer when the air is less humid.
- Nasal Membranes Are Drier: Feels dry and cracked. These cracks make you more vulnerable to infection. Staying hydrated and using a saline nasal spray can help.
- Other Illnesses Cause Coughing and Sneezing: It's possible to have co-infections of COVID-19 and say, the seasonal flu. So even if a person has an asymptomatic case of COVID-19, another infection may cause the coughing and sneezing that is known to increase the spread of the coronavirus.
- The virus lipid membrane may get thicker.

Mask Fatigue and Air Travel

- It's getting harder for some people to comply with the safety rules but a mask is life-saving.
- Don't wear gloves, it gives you a false sense of security—just use your hands and wash them when you get home.
- If you do need to fly, wear eye protection, a mask and minimize the time the mask is down. For instance, eat a protein bar, then put up your mask immediately after you take a bite while you chew. There are studies on how air circulates on

airplanes; it goes in a downward direction which reduces the transmission between rows as well.

- When you arrive at your destination, change your clothes and take a shower to minimize the risk. COVID does live on the skin for up to 6-9 hours and can live on surfaces. It's been shown to live on plastic for up to 72 hours and on cardboard and paper for 24 hours.
- Don't eat indoors with people outside of your household. That is a major scientifically-proven mechanism of transmission. If you are sitting across the table from someone, you can still transmit it.

Mucocutaneous Manifestations of MIS-C

DG Alerts: Mucocutaneous manifestations of multisystem inflammatory syndrome in children: An array of mucocutaneous findings was identified in hospitalized children with multisystem inflammatory syndrome in children (MIS-C) or suspected MIS-C during the COVID-19 pandemic, reported a case series published in *JAMA Dermatology*.

Of the patients assessed, 83% developed mucocutaneous changes, with the most common being conjunctival injection, palmoplantar erythema, lip hyperemia, periorbital erythema and edema, strawberry tongue and malar erythema. Other cutaneous morphologic findings included scarlatiniform eruptions, morbilliform eruptions, urticarial eruptions and reticulated eruptions. Among those with mucocutaneous changes, 19 patients experienced fever a mean of 2.7 days (range, 1-7 days) prior to the recognition of the first mucocutaneous finding. The duration of mucocutaneous findings ranged from hours to days (median duration, 5 days [range, 0-11 days]).

Overall, 19 patients had cardiac involvement as noted by elevated troponin and/or brain natriuretic peptide levels, while 10 had abnormal echocardiogram findings; 5 patients with cardiac involvement needed inotropic support. Ten patients were admitted to the intensive care unit (ICU). There appeared to be no statistically significant associations between the presence of mucocutaneous findings and cardiac dysfunction, need for inotropic support or ICU admission, which suggests that mucocutaneous changes were not tied to disease severity in MIS-C.

Conjunctivitis, lip hyperemia or cracking, and palmoplantar erythema exhibited an even distribution across all ages; however, urticarial eruptions were noted in those below 2 years of age, and periorbital and palmoplantar edema were evident in those younger than 6 years. (*Source: JAMA Dermatology*)

Baricitinib *plus* Remdesivir

Baricitinib *plus* remdesivir shows promise in treatment of COVID-19: The combination of baricitinib, an anti-inflammatory drug and remdesivir, an antiviral, was found to reduce the time to recovery among hospitalized COVID-19 patients, suggested clinical trial results published in the *New England Journal of Medicine*. The study was supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

The ACTT-2 trial started on May 8, 2020 and recruited 1,033 volunteers at sites in 8 countries. **Participants were randomized to receive either oral baricitinib tablets and intravenous (IV) remdesivir or oral placebo tablets and IV remdesivir.**

Combination of baricitinib and remdesivir reduced median time to recovery among hospitalized COVID-19 patients from 8 days to 7 days. Patients requiring high-flow oxygen or noninvasive ventilation during hospitalization were shown to obtain the largest benefit. The median time to recovery in these patients was reduced from 18 days to 10 days. Furthermore, participants' condition at Day 15 (measured by **an eight-category ordinal scale** which ranked the severity of their condition) was significantly improved when they received the combination therapy. Those who were given the two treatments also had slightly fewer serious adverse effects. (*Source: NIH*)

IMA-CMAAO Webinar on "COVID Experience in Mumbai"

28th November, 2020 (4-5 pm)

Participants: Dr KK Aggarwal, President-CMAAO; Dr RK Datta; Dr Jayakrishnan Alapet; Dr Brijendra Prakash; Dr S Sharma

Faculty: Dr Rahul Pandit, Director Critical Care Medicine & ICU, Fortis Hospital, Mumbai COVID Task Force Member, Maharashtra

Key points from the discussion

- Cases in Mumbai have reduced since November and are now 400-500/day. In September, there were around 2,000 cases every day.
- Children are protected due to a reasonable amount of immunity from the thymus gland, which is present in an active child up to 8-10 years of age.

- An exploratory trial was conducted with thymosin alfa in 15 patients to examine if it could activate CD4 and CD8 cells and increase lymphocyte count. Critically ill patients (as per ICMR criteria) were selected for the trial. Thymosin was started on Day 1 (3.2 mg TDS SC). Patients started showing improvement in CD4, CD8 and lymphocyte cell count by Day 4 and there was statistically significant improvement by Day 7. Cytokine markers also reduced (C-reactive protein [CRP], D-dimer); ferritin was not so robust. Lactate dehydrogenase (LDH) did not change much. These findings need to be tested in a large trial.
- The average lymphocyte counts in these patients were in single digits when they were in ICU. The average total leukocyte count (TLC) was 4,100; the lymphocyte count was 9.2% (average). So, if we act on moderate disease patients, perhaps we can stop progression to severe disease.
- Thymosin alfa has not been tried in human immunodeficiency virus (HIV) patients; no patient in the trial had co-existing HIV. It had no effect on monocytes and eosinophils. Neutrophil count reduced.
- Exploratory studies needed to study if these cases produced more antibody levels.
- Tocilizumab (single cytokine blocker) is losing its role in COVID-19. If supportive care and steroids are given in time in hypoxia, it is not needed. But in some patients where cytokine storm is just in place, it may have some role.
- Multiple cytokine inhibitors (Baricitinib) seem promising, but whether there is a need to use them is not clear.
- Oral baricitinib is available in India; it blocks inflammation in 72 hours, but not thrombosis. It is given in rheumatoid arthritis patients.
- Favipiravir and remdesivir should be given when the virus is replicating; they have no role if given after 7-9 days when replication is over; should be started on 3rd-4th day.
- There is less data on ivermectin and doxycycline in Mumbai; seem promising and a good randomized controlled trial (RCT) is needed.
- To prevent thrombosis, aspirin can be given; if the patient has developed a slightly higher microvascular state, low molecular weight heparin (LMWH), warfarin, acenocoumarol, dabigatran, rivaroxaban and apixaban. If these do not work, then thrombolysis can be done with streptokinase, tenecteplase.
- When we treat COVID-19, there are three options: Attack the virus within 48 hours; attack the inflammation (early diagnosis); attack the thrombosis and recover the damage (fibrosis) done.
- Up till now, mucosal vaccines have been only up to 60-70% effective. So, re-dosing (multiple doses) is required.
- All nucleic acid vaccines are highly inflammatory and may cause inflammatory reactions.

Minutes of Virtual Meeting of CMAAO NMAs on "Can I Refuse Vaccine"

12th December, 2020 (Saturday, 9.30 am-10.30 am)

Participants, Member NMAs: Dr KK Aggarwal, President-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer-CMAAO; Dr Marthanda Pillai, India, Member-World Medical Council; Dr Marie Uzawa Urabe, Japan Medical Association; Dr Angelique Coetzee, President-South African Medical Association; Dr Md Jamaluddin Chowdhury, Bangladesh Medical Association; Dr Ashraf Nizami, Pakistan Medical Association

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

Key points from the discussion

- Analysis of graphs of the top 15 countries in the world shows that India, Argentina and Poland are still experiencing the first wave of the infection. The remaining 12 countries have seen more than one wave; of these, the second wave is shorter than the first wave only in Brazil and Colombia. In the rest, the second peak is significantly higher than the first wave.
- There is a law in the US where employers can fire employees who have not taken the flu vaccine. Relief has been granted three times on religious, medical grounds and personal liberty.
- Vaccine is now available in the UK, US, UAE and China.
- With the impending arrival of the COVID-19 vaccine in many more countries, many questions will come up, which need to be answered.
- Can a government/hospital mandate vaccination?
- Is informed consent required before vaccination?

- Is an employer exempt from paying workers' compensation to an employee who refuses to be vaccinated and then contracts the virus while on the job?
- Can a prospective employer require COVID-19 vaccination as a pre-condition of employment?
- Can a patient refuse treatment from a doctor who has not taken the vaccine?
- If a hospital allows employees to refuse vaccination and keep working and an outbreak occurs, and it is suggested through contact tracing that unvaccinated workers infected patients, will a court hold the hospital liable for patient's damages?
- It was suggested that CMAAO countries could develop an awareness program about the efficiency and side effects of the vaccine, including the need of the vaccine.
- It is important to maintain the recommended storage temperature and transport temperature. Storage temperature for the Pfizer COVID-19 vaccine is -70°C, which is not feasible in developing countries.
- How will the vaccine act if given to an asymptomatic positive individual?
- If a person already infected with the virus is given the vaccine, will there be a reaction?
- CDC says that people who have already had COVID "may still benefit from getting vaccinated". WHO has not defined any selection criteria. All must take it.
- Professional autonomy is not absolute. So, if the law says that vaccine has to be taken, we have to take it.
- Pfizer has been granted legal indemnity by the UK government and the company will not be liable for any adverse event due to COVID-19 vaccine.
- Patients with history of severe allergy/ anaphylactoid reaction should not take the m-RNA vaccine.
- Health officials have cautioned that those who take Sputnik V vaccine should give up alcohol for almost 2 months. This has already caused a backlash.
- No vaccine is mandatory but people still take it. But it cannot be given without informed consent.

Colchicine in Patients with Stable Coronary Artery Disease

For patients with chronic coronary disease receiving other secondary preventive strategies, colchicine 0.5 mg (or 0.6 mg) daily should be added to the medical regimen (Grade 2B).

Chronic inflammation is a risk factor for CAD events, such as myocardial infarction (MI), and colchicine is known to have anti-inflammatory effects.

In the LoDoCo2 trial, more than 5,500 patients with chronic coronary disease were randomized to receive 0.5 mg of colchicine once a day or placebo. After a median follow-up of around 2½ years, those receiving colchicine had a decreased risk of MI (3.0% vs. 4.2%) and ischemia-driven coronary artery revascularization (4.9% vs. 6.4%) in comparison with the control group. Treatment was well-tolerated except for a small increase in myalgias. Uptodate suggests adding colchicine 0.5 mg (or 0.6 mg) once daily to other secondary preventive strategies in patients with stable CAD.

Trial

The LoDoCo2 trial randomly assigned 5,522 patients, 85% men, with chronic coronary disease to 0.5 mg of colchicine once per day or placebo.

After a median follow-up of around 2½ years, the risk of MI was 30% lower in the colchicine group (3.0% vs. 4.2%), and there was a 25% lower risk of ischemia-driven coronary artery revascularization (4.9% vs. 6.4%).

The difference between the two groups in the risk of death from any cause (2.6% vs. 2.2%, respectively) was insignificant. Except for a somewhat greater rate of myalgia with colchicine (21.2% vs. 18.5%), no other significant adverse events were seen.

(*Source: UpToDate; N Engl J Med. 2020;383(19):1838.)*

Effect of Colchicine on hs-CRP

- Among patients with stable CAD, raised levels of biomarkers of inflammation, including high-sensitivity CRP (hs-CRP) ≥2.0 mg/L, predict future vascular events.
- Long-term low-dose colchicine is safe and effective for dampening inflammation.
- An open-label pilot study evaluated whether colchicine could significantly lower hs-CRP in patients with stable CAD having hs-CRP was ≥2.0 mg/L, despite taking both aspirin and high-dose atorvastatin therapy.
- Plasma hs-CRP level was measured in 200 patients

with clinically stable CAD taking aspirin and atorvastatin.

- In 64 patients, hs-CRP was ≥2.0 mg/L.
- In 20 of these patients, hs-CRP was measured again at 2 weeks (no treatment group), and in 44 patients, hs-CRP was measured again after 4 weeks of colchicine 0.5 mg twice daily (treatment group).
- In the no treatment group, mean baseline hs-CRP did not decrease significantly, (4.28 ± 2.03 mg/L at baseline and 3.70 ± 2.30 mg/L after repeated measurement; mean change 11.0%).
- hs-CRP appeared to decrease in all patients given colchicine treatment (mean baseline hs-CRP decreasing from 4.58 ± 2.05 to 1.78 ±1.38 mg/L ($p < 0.001$), absolute decrease of 2.80 mg/L and a relative decrease of 60%).
- In 28 patients (64%) in this group, the decrease in hs-CRP was >50% from baseline, and in 31 patients (70%), hs-CRP decreased to <2.0 mg/L.
- There were no significant side effects. Low-dose colchicine (0.5 mg twice daily) has the potential to effectively decrease hs-CRP in patients with clinically stable CAD and increased hs-CRP independent of aspirin and atorvastatin use.

(*Source: Am J Cardiol. 2007; 99(6):805-7.*)

Colchicine is an anti-inflammatory drug, indicated for the treatment of pericarditis or gout. In the COLCOT trial, 4745 patients with MI within 30 days who were receiving optimal medical therapy were randomized to colchicine 0.5 mg daily or placebo.

After a median follow-up of about 2 years, the risk of primary composite endpoint (death from cardiovascular causes, resuscitated cardiac arrest, MI, stoke or urgent hospitalization for angina leading to coronary revascularization) was found to be lower in the colchicine group.

This result was largely guided by lower risks of angina and stroke. Adverse events were generally similar in the two groups.

While the results of COLCOT appear promising, treatment with colchicine is not given on account of the absence of improvement in hard endpoints such as cardiovascular death or MI and a relatively high discontinuation rate (about 18.5% in both groups).

(*Source: N Engl J Med. 2019;381(26):2497.*)

In Non-CU Patients, Day 2 Blood Sugar of Over 250 or Less Than 70 Associated with Poor Outcomes in Patients with COVID-19

Both hyperglycemia and hypoglycemia were found to be associated with poor outcomes in patients with COVID-19, in a study published in *Diabetes Care*.

An analysis of 1,544 patients with COVID-19 from 91 hospitals in 12 states revealed that glucose level at admission was a robust predictor of death among the 360 patients directly admitted to ICU and severe hyperglycemia after admission strongly predicted death among the 1,184 patients admitted to a non-ICU setting. Of the patients, 279 (18.1%) died in the hospital. The mortality for ICU patients (31%) appeared to be nearly twice that in non-ICU patients (16%).

Among non-ICU patients, severe hyperglycemia (blood glucose >250 mg/dL) on **Days 2 to 3 had an independent association** with high mortality compared with patients with blood glucose <140 mg/dL. This relationship was not significant for admission glucose.

In patients who were admitted directly to the ICU, severe hyperglycemia on admission was tied to increased mortality. This relationship was not significant on Day 2. Hypoglycemia (blood glucose <70 mg/dL) was also found to be linked with increased mortality.

(*Reference: https://care.diabetesjournals.org/content/diacare/early/2020/12/08/dc20-1857.full.pdf; Source: Diabetes Care*)

Are Old Vaccines Helpful Against COVID-19?

Vaccines stimulate broad, innate immune response, which plays a vital role in fighting COVID-19. Can this approach bridge the time until entire populations are vaccinated, particularly against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)?

Three vaccines are dominating the discussion:

- Bacillus Calmette-Guérin (BCG) has been tied to milder courses of infection for respiratory syncytial virus, human papillomavirus, herpes simplex and influenza. Fifteen clinical trials are evaluating it for COVID-19; however, a drawback is the 1% rate of adverse events.
- Oral polio vaccine (OPV) has also been associated with milder infections for decades. It decreases the morbidity from influenza 3.8-fold.
- Measles-mumps-rubella (MMR) drew the focus in the spring when 955 sailors aboard the U.S.S. Roosevelt tested positive for COVID-19, while only 1 was hospitalized. As recruits routinely

receive MMR, re-vaccination of others might prevent the fatal inflammation of COVID-19.

A virus that enters the body comes across the complex cascade of defensive proteins that make up innate immunity. This includes cytokines, present in mucosal sites in the lungs, nose and genitals, and that recruit immune cells. Complement proteins also kill the viruses. Being non-specific responses, they're called innate. Cells of innate immunity include **macrophages, neutrophils and natural killer cells,** and the **epithelial and endothelial cells** that interface the circulation. If innate immunity is unable to contain an infection, **the adaptive immune system starts work: T cells, B cells and antibodies** bring specificity and memory. Adaptive immunity also hikes cytokine and complement secretion.

A cytokine storm is the **turn to the dark side of the innate response.**

An RNA virus delays interferon (a cytokine) production, blocks signals and escapes natural killer cells, and replicates explosively until it invades the bloodstream. A wave of inflammation goes through linings and lymphoid tissues as the adaptive response pours out more cytokines. **This scenario would not happen if the innate immune system is 'trained' to make interferon early** and get ahead of the virus. It will recruit cells to clear the damage so that the adaptive immunity isn't kicked into overdrive. The virus will be controlled, or at least slowed, and the patient will be better.

Children have a strong innate immune system because they don't have pre-existing antibodies and T cells, because they haven't seen the pathogens. Children have enough innate response to SARS-CoV-2 even if viral loads in the nose are high. But they don't get as sick with respect to the respiratory tract, developing pneumonia. **Innate immunity is even intact in MIS-C, which points to a delayed impairment of adaptive immunity.**

(*Source: Medpage Today*)

US FDA Grants EUA for Moderna's COVID-19 Vaccine

The US Food and Drug Administration (FDA) becomes the second vaccine to be authorized for emergency use in the United States, and will likely increase the number of doses available in the coming days. The EUA for the Moderna vaccine comes after a review by the independent Vaccines and Related Biological Products Advisory Committee (VRBPAC) members on December 17, which voted 20-0 with one abstention, recommending the EUA. The vaccine is authorized for use in individuals aged 18 years and above. (*Medscape*)

Johnson & Johnson may Apply for EUA in February

Johnson & Johnson has recruited 45,000 participants in phase III clinical trials of its coronavirus vaccine and hopes to apply for a EUA from the FDA in the month of February. Data from phase III is expected to be available by January end.

If the data suggest that the vaccine is safe and effective, the company is expected to submit an application for EUA to the US FDA in February.

This vaccine doesn't need to be frozen and only requires one dose. Johnson & Johnson had to halt its clinical trials in the fall as a participant developed an "unexplained illness". However, the trials were re-started 2 weeks later.

Johnson & Johnson said earlier this month that it would reduce the number of phase III participants from its original aim of 60,000. (*Medscape*)

Two Doses of Oxford/AstraZeneca Vaccine Provoked Good Immune Response: Early Data

Oxford's COVID-19 vaccine candidate induces a better immune response when a two full-dose regimen is used rather than a full-dose followed by a half-dose booster, as per the university. The vaccine candidate, licensed to AstraZeneca, had in previously published interim late stage trial results, shown higher efficacy when a half-dose was followed by a full-dose, compared to a two full-dose regimen. More work is needed; however, to confirm the result. The subgroup details from the Phase I/II clinical trials made no reference to the half-dose/full-dose regimen, which, according to Oxford, had been "unplanned" but approved by regulators. (*Reuters*)

Vitamin D Deficiency in COVID-19 Quadrupled Death Rate

- Vitamin D deficiency on hospital admission was found to be associated with 3.7-times increased likelihood of dying from COVID-19, suggests a new study.
- Around 60% of patients with COVID-19 were vitamin D deficient at the time of hospitalization, with men in the advanced stages of COVID-19 pneumonia having the greatest deficit.
- The results were independent of comorbidities known to be affected by vitamin D deficiency, stated the authors, led by Dieter De Smet, MD, from AZ Delta General Hospital, Roeselare, Belgium.

The findings emphasize the need for RCTs specifically focused at vitamin D-deficient patients at intake, and urge for general avoidance of vitamin D deficiency as a safe and inexpensive possible mitigation of the pandemic, suggest researchers in their article, published online in the *American Journal of Clinical Pathology*.

A 3.7-fold hike in death rate if someone's vitamin D level was below 20 [ng/mL] is staggering. It is among the most important risk factors to consider.

It is not clear if vitamin D levels act as an acute-phase reactant, declining due to the infection, with larger fall indicating more severe disease, or whether vitamin D deficiency is leading to worse outcomes.

This is possibly due to the loss in the protective action of vitamin D on the immune system and against the SARS-CoV-2-induced cytokine storm.

The study had reported more prevalent vitamin D deficiency among men compared to women, most likely because women are more often treated with vitamin D for osteoporosis.

The study should prompt all clinicians and health authorities to consider vitamin D supplementation as an additional tool in the fight against COVID-19, more so for the prevention of infection in individuals at high risk of both COVID-19 and hypovitaminosis D, such as the elderly. (*Medscape*)

Can RAS Dysfunction Explain COVID Effects?

An article published in the *New England Journal of Medicine* proposed endothelialitis as the unifying mechanism for the extensive pathology of COVID-19. An alternative view indicates that virus-induced upregulation of the renin-angiotensin system (RAS) is accountable for the diverse systemic effects of COVID-19. (*Medscape*)

Results of ACTIV-3 Trial Published

Preliminary results of a Phase 3, randomized, placebo-controlled clinical trial evaluating the investigative monoclonal antibody LY-CoV555 in hospitalized COVID-19 patients have been published in *The New England Journal of Medicine*. The antibody was found not to yield clinical benefit compared to placebo. (*NIH*)

REGN-COV2 in Outpatients with COVID-19

REGN-COV2, a neutralizing antibody cocktail, was shown to reduce viral load in nonhospitalized patients with COVID-19, with a greater effect seen in patients whose immune response had not yet been initiated or who had a high viral load at baseline, in an interim analysis of an ongoing phase 1-3 trial published in *The New England Journal of Medicine*. (*DG Alerts*)

Pulse Oximeters

- Pulse oximeters have 3-fold higher odds of missing oxygen starvation in Blacks as compared to whites.
- Among 1,609 patients treated earlier this year at the University of Michigan Hospital, in Ann Arbor, 11.7% of Blacks were found to have an alarming arterial oxygen saturation of <88%, measured directly in the blood, despite their pulse oximetry levels showing the normal range of 92-96%. The devices, originally designed for people with light skin, missed low oxygen levels in only 3.6% of whites, which represented a statistically significant difference.
- When investigators assessed data from 8,392 other patients treated at 178 ICUs during 2014 and 2015, pulse oximeters appeared to miss low blood oxygen levels in 17.0% of Black patients compared to 6.2% of whites; again a significant difference.
- Dr Michael Sjoding of the University of Michigan Medical School, and colleagues noted that reliance on pulse oximetry to triage patients and adjust supplemental oxygen levels may place Black patients at an escalated risk for hypoxemia. The analysis is published in the *New England Journal of Medicine*.
- The devices make use of red and infrared light to gauge the color of hemoglobin, which darkens to purple-red as the oxygen levels decline. Since pulse oximeters were mostly tested on whites when they were developed, they are calibrated for light skinned individuals.
- The racial discrepancy was evident even after the investigators excluded people with diabetes and elevated carboxyhemoglobin levels. (*Source: Medscape*)

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News and Views

Influence of Childhood Obesity on Liver Health

Occurrence of childhood obesity, a worrisome worldwide epidemic has augmented over the last 3 decades. This rapidly increasing trend warrants the need to consider accurate body mass index (BMI) classification, as well as metabolic and cardiovascular, and hepatic outcomes. The author of the current study reviewed literature in PubMed and EMBASE and highlighted data that assessed the effects of obesity on cardiovascular and liver health.

In addition, investigators also determined the current literature that studied the role of excessive body fat accumulation in childhood and across adulthood on cardiovascular and hepatic alterations. Besides, the influence of physical and dietary behaviors starting from childhood on cardio-metabolic consequences was also considered.

It was observed that in children, due to increasing obesity, nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease. Similarly, nonalcoholic steatohepatitis (NASH) in children may evolve to fibrosis, cirrhosis and liver failure, as evidence suggest that these changes can begin as early as 8 years. However, correlation between NAFLD and NASH, in children is not as strong as adults, suggesting a milder phenotype of NAFLD. Therefore, early identification of NAFLD along with comorbidities in children can act as a preventive measure against death because of cardiovascular disorders in adults. Various trials revealed that while diagnosing through elevated serum aminotransferases, imaging or liver biopsy, prevalence of NAFLD in children and adolescents and in obese children ranges between 6 and 38%, varying according to the context, the population studied and the ethnicity.

Thus, epidemic of obesity and obesity-related comorbidities worldwide pose a significant challenge regarding the impact of early abnormalities during childhood and adolescence. Hence, early identification with the proper metabolic screening along with dietary interventions and physical activity can act as an important aid in children to prevent the onset of obesity, cardiovascular diseases (CVDs) and diabetes risk during adulthood.

(*Source: World J Pediatr. 2020;1-8.*)

ADA 2021 Standards Address Financial Barriers to Care in Diabetes

For 2021, the American Diabetes Association (ADA) offers new guidance on assessment of patients' financial and social barriers to care, particularly considering the coronavirus disease 2019 (COVID-19) pandemic, individualizing treatment for patients with type 2 diabetes and the use of diabetes technology.

The annual ADA update includes new clinical information that has become available since the last Standards were published. "Standards of Medical Care in Diabetes—2021," was published online as a supplement to *Diabetes Care*. In the new Standards, the ADA advises that patients must be assessed for food and housing insecurity, social support and cost-related medication nonadherence, and those who are identified as having difficulty must be referred to appropriate community resources… (*Medscape*)

WHO Launches Labour Care Guide

The World Health Organization (WHO) and HRP have launched the "Labour Care Guide" in a bid to improve every woman's experience of childbirth, and to ensure health and well-being of women and their babies.

The WHO Labour Care Guide is a new tool, putting the WHO recommendations on intrapartum care into practice. It is aimed at assisting skilled healthcare personnel to provide woman-centered, safe and effective care and to enhance the outcome and experience of childbirth for every woman and baby. This tool tends to advance an individual-centered approach to monitoring a woman's as well as her baby's health and well-being from active first stage of labour to the end of second stage of labour… (*WHO*)

FDA Authorizes Antigen Test as First OTC At-Home Diagnostic Test for COVID-19

The US Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) for the first over-the-counter (OTC) complete at-home test for the diagnosis of COVID-19.

The Ellume COVID-19 Home Test is a rapid, lateral flow antigen test. In this test, a liquid sample runs along a surface with reactive molecules. The test identifies fragments of proteins of the severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) virus from a nasal swab sample from an individual 2 years of age or older. The FDA has provided authorization to over 225 diagnostic tests for COVID-19 since the outset of the pandemic, including more than 25 tests that allow for home sample collection, followed by sending them to a lab for testing. The Ellume COVID-19 Home Test is the first COVID-19 test that can be used completely at home without the need for a prescription… (*FDA*)

Risk of Bone Fractures Increased in Non-meat Eaters

Compared with meat eaters, vegans were found to be at a heightened risk of total and site-specific fracture of the hip, leg and vertebrae, in a study published in *BMC Medicine*. Vegetarians and fish eaters also had a higher risk of hip fractures than meat eaters.

Investigators collected dietary information of 54,898 participants in the EPIC-Oxford study at baseline (1993-2001) and follow-up (2010). Participants were followed continuously for 17.6 years on average until 2016 for the occurrence of fractures. After adjusting for socioeconomic factors, lifestyle confounders and BMI, compared with meat eaters, the risks of hip fracture were higher in fish eaters (adjusted hazard ratio [aHR], 1.26; 95% confidence interval [CI], 1.02-1.54), vegetarians (aHR, 1.25; 95% CI, 1.04-1.50), and vegans (aHR, 2.31; 95% CI, 1.66-3.22). Vegans also appeared to have higher risks of total fracture, hip fracture, leg fracture and other main site fractures… (*Medscape*)

Fast Walking in Narrow Corridors can Increase COVID Transmission Risk, Says Study

According to a study published in the journal *Physics of Fluids*, fast walking in narrow spaces behind a group of people can cause a significant rise in COVID-19 transmission risk, particularly in children. The study noted that respiratory droplets carrying the virus can trail behind infected individuals moving through narrow corridors.

Results of the computer simulation highlighted the importance of the shape of spaces in predicting how virus-laden droplets travel through the air. The study suggests that if a person walking through a corridor coughs, their breath expels droplets that can move around and behind their body, thus forming a wake, just like that formed by a boat in water as it travels. Researchers noted a "re-circulation bubble" directly behind the person's torso and a long wake streaming out behind the individual at about the height of the waist… (*HT – PTI*)

Baseline Report for Decade of Healthy Ageing Launched by WHO

Around 14% of all people aged 60 years and above, amounting to over 142 million people, are unable to meet their basic daily needs, suggests the Baseline report for the Decade of Healthy Ageing, launched by the WHO.

The Decade of Healthy Ageing begins in 2021 and aims at optimizing functional ability. It focuses on five interrelated abilities that must be enjoyed by all older people and include the ability to meet basic needs; to continue to learn and make decisions; to be mobile; to build and maintain relationships and to contribute to society. The Baseline report also puts forward the experience of countries which have successfully initiated healthy ageing initiatives in these areas, such as Ireland, Mexico and Viet Nam… (*WHO*)

Babies Born to COVID-19 Mothers have Antibodies: Singapore Study

All five babies born to women with COVID-19 infection have had antibodies against the virus, revealed a study in Singapore. However, the investigators stated that it was not clear what level of protection this may offer.

The study of 16 women also noted that most were mildly infected, and more severe reactions were observed in older women with a high BMI. The number of antibodies in the babies varied, and was found to be greater among those whose mothers had contracted the infection closer to the time of delivery. Researchers stated that further monitoring will be needed to determine whether the antibodies will fall as the babies get older… (*Reuters*)

FDA Authorizes Home Use of 15-minute COVID-19 Antigen Test

The US FDA has granted EUA for COVID-19 Ag Card rapid antigen test for SARS-CoV-2 detection. The test can now be used at home with a prescription.

In August, the COVID-19 Ag Card was authorized by the FDA as a point-of-care test in clinical settings, while the new EUA has cleared the test for prescription use at home with self-collected nasal swab samples for individuals 15 years of age or above who are suspected of having COVID-19, within the first week of onset of symptoms. It has also been authorized for use with adult-collected nasal swab samples from individuals aged 4 years or older suspected of having COVID-19 within 7 days… (*Medscape*)

Protecting Eyes from COVID-19

Dr Anthony Fauci has suggested that eyewear, including goggles or face shields, can provide more complete protection from the coronavirus in comparison with covering just the nose and mouth.

Fauci backs the use of eyewear for those who want "perfect protection of the mucosal surfaces", including the eyes. However, for the general public, it is optional to use eye protection, but could act as an effective means to reduce the risk for COVID-19, depending on the environment.

In updated guidance - Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the COVID-19 Pandemic - the Centers for Disease Control and Prevention (CDC) recommends the use of eye protection for healthcare providers caring for patients with suspected or confirmed SARS-CoV-2 infection, and those working in facilities located in areas with moderate to substantial community transmission who have greater odds of encountering asymptomatic or presymptomatic patients with SARS-CoV-2 infection (*Medscape*)

First Oral Hormone Therapy for Advanced Prostate Cancer Approved

The US FDA has granted approval for relugolix for the treatment of adult patients with advanced prostate cancer.

The safety and efficacy of the drug were assessed in a randomized, open-label trial in men with advanced prostate cancer. The patients were randomized to receive either relugolix once daily or injections of leuprolide, every 3 months for 48 weeks. Investigators assessed if relugolix achieved and maintained low enough levels of testosterone (castrate levels), by Day 29 through end of the treatment course. Among the 622 patients who received relugolix, the castration rate was found to be 96.7%. The most common side effects of the drug include hot flush, raised glucose, increased triglycerides, musculoskeletal pain, reduced hemoglobin, fatigue, constipation, diarrhea and raised levels of certain liver enzymes… (*FDA*)

COVID-19 More Serious Than Flu, Says Study

Nearly twice as many patients were admitted to hospitals in France for COVID-19 over a 2-month period compared to those admitted for seasonal influenza during a 3-month period the previous year, reported a study published online in *The Lancet Respiratory Medicine*.

In-hospital mortality was around three-fold higher for COVID-19 compared to that for seasonal influenza, noted the researchers. Patients with COVID-19 appeared to have a higher likelihood of requiring invasive mechanical ventilation (9.7% vs. 4%) and also had longer average ICU stays (15 days vs. 8 days). The death rate was found to be 16.9% among patients hospitalized with COVID-19, in comparison with 5.8% among patients hospitalized with influenza… (*Medscape*).

2020 List of 100+ Outstanding Women Nurses and Midwives Unveiled

Marking the end of the Year of the Nurse and Midwife, the 2020 List of 100+ Outstanding Women Nurses and Midwives has been unveiled.

The partnership of the WHO, United Nations Population Fund (UNFPA), Nursing Now, International Council of Nurses (ICN), International Confederation of Midwives (ICM) and Women in Global Health (WGH), highlights the achievements and contributions of nurses and midwives from 43 countries, across 6 global regions, and recognizes these women as well as millions of nurses and midwives across the globe. Midwives and nurses form the backbone of primary health systems and their care during this year of the pandemic has had an impact far beyond the facilities where they work… (*WHO*)

US Frontline Essential Workers, People 75 and Older, should be Next for COVID Vaccination, Says CDC Panel

A US Centers for Disease Control and Prevention advisory panel has recommended that frontline essential workers and individuals aged 75 years and above should be next to receive a COVID-19 vaccine.

The Advisory Committee on Immunization Practices (ACIP) voted 13 to 1 recommending frontline essential workers, including first responders, teachers, food and agriculture, manufacturing, postal service, public transit and grocery store workers, to be the next priority for vaccination. The step would make 51 million people eligible to get vaccinated in the next round. However, it wasn't immediately clear when the next round would start. Frontline healthcare workers and nursing home residents had already been recommended by the panel to be the first priority groups… (*Reuters*)

Johnson & Johnson Hopes to Apply for EUA for its COVID-19 Vaccine in February

Johnson & Johnson has recruited 45,000 participants in phase III of its clinical trials for a COVID-19 vaccine and

hopes to apply for a EUA from the FDA in the month of February, stated the company in a news release.

It is expected that data from phase III will be available by the end of January. The Johnson & Johnson vaccine differs from the Pfizer and Moderna vaccines as it doesn't need to be frozen and only requires one dose. Trials of the Johnson & Johnson vaccine were halted in the fall as a participant developed an "unexplained illness". However, the trials were started again 2 weeks later… (*Medscape*)

LVAD Approved for Children

The HeartMate 3 left ventricular assist device (LVAD) has been approved for pediatric patients with advanced heart failure, stated Abbott. The approval includes both bridge to transplant and destination therapy for children not eligible for a transplant owing to potential complications or risk related to the procedure. The HeartMate 3 device only fits in large children or teens.

The pediatric approval for the device was based on findings from 9 centers in the Advanced Cardiac Therapies Improving Outcomes Network (ACTION) consortium of US pediatric centers. Among 35 patients implanted, with a median age of 16 years, most with dilated cardiomyopathy alone (63%) or in the setting of neuromuscular disease (20%), the survival rate was found to be 97% to median 78 days of follow-up. The device was shown to be successful in children as small as 19 kg… (*Medpage Today*)

COVID-19's Impact on Epilepsy Around the World

The COVID-19 pandemic has placed an enormous strain on patients with epilepsy across the world, suggests new research.

Nearly 30% of respondents to a global survey, on the impact of the COVID-19 pandemic on epilepsy patients and services, reported mental strain and 20% reported sleep problems. These could act as triggers for worsening seizures and could point to increasing epilepsy risks, noted study investigator Arjune Sen. The most notable finding of the study was that people with epilepsy and their caregivers reported poor communication on epilepsy-associated risks, stated Sen. The study was presented at the virtual American Epilepsy Society (AES) 74th Annual Meeting 2020… (*Medscape*)

GI Bleeds Linked with Worse Prognosis for COVID-19 Inpatients

Gastrointestinal (GI) bleeding was noted in 3% of hospitalized COVID-19 patients, and a bleed developing during hospitalization was associated with greater mortality, revealed a large New York cohort study.

Anticoagulation or antiplatelet agents were not found to be the risk factors for GI bleeding, but they did not protect against them either, reported researchers. Patients treated at a large health system in the metropolitan New York area between March 1 and April 27, 2020 were included in the study. Out of 11,158 polymerase chain reaction (PCR)-positive COVID-19 inpatients, 314 were found to have GI bleeding, for a rate of 3%, and a GI bleed during hospitalization was tied to an increased mortality risk with an odds ratio of 1.58. The study was published online in the *Journal of Internal Medicine*… (*Medpage Today*)

Bariatric Surgery Might Reduce COVID-19 Severity

Individuals with obesity who lost weight after bariatric surgery and later contracted COVID-19 appeared to have lesser odds of being admitted to the hospital for COVID-19, and the disease was found to be less severe than among COVID-19 patients with obesity who had not undergone the surgery, suggested a new retrospective analysis. Investigators matched 33 COVID-19 patients who had undergone metabolic surgery with 330 control patients with obesity who were infected with COVID-19 during the first wave of the pandemic. Surgery appeared to be associated with a 69% reduction in the risk of being hospitalized due to COVID-19. None of the surgery patients needed intensive care, mechanical ventilation or dialysis, and none of them died. The findings were published in *Surgery for Obesity and Related Diseases*… (*Medscape*)

After COVID-19 Infection, Antibodies Highly Protective for Months: Study

Following SARS-CoV-2 infection, antibodies protect most healthcare workers from reinfection for up to 6 months, suggested the first prospective study of the subject. Investigators looked for the presence of two antibodies to SARS-CoV-2 among 12,541 healthcare workers in the United Kingdom, including nearly 10% who had a history of PCR-confirmed infection. In all, 223 who did not have antibodies tested positive on PCR for the virus during 31 weeks of follow-up; two participants who did not have antibodies at baseline tested positive. The odds of a subsequent positive PCR test result were 1.09 per 10,000 days at risk among individuals who did not have antibodies, compared to 0.13 per 10,000 days among those with anti-spike antibodies. The findings were published online in *The New England Journal of Medicine*… (*Medscape*)

COVID-19 Immunity Lasts At Least 8 Months: Study

People who have recovered from COVID-19 infection have immune memory to protect against reinfection for at least 8 months, suggests a new study published in the journal *Science Immunology*. The study provides robust evidence that COVID-19 vaccines will likely work for long periods.

Earlier studies have; however, shown that antibodies against the coronavirus dwindle after the first few months of infection. Investigators enrolled a cohort of 25 COVID-19 patients and took 36 blood samples from them from Day 4 post infection to Day 242 post infection. Antibodies against the virus started to decline after 20 days post infection. However, all patients continued to have memory B cells that recognized one of the two components of the virus - the spike protein and the nucleocapsid proteins. Investigators noted that the virus-specific memory B cells were present for as long as 8 months after infection… (*NDTV – PTI*)

Bamlanivimab Ineffective in Hospitalized COVID-19 Patients

Use of bamlanivimab (LY-CoV555), a monoclonal antibody for COVID-19, with remdesivir was found not to be effective for patients hospitalized with COVID-19 in a randomized trial.

Investigators noted no significant difference in sustained recovery over a 90-day period with the combination compared to remdesivir and placebo (rate ratio [RR] 1.06, 95% CI 0.77-1.47). There appeared to be no significant difference in the primary safety outcome as well. The rate of experiencing an adverse outcome (death, serious adverse events or clinical Grade 3 and 4 adverse events through Day 5) was 19% in the investigational group compared to 14% in the placebo group (odds ratio [OR] 1.56, 95% CI 0.78-3.10, p = 0.20), reported researchers in the *New England Journal of Medicine*… (*Medpage Today*)

Sex Differences in Post-CABG Mortality

A new study, published online December 23 in *JAMA Cardiology*, has revealed sex differences in mortality rates among patients undergoing coronary artery bypass grafting (CABG).

Researchers noted that 7 years following a CABG procedure, mortality was lower in men, but not in women, who had been subjected to multiple rather than single arterial grafting. On stratifying patients based on their estimated risk for death, both low-risk men and women appeared to have a lower mortality rate with multiple arterial grafting, but not high-risk patients of both sexes; this risk cut-off was different among the two genders. Women, therefore, seem to have a worse preoperative profile than men… (*Medscape*)

Ultraprocessed Food Tied to Increased CVD, Death

A longitudinal analysis of over 22,000 men and women from southern Italy has shown that those who consumed the most ultra-processed food (UPF) had the highest risk for CVD and all-cause mortality, likely driven by a diet high in sugar. High consumption of UPF in this Mediterranean cohort was found to be linked with a 58% greater risk for CVD mortality and 52% higher risk of death from ischemic heart disease (IHD) and cerebrovascular causes, independent of known risk factors for CVD, even among those who adhered to the Mediterranean diet. The findings were published online in the *American Journal of Clinical Nutrition*… (*Medscape*)

Nurse Burnout has Increased During Pandemic: Survey

Nurses and advanced practice registered nurses (APRNs) were asked to rate their burnout before the pandemic and 6 months into it, and levels reported were found to have quadrupled in some cases.

The Medscape Nurse Career Satisfaction Report 2020 gathered responses from over 10,000 nurses and APRNs in the United States and revealed that in every group, more nurses rated themselves as very or somewhat burned out in comparison with the pre-pandemic time. Survey authors noted that the burnout numbers came in the summer, before the number of patients in the fall started overwhelming hospitals across the country. Most respondents had cared for COVID-19 patients by the end of summer. CRNAs were most likely to have treated COVID-19 patients (73%), while central nervous systems were the least likely (38%)... (*Medscape*)

Spinal Benefits Seen with Secukinumab in Psoriatic Arthritis

Secukinumab was found to be effective for axial manifestations of psoriatic arthritis in a 52-week multicenter phase III study.

Investigators noted that the primary endpoint of a 20% response on the criteria of the Assessment of SpondyloArthritis international Society (ASAS20) at Week 12 was met by 63% and 66% of patients randomized to subcutaneous secukinumab, 300 mg or 150 mg every 4 weeks, in comparison with 31% in the placebo group, reported researchers in *Annals of the Rheumatic Diseases*. The odds ratios of achieving ASAS20 responses were

3.8 (95% CI 2.4-6.1) and 4.4 (95% CI 2.7-7, p < 0.0001) in the 300 mg and 150 mg groups, respectively, in comparison with placebo… (*Medpage Today*)

Total Body Irradiation or Chemotherapy Conditioning in Pediatric ALL

Survival in pediatric acute lymphoblastic leukemia (ALL) was found to improve significantly with total body irradiation (TBI) and etoposide prior to allogeneic hematopoietic stem-cell transplant (HSCT) in comparison with combination chemotherapy in a randomized trial.

Estimated overall survival (OS) at 2 years improved from 75% with chemo conditioning to 91% with TBI *plus* etoposide (p < 0.0001). As-treated analyses provided similar results irrespective of the chemotherapy conditioning regimen given to the patients. TBI was also associated with a significantly lower 2-year cumulative risk of relapse and treatment-related mortality (TRM). The incidence of acute and chronic graft-versus-host disease (GVHD) did not differ between treatment groups, reported researchers in the *Journal of Clinical Oncology*… (*Medpage Today*)

Conservative Approach to Inpatient BP Spikes could be Safer

Treating asymptomatic hypertension in patients admitted for noncardiac causes appeared to be linked with more end organ damage as compared to when it was left alone, suggests an observational study.

Such antihypertensive-treated patients were shown to have a higher incidence of subsequent inpatient acute kidney injury (10.3% vs. 7.9%, p < 0.001) and myocardial injury (1.2% vs. 0.6%, p = 0.003), compared to non-treated counterparts in a propensity-matched analysis of 4,520 patient-pairs, reported researchers online in *JAMA Internal Medicine*. Investigators noted that the associated harms were similar for oral and IV treatments and were observed across systolic blood pressure intervals. There was no group of patients whose outcomes were better with treatment… (*Medpage Today*)

ICMR Says Careless Use of Therapies may Lead to Mutations

The Indian Council of Medical Research (ICMR) has cautioned against non-judicious use of therapies that have not been established for the treatment of COVID-19 as it can result in immune pressure on the SARS-CoV-2 virus, eventually leading to mutations. ICMR Director General Balram Bhargava stated that even vaccine administration has to be carefully observed, adding that immunity breakthrough may occur because of the vaccine. He said, "Genetic mutations occur in the respiratory viruses and these minor drifts may occur from time to time but once several drifts occur it has higher transmissibility rate as it happened in the United Kingdom. So that is a point of concern although we are testing in India for virus variants regularly." (*ET Healthworld – TNN*)

First Generic of Drug Used to Treat Severe Hypoglycemia Receives FDA Approval

The US FDA has granted approval to the first generic of glucagon for injection USP, 1 mg/vial, to treat severe hypoglycemia.

The drug is also used as a diagnostic aid in the radiologic examination of the stomach, duodenum, small bowel and colon when reduced intestinal motility would be beneficial. The generic glucagon for injection is a synthetic version of human glucagon. Glucagon causes the liver to increase blood sugar levels rapidly. It also diminishes the movement of the gastrointestinal tract. The most common side effects of glucagon for injection include nausea and vomiting, a temporary escalation in heart rate, and redness and swelling of the injection site… (*FDA*)

10.4 Million Children in DRC, Northeast Nigeria, Central Sahel, South Sudan and Yemen will Suffer from Acute Malnutrition in 2021

The UNICEF has expressed concern over the health and well-being of 10.4 million children projected to suffer from acute malnutrition in 2021 in the Democratic Republic of the Congo (DRC), northeast Nigeria, the Central Sahel, South Sudan and Yemen.

All these countries or regions are experiencing appalling humanitarian crises while dealing with increasing food insecurity, a pandemic and, except for the Central Sahel, an imminent famine. In the DRC alone, 3.3 million children under five are estimated to suffer from acute malnutrition in 2021, including at least 1 million with severe acute malnutrition. In all these countries as well as in other parts, UNICEF calls on humanitarian actors on the ground and the international community to work towards expanding access to and support for nutrition, health, as well as water and sanitation services for children and their families… (*UNICEF*)

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Importance of Silence

KK AGGARWAL

True silence is the silence between thoughts and represents the true self, consciousness or the soul. It is a web of energized information ready to take all provided there is a right intent. Meditation is the process of achieving this silence.

Observing silence is another way of getting benefits of meditation. Many yogis in the past have recommended and observed silence now and then. Mahatma Gandhi used to spend one day of each week in silence. He believed that abstaining from speech brought him inner peace and happiness. On these days, he communicated with others only by writing on paper.

Hindu principles also talk about a correlation between mauna (silence) and shanti (harmony). Mauna Ekadashi is a ritual followed traditionally in our country. On this day, the person is not supposed to speak at all and keep complete silence throughout day and night. It gives immense peace to the mind and strength to the body. In Jainism, this ritual has a lot of importance. Nimith was a great Jain saint, who long ago, asked all Jains to observe this vrata. Some people recommend that on every ekadashi one should observe silence for few hours in a day if not the whole day.

Deepak Chopra, in his book 7 Laws of Spiritual Success, talks in great detail about the importance of observing silence in day-to-day life. He recommends that everyone should observe silence for 20 minutes every day. Silence helps to redirect our imagination towards self from the outer atmosphere. Even Swami Sivananda, in his teachings has recommended daily observation of mauna for 2 hours, milk and fruits every day, studying one chapter of Bhagwad Gita daily, regular charity and donating one-tenth of the income in the welfare of the society. Ekadashi is the 11th day of Hindu lunar fortnight. Ekadashi is the day of celebration occurring twice a month, meant for meditation and increasing soul consciousness.

Vinoba Bhave was a great sage of our country who is known for the Bhoodaan movement. He was a great advocator and practical preacher of mauna vrata.

Mauna means silence and vrata means vow; hence, mauna vrata means vow of silence. Mauna was practiced by saints to end enmity. Prolonged silence as a form of silence is observed by rishi munis.

Silence is a source of all that exists. Silence is where conscious dwells. There is no religious tradition that does not talk about silence. It breaks outward communication and forces a dialogue towards inner communication. This is one reason why all prayers, meditation and worship or any other practice whether we attune our mind to the spiritual consciousness within are done in silence. After the death of a person, it is a practice to observe silence for 2 minutes. The immediate benefit is that it saves a tremendous amount of energy.

Silence is cessation of both sensory and mental activity. It is like having a still mind and listening to the inner mind. Behind this screen of our internal dialogue is the silence of spirit. Meditation is the combination of observing silence and the art of observation.

Group Editor-in-Chief, IJCP Group

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Determination and Persistence

Engineer John Roebling started building the Brooklyn Bridge in New York, USA back in 1870. The bridge was completed in 1883, 13 years later.

This creative engineer was excited about an idea of building a bridge that would connect New York with the Long Island. Bridge building experts across the world; however, were of a different opinion and considered this to be an impossible feat. Everyone told Roebling to forget the idea; It was not practical; It had never been done before.

Roebling; however, could not let go of the vision he had in his mind. He thought about it all the time and knew somewhere deep down that it could be done. After much persuasion, he convinced his son Washington, a budding engineer, that the bridge could be built.

The father and son worked together on concepts of how it could be done and how the obstacles could be overcome. With great excitement they hired their crew and began to build their dream bridge.

The project started well, but only a few months underway, John Roebling lost his life in a tragic accident on the site. Washington was also injured and sustained some brain damage, which resulted in him not being able to talk or walk.

"We told them so." "Crazy men and their crazy dreams." "It's foolish to chase wild visions." Everyone had a negative comment to make and felt that the project should be shut.

Despite his handicap, Washington still wanted to complete the bridge and his mind was still as sharp as ever. He tried to inspire some of his friends, but they were too daunted by the task.

As he lay one day on his bed in his hospital room, suddenly an idea hit him. He could only move one finger and decided to make the best use of it. He gradually developed a code of communication with his wife.

He touched his wife's arm with that finger, suggesting that he wanted her to call the engineers again. He used the method of tapping her arm to tell the engineers what to do. The project was under way again.

For 13 years, Washington would tap out his instructions on his wife's arm, until the bridge was finally completed. The magnificent Brooklyn Bridge stands today in all its glory as a tribute to the triumph of one man's invincible spirit and his determination. It also stands as a tribute to the engineers and their team work, and to their faith in a man who was considered mad by the world. It stands too as a monument to the love and devotion of his wife who patiently decoded the messages of her husband for the engineers.

This is among the best examples of a never-say-die attitude to achieve an impossible goal.

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Patients with Cancer a 'High Priority' Group for COVID-19 Vaccine: AACR

As the COVID-19 vaccines are being distributed, the American Association for Cancer Research (AACR) has called for people with cancer to be considered as a high priority group.

The AACR's COVID-19 and Cancer Task Force has stated that the available evidence suggests that patients with cancer, especially those with hematological malignancies, must be considered among the high-risk groups for priority COVID-19 vaccination. Literature review suggests that COVID-19 fatality rates among patients with cancer were twice that of individuals without cancer. The higher mortality rates showed an upward trend even after adjusting for confounders including age, sex and comorbidities. This suggests that there is a greater risk for severe disease and COVID-19-related mortality. The AACR position paper appears online in *Cancer Discovery*… (*Medscape*)

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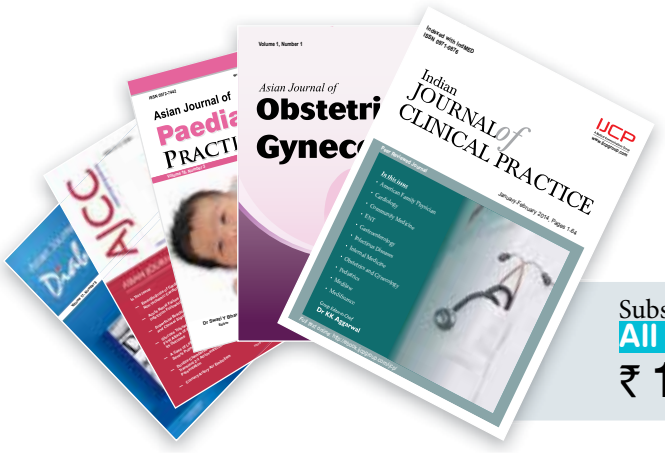

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Lighter Side of Medicine

HUMOR

MY GRADES

A high school student came home one night rather depressed.

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

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

"What do you mean 'all wet?'"

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

GORGEOUS, BEAUTIFUL

A man was just waking up from anesthesia after surgery, and his wife was sitting by his side.

His eyes fluttered open and he said, "You are gorgeous."

Then he fell asleep again. His wife had never heard him say that, so she stayed by his side.

A few minutes later, his eyes fluttered open and he said, "You are beautiful!"

Then he fell asleep again.

After a few minutes, he again opened his eyes and said, "You are cute!"

The wife was disappointed because instead of 'gorgeous' or 'beautiful,' it was now just 'Cute.'

She said, "What happened to 'gorgeous, beautiful'?"

Her husband replied, "The drugs are wearing off!"

RAILROAD ACCIDENT

In a terrible accident at a railroad crossing, a train smashed into a car and pushed it nearly 400 yards down the track. Though no one was killed, the driver took the train company to court.

At the trial, the engineer insisted that he had given the driver ample warning by waving his lantern back and forth for nearly a minute. He even stood and convincingly demonstrated how he'd done it. The court believed his story, and the suit was dismissed.

"Congratulations," the lawyer said to the engineer when it was over. "You did superbly under cross-examination."

"Thanks," he said, "but he sure had me worried."

"How's that?" the lawyer asked.

"I was afraid he was going to ask if the lantern was lit!"

ON TRIAL

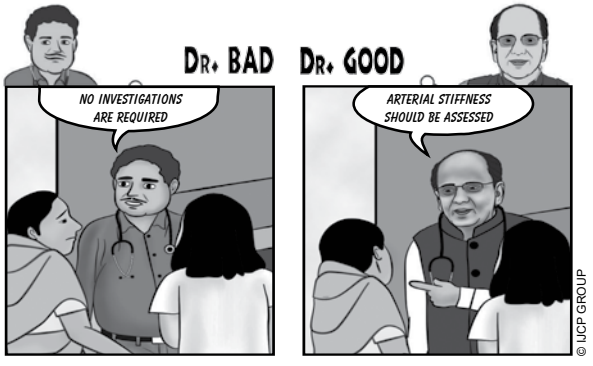
After a trial had been going on for 3 days, Finley, the man accused of committing the crimes, stood up and approached the judge's bench. "Your Honor, I would like to change my plea from 'innocent' to 'guilty' of the charges."

The judge angrily banged his fist on the desk. "If you're guilty, why didn't you say so in the first place and save this court a lot of time and inconvenience?" he demanded.

Finley looked up wide-eyed and stated, "Well, when the trial started I thought I was innocent, but that was before I heard all the evidence against me."

Dr. Good and Dr. Bad

SITUATION: A 53-year-old woman with type 2 diabetes had increased heart rate since the past 1-2 days.



LESSON: An observational, cross-sectional study reported that female gender and faster heart rate display an independent association with increased arterial stiffness in patients with type 2 diabetes. Furthermore, prior stroke is more common in females with increased arterial stiffness. Moreover, elevated postprandial 2-hour C-peptide level was also independently related to increased arterial stiffness.

Anatol J Cardiol. 2017;18(5):347-52.

Indian
JOURNAL of
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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

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