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COVID Facts and Myth Busters

COVID-19 PATIENTS CANNOT SHED VIRUS AFTER SYMPTOMS DISAPPEAR

No. A new study suggests that half of the patients treated for mild coronavirus disease (COVID-19) infection still had coronavirus for up to 8 days after symptoms disappeared (*published online March 23, 2020, American Journal of Respiratory and Critical Care Medicine).* It is possible that more severe infections may have even longer shedding times. The time from infection to onset of symptoms, i.e., the incubation period, was noted to be 5 days among all patients expect one. The average symptom duration was 8 days, while the length of time patients remained contagious after the symptoms disappeared ranged from 1 to 8 days. Two patients had diabetes and one had tuberculosis. Neither condition affected the timing of course of COVID-19 infection.

COVID-19 CANNOT BE AIRBORNE

Airborne transmission may be possible in specific circumstances wherein procedures that generate aerosols are performed, such as endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy and cardiopulmonary resuscitation (WHO). An analysis of 75,465 COVID-19 cases in China did not report airborne transmission (*JAMA. Published online March 4, 2020*).

LIKE SARS, COVID-19 CAN TRAVEL THROUGH FECO-ORAL ROOT

No. Some evidence suggests that COVID-19 infection may cause intestinal infection and be present in feces. Until today, only one study has cultured the COVID-19 virus from a single stool specimen (*China CDC Weekly. 2020;2(8):123-4*). There have been no reports of fecal-oral transmission of the COVID-19 virus till today (*WHO*).

MOSQUITOES CAN ALSO TRANSMIT CORONAVIRUS

No. To date there has been neither information nor evidence to suggest that the new coronavirus could be transmitted by mosquitoes. It is a respiratory virus, which spreads primarily through droplets generated when an infected person coughs or sneezes, or through droplets of saliva or discharge from the nose.

FACE-TO-FACE EATING IS SAFE

No. To gain access to your cells, the viral droplets need to enter through the eyes, nose or mouth. Sneezing and coughing are most likely the primary forms of transmission. Talking loudly face-to-face or sharing a meal with someone could also pose a risk. If you are able to smell what someone had for lunch, you are inhaling what they are breathing out, including any virus in their breath. The virus is smart; it makes the nose loose the smell, so to experience the smell you inhale deeply.

THERE ARE NO PREDICTORS OF TRANSMISSION

No. There are four factors that likely play a role in transmission: how close you get, how long you are near the person, whether that person projects viral droplets on you and how much you touch your face.

LOSS OF SMELL AND TASTE IS NOT A SCREENING TEST

No. The American Academy of Otolaryngology-Head & Neck Surgery (AAO-HNS) has proposed to **add anosmia and dysgeusia to the list of screening items for potential COVID-19**. Informally, these symptoms have been noted among some patients who have tested positive for COVID-19, and in some cases, anosmia was the only symptom. Therefore, in the absence of other respiratory disease (e.g., rhinosinusitis, allergic rhinitis), anosmia, hyposmia and dysgeusia should "warrant serious consideration for self-isolation and testing of these individuals" (AAO-HNS).

COVID VIRUS BEHAVES LIKE ANY OTHER VIRUS

No. Dengue taught us the value of platelet count to be interpreted along with hematocrit and COVID-19 is now teaching us the value of lymphocytes in blood test. It has been a standard teaching that all viral fevers will have high lymphocyte counts. Lymphopenia will only occur with human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS)-like illness, measles and hepatitis. **COVID-19 leads to low lymphocyte count**. Now all studies have shown it to be an important marker of COVID-19. Clues for COVID-19 include leukopenia, evident in 30-45% of patients, and lymphocytopenia, in 85% of the patients in the case series from China.

In the latest study published on March 9, 2020, in *The Lancet*, the authors showed that baseline lymphocyte count was significantly higher in survivors than nonsurvivors; in survivors, lymphocyte count was lowest on Day 7 after illness onset and improved during hospitalization, whereas severe lymphopenia was observed until death in nonsurvivors.

LUNG INVOLVEMENT IS UNILATERAL

No. In a report from a hospital in Shanghai, investigators reviewed the key initial CT findings in 51 consecutive patients hospitalized due to COVID-19 disease. All patients had thin-section noncontrast scans. Mean age was 49 (range, 16-79), and median time from symptom onset to CT was 4 days (*Radiology 2020 Apr*). Almost all patients had extensive multifocal involvement; **bilateral abnormalities were seen in 86% of cases**. Lesions were seen in the lower lobes, posterior lung fields, and peripheral lung zones. Three quarters of patients had ≥3 involved lobes. Various combinations of pure ground-glass opacities (GGOs), GGOs plus reticular or interlobular septal thickening, and GGOs plus consolidation were commonly noted. GGOs were predominant in patients whose symptoms started ≤4 days prior to CT, and areas of consolidation became increasingly evident in those with >4 days of symptoms.

Most Fevers cannot be Differentiated Clinically

No, here are some tips:

- Fever with cough and cold - Think of flu
- Fever with retro-orbital eye pain - Think of dengue
- Fever with joint pain which improves on bending - Think of Chikungunya
- Fever with lymphocytosis - Think of viral fever
- Fever with lymphopenia - Think of COVID-19, acute hepatitis, HIV
- Fever with jaundice - Rules out viral hepatitis
- Fever subsides capillary leakage appears - Think of dengue
- Low grade evening rise fever - Think of TB
- Fever with chills and rigors - Think of malaria, filaria, urinary tract infection, sepsis
- Fever with cough and breathlessness - Think of COVID-like illness
- Fever with ESR >100 - Think of painful thyroiditis, sepsis
- Fever with SGOT > SGPT - Think of dengue
- Fever with angry looking throat with no cough - Think of streptococcal sore throat
- Fever with red eyes - Think of Zika illness
- Fever with eschar - Think of scrub typhus
- Fever with single chills - Think of pneumonia
- Fever with jaundice - Rule out leptospirosis
- Fever with involvement of skin, joint and/or kidney - Rule out autoimmune disease
- Fever with TLC >15,000 - Think of sepsis
- Fever with positive thump sign - Rule out liver abscess

CAN RT-PCR BE FALSE-NEGATIVE?

Yes. Negative reverse-transcription polymerase chain reaction (RT-PCR) tests on oropharyngeal swabs despite CT findings suggestive of viral pneumonia have been reported in some patients who ultimately tested positive for SARS-coronavirus 2 (SARS-CoV-2) (*Radiology. 2020*). A false-negative test may be due to poor quality of specimen, or specimen collected late or very early, the specimen was not handled and shipped appropriately or technical reasons (*WHO*).

CAN A PERSON BE RT-PCR NEGATIVE AND IGM POSITIVE?

Yes. Serologic tests, as soon as generally available and adequately evaluated, should be able to identify patients who have either current or previous infection but a negative RT-PCR.

In a study of 58 patients with clinical, radiographic and epidemiologic features suspicious for COVID-19 but with negative RT-PCR testing, an immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) was positive in 93% (and was negative when tested separately on plasma specimens that predated the COVID-19 outbreak) (*Clin Infect Dis. 2020*).

CAN A VIRAL CULTURE BE DONE?

No. For safety reasons, specimens from a patient with suspected or documented COVID-19 should not be submitted for viral culture.

D-DIMER IS THE ONLY LAB CRITERIA FOR SEVERITY

No. Absolute lymphocytic count <800, D-dimer >100, creatine phosphokinase (CPK) >2 x ULN (upper limit of normal), C-reactive protein (CRP) >100, lactate dehydrogenase (LDH) >245, Trop I rising, ferritin >300 are also indicators of severity of infection.

THERE ARE NO STANDARD LAB GUIDELINES

- Daily tests: Complete blood count (CBC) with differential lymphocytes, comprehensive metabolic panel (CMP), CPK
- Risk stratification Q2-3 Day PRN (as needed): D-dimer, ferritin, ESR, CRP
- Once: HBV, HCV, HIV, Influenza A/B, RSV, Respiratory Panel (respiratory viral and bacterial pathogens), tracheal aspirate (if intubated).

ONLY TESTING CAN PICK UP HOTSPOTS

No, clusters can be identified by:

- Smart thermometers
- Social site postings pattern
- Spurt in low lymphocytes count noted by labs in an area
- Spurt in bilateral pneumonias noted by Radiologists in an area
- Spurt in ground glass appearances on chest CT noted by Radiologists in an area
- Spurt of cases with fever and cough noted by general practitioners (GPs)
- Spurt of cases with loss of taste or smell in an area
- Spurt of cases of interstitial pneumonia noted by Radiologists on ultrasound in an area.

ALL VIRAL INFECTIONS RAISE CRP LEVELS

No. CRP levels are increased (150-350 mg/L) in acute bacterial infections, while acute viral infections are associated with lower levels. But uncomplicated infections caused by COVID-19, adenovirus, influenza and cytomegalovirus can be associated with CRP levels of up to 100 mg/L (*Pediatr Infect Dis J. 1997;16(8):735-46; quiz 746-7*). Increased CRP in COVID patients indicates disease severity and poor prognosis.

ONLY TESTING CAN DECIDE THAT I HAVE RECOVERED

Myth: No. While the CDC has advised that all confirmed and suspected patients should be symptom-free and test negative twice within at least 24 hours to be considered as having recovered (Re-testing method), the **updated CDC guidance suggests a second method to determine recovery from COVID-19 without a test** (Non-testing method). If a confirmed or suspected COVID-19 patient is free of fever without the use of fever-reducing medication for at least 3 days, if it has been at least 7 days since the symptoms first appeared, the person can be considered recovered. Respiratory symptoms must also be improving during that time, but do not necessarily have to disappear completely by 7 days for the patient to be considered recovered.

NON-TESTING METHOD IS OK FOR HOSPITALIZED PATIENTS

Myth: No. Some patients infected with COVID-19 may be contagious for a longer period than others.

Testing method is the preferred option for those who are hospitalized, or severely immunocompromised, or being transferred to long-term care of assisted living facility, suggests CDC. Non-test-based strategy would prevent most, but may not be able to prevent all instances of secondary spread of contagion.

ALL PNEUMONIA PATIENTS NEED ADMISSION

No. Admission is needed when:

- Temperature >38°C
- Respiratory rate >20
- Heart rate >100 with new confusion
- Oxygen saturation <94%.

THERE ARE NO CLEAR CUT RED FLAGS FOR COVID-19

No. The red flags include:

- Severe shortness of breath at rest
- Difficulty in breathing
- Pain or pressure in the chest
- Cold, clammy, pale and mottled skin
- New confusion
- Becoming difficult to rouse
- Blue lips or face
- Little or no urine output
- Coughing up blood
- Neck stiffness
- Nonblanching rash.

THERE IS NO DEFINITION OF "HOW CLOSE IS TOO CLOSE"

The US CDC recommends keeping a distance of 6 feet from others to minimize the chances of infection. (6 feet is roughly twice the length of the average person's extended arm.) The WHO emphasizes 3 feet as the distance that is particularly risky when standing near a person who is coughing or sneezing. Other public health experts state that at this crucial moment, when the world still has an opportunity to slow the transmission of the coronavirus, **any number of feet is too close**. By cutting out all except essential in-person interactions, the curve can be flattened, keeping the number of sick people to levels that medical providers can manage. (*NY Times*)

THERE IS NO LINK WITH DURATION OF EXPOSURE

No. A person who has had face-to-face contact with a COVID-19 patient within 2 m and >15 minutes or a person who has been in a closed environment, such as classroom, meeting room, hospital waiting room, etc., with a COVID-19 patient for >15 minutes and at a distance of <2 m is at risk of infection (*Public health management of persons, including healthcare workers, having had contact with COVID-19 cases in the European Union, 25th February 2020*).

DOCTORS CAN RESUME WORK ONCE RECOVERED AFTER 1 WEEK

Myth - not without precautions: The CDC has provided new guidance for healthcare workers, who have tested positive for coronavirus, or who think they had it, and are now considered recovered without a test. They are required to wear a facemask at all times when in the healthcare facility until all symptoms are completely resolved or until 14 days after illness onset, whichever is longer. Restrict from contact with severely immunocompromised patients until 14 days of illness onset.

CAN COVID-19 RECUR?

The WHO is investigating reports of some recovered coronavirus patients testing positive for the illness after initially testing negative.

WHY IS THE WHO INVESTIGATING REINFECTIONS?

The move is in response to a report from South Korea on April 11 that 91 patients who had been cleared of COVID-19 and were being prepared for discharge tested positive again. Officials say that, rather than being re-infected, patients may be suffering from a "re-activated" coronavirus.

WHAT ARE THE 4 BENCHMARKS FOR A RETURN TO NORMALCY?

- Hospitals must be able to safely treat all patients requiring hospitalization, without the need for crisis standards of care. This translates to having adequate beds, ventilators and staff.
- Authorities must be able to test at least everyone who has symptoms, and to get reliable results in a timely manner.
- Health agencies must be able to monitor confirmed cases, trace contacts of the infected patients, and have at-risk people go into isolation or quarantine.
- There must be a sustained reduction in cases for at least 14 days. Because it can take up to 2 weeks for symptoms to emerge, any infections that have already happened can take that long to appear.

Hydroxychloroquine Myth Busters

Hydroxychloroquine causes retinal toxicity

No. Retinal toxicity, which can result in irreversible retinopathy, is mainly associated with high daily doses and more than 5 years of use of chloroquine or hydroxychloroquine in the treatment of rheumatic diseases. This side effect is seen with long-term use of chloroquine. With hydroxychloroquine, it is only a caution only after years of use. The risk of toxicity depends on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is <1% and up to 10 years is <2%. However, it increases to nearly 20% after 20 years. Even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year (*Ophthalmology. 2016;123(6):1386-94).*

Hydroxychloroquine causes QT prolongation

It can cause QT prolongation, only if used with azithromycin.

It cannot be given to persons aged ≥60 years.

No, there is no such evidence. All international travelers have been taking it once a week as malarial prophylaxis

It can cause hemolysis in G6PD deficiency

There is no evidence. While manufacturer's labeling recommends that caution should be exercised while using chloroquine in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to a potential for hemolytic anemia, there is limited data to support this risk. Many experts consider chloroquine, given in usual therapeutic doses to WHO Class II and III G6PD deficient patients, as probably safe (*Cappellini 2008; Glader 2017; Luzzatto 2016; Youngster 2010*). Safety is; however, unknown in Class I G6PD deficiency (severe form of the deficiency associated with chronic hemolytic anemia) (*Glader 2017*). A study in West Africa including 74 G6PD deficient patients (predominantly Class III deficiency) reported that there were no cases of hemolysis following exposure to usual doses of chloroquine (*Mandi 2005*). The ACR Rheumatology guidelines do not specify the need to evaluate G6PD levels before initiating therapy (*Singh 2015*).

It has many contraindications

No. Only contraindication is hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of the formulation.

Hydroxychloroquine is contraindicated in children

No, it is not given for COVID-19 in children as they have high chances of natural recovery.

It is an OTC drug

No, it is a Schedule H1 drug and given only on the prescription of a registered medical practitioner.

It can damage the kidneys

There is no evidence.

CAN TWO PERSONS WITH SAME COVID-19 DISEASE STAY IN ONE PLACE?

There is no evidence to suggest that if everyone in a family is already sick, they can reinfect each other with more and more virus. For other viruses, once you are infected, it's quite hard to get infected with the same virus on top.

AVOID BLOOD DONATION IN COVID-19 SITUATION

No. Most blood banks have introduced a postponement period of 28 days for donation for donors returning from overseas following updated public health advice that anyone coming from overseas is considered to have returned from a high- or moderate-risk country and should practice social distancing outside of work. A 28-day postponement has been introduced for any donors who have been in contact with a confirmed case of coronavirus. This means that if someone has been in contact with a person who has had coronavirus and was infectious at the time then he/she will not be able to donate for 28 days.

If someone has had coronavirus himself, he will not be able to donate for 3 months following recovery. Earlier, people with a mild runny nose with no fever were allowed to donate plasma. Blood banks follow that anyone with minor cold-like symptoms will be deferred until they are recovered.

■■■■

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COVID-19: A GP's Perspective

KK AGGARWAL

ABSTRACT

There is a pandemic of coronavirus disease (COVID-19). It is an infectious disease caused by the new coronavirus, a highly contagious virus. The most common symptoms of COVID-19 are fever, tiredness and dry cough. Most people (about 80%) usually recover from the infection. COVID-19 is a new disease and new data is coming out every day. The general practitioner (GP) is not actively involved in management of active cases. But, as the first point of contact, a GP has an important role in preventing its spread by prompt detection and timely referral of suspected cases. Hence, it is important for the GP to be aware of the key aspects of the disease.

Keywords: Coronavirus, dry cough, fever, general practitioner

The coronavirus disease (COVID-19) pandemic emerged from Wuhan, China, where few cases of viral pneumonia were detected on 31st December, 2019.[1] Initially called "pneumonia of unknown etiology",[2] the disease has been termed as Coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO) following identification of a new coronavirus (2019-nCoV) as the cause. The virus has now been officially named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of its genetic similarity (86%) with SARS-CoV.[3]

BURDEN OF DISEASE

The coronavirus outbreak was declared a pandemic on 11th March, 2020. Since then, the pandemic has been "accelerating" (WHO); the first 1 lakh cases were reached in 67 days, 2nd 1,00,000 cases in 11 days, 3rd 1,00,000 cases in 4 days, 4th 1,00,000 cases in 3 days, 5th 1,00,000 cases in 2.5 days, 6,00,000 in 2 days and 7,00,000 in 2 days.

The total number of cases and deaths outside China now exceed those in China. The epicenter of the pandemic shifted from China to Europe (March 13) and now the United States has become the epicenter of the coronavirus pandemic (March 26) with the highest number of coronavirus cases, followed by Italy and Spain.

President, CMAAO and Heart Care Foundation of India
Past President, Indian Medical Association

Global Scenario

Total coronavirus cases	Total deaths	Recovered
2,000,943	1,26,781	4,84,979

Source: https://www.worldometers.info/coronavirus/#countries. Accessed April 15, 2020.

India Scenario

Total coronavirus cases	Total deaths	Recovered
11,555	396	1,362

Source: https://www.worldometers.info/coronavirus/country/india/. Accessed April 15, 2020.

ROUTES OF TRANSMISSION

When it was first detected, COVID-19 was linked to the Huanan seafood wholesale market in Wuhan and therefore presumed to have been transmitted from animals to humans. But, person-to-person transmission was soon confirmed to be the primary mode of transmission.

Person-to-person Transmission

The COVID-19 virus spreads from person-to-person mainly via respiratory droplets expelled from the mouth and nose when the infected person coughs or sneezes or just talks.[4] Droplets are >5 μm in diameter and are transmitted only over a limited distance (e.g., ≤1 m).[5]

These droplets land on objects and surfaces around the person. Indirect spread can occur by touching the surface or object that has the virus on it and then touching the mouth, nose or possibly the eyes (CDC). The virus was found to survive on various surfaces up to 17 days after cabins of both symptomatic and asymptomatic infected passengers were vacated (before

disinfection) on the Diamond Princess cruise ship.[6] The COVID-19 virus can survive up to 72 hours on plastic and stainless steel, for 4 hours on copper and for up to 24 hours on cardboard.[7]

People can also acquire the virus if they directly breathe in the droplets. This is why, it is important to stay more than 1 meter (3 feet) away from a person who is coughing or sneezing.[8] This is the rationale of social distancing, which is recommended to stop the spread of the infection.

Airborne transmission of COVID-19 has not yet been reported. But, procedures that produce aerosols such as endotracheal intubation, bronchoscopy, open suctioning, disconnecting the patient from the ventilator, may increase the likelihood of airborne transmission.[4] Airborne transmission occurs via droplet nuclei, which are <5 μm in diameter, can remain in the air for long periods of time and be transmitted over distances >1 m.[4]

The COVID-19 virus has been isolated from stool, but there have been no reports of fecal-oral transmission of the COVID-19 virus to date.[4]

Transmission of infection from an asymptomatic contact has also been reported.[9]

Vertical Transmission

Although cases of the new coronavirus in newborns have been reported from China and the UK, mother-to-child transmission is yet to be confirmed. A series of 9 pregnant women found no evidence to suggest that intrauterine infection may result from affected women due to vertical transmission. All samples examined (amniotic fluid, cord blood, breast milk, and neonatal throat swab samples) tested negative for the virus.[10]

CLINICAL PRESENTATION

The incubation period for COVID-19 is 1-14 days, usually around 5 days (WHO). Hence, those who may have been exposed to the virus will present with symptoms on the 5th day of the exposure. This is why, close contacts of COVID-19 patients are tested between 5 to 14 days.

SPECTRUM OF ILLNESS

Most infections are self-limiting. The illness is severe in the elderly and in those with comorbidities. The severity of illness can be categorized as follows:[11]

- Mild illness in 81% patients
- Severe illness (hypoxemia, >50% lung involvement on imaging within 24 to 48 hours) in 14%
- Critical disease (respiratory failure, shock, multiorgan failure) in 5%.

The WHO has estimated the global death rate for the novel coronavirus to be 3.4%.

CLINICAL FEATURES

The most common symptoms of COVID-19 are fever, cough and expectoration. Serious cases can have severe pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ failure resulting in death.[12]

Other symptoms may include headache, sore throat, rhinorrhea (runny nose) and/or gastrointestinal symptoms.[13]

Researchers from King's College London have suggested that a sudden loss of smell (hyposmia/anosmia) and taste (dysgeusia) may be an early symptom of COVID-19. The American Academy of Otolaryngology - Head & Neck Surgery (AAO-HNS) has proposed adding anosmia and dysgeusia to the list of screening items for potential novel coronavirus disease (COVID-19). *"Anosmia, hyposmia and dysgeusia in the absence of other respiratory disease such as allergic rhinitis, acute rhinosinusitis or chronic rhinosinusitis should alert physicians to the possibility of COVID-19 infection and warrant serious consideration for self-isolation and testing of these individuals".*[14]

Case Definition

The criteria for suspect case, probable case and confirmed case have been defined by the WHO.

Suspect case

- A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; or
- A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; or
- A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

- A suspect case with inconclusive testing for COVID-19, or
- A suspect case for whom testing could not be performed for any reason.

Confirmed case

A person with laboratory confirmation of COVID-19 infection, regardless of clinical signs and symptoms.

Global surveillance for COVID-19 caused by human infection with COVID-19 virus: Interim guidance, WHO, 20 March 2020.

LABORATORY DIAGNOSIS

White Blood Cell Count

Patients with COVID-19 may have lymphocytopenia (83.2%) and leukopenia (33.7%).[15] Compared to nonsurvivors, survivors had significantly higher baseline lymphocyte count; in survivors, lymphocyte count was lowest on Day 7 after onset of illness and improved during hospitalization, while severe lymphopenia was observed until death in nonsurvivors.[16]

Platelet Count

Thrombocytopenia has been observed in 36.2% cases with COVID-19.[15]

Serum Procalcitonin

In uncomplicated infection, serum procalcitonin level is normal. High procalcitonin levels are indicative of bacterial coinfection (sepsis).[17]

C-reactive Protein

C-reactive protein (CRP) levels are raised in most patients.[15]

Laboratory Abnormalities Indicative of Poor Prognosis[17]

Increased white blood cell count	Increased total bilirubin
Increased neutrophil count	Increased creatinine
Decreased lymphocyte count	Increased cardiac troponin
Decreased albumin	Increased D-dimer
Increased lactate dehydrogenase (LDH)	Increased prothrombin time (PT)
Increased alanine aminotransferase (ALT)	Increased procalcitonin
Increased aspartate aminotransferase (AST)	Increased CRP

All suspect cases (as per the criteria above) should be tested for SARS-CoV-2 in throat and nasal swabs (preferred sample) or nasopharyngeal swab, bronchoalveolar lavage or endotracheal aspirate (alternate samples).[18] The induction of sputum is not recommended.[19] Sampling should be done under strict airborne infection control precautions.

Patients should also be tested for other pathogens as per guidelines for the management of community-acquired pneumonia.[20]

ICMR Current Testing Strategy

- All asymptomatic individuals who have undertaken international travel in the last 14 days:
  - They should stay in home quarantine for 14 days
  - They should be tested only if they become symptomatic (fever, cough, difficulty in breathing)
  - All family members living with a confirmed case should be home quarantined.
- All symptomatic contacts of laboratory confirmed cases.
- All symptomatic healthcare workers.
- All hospitalized patients with severe acute respiratory illness (fever AND cough and/or shortness of breath).
- Asymptomatic direct and high-risk contacts of a confirmed case (those who live in the same household with a confirmed case and healthcare workers who examined a confirmed case without adequate protection) should be tested once between Day 5 and Day 14 of coming in his/her contact.

Indian Council of Medical Research, Dept. of Health Research, Revised Strategy of COVID19 testing in India (Version 3, dated 20/03/2020).

The diagnosis of COVID-19 is confirmed by the detection of virus RNA by reverse-transcription polymerase chain reaction (RT-PCR). However, a negative test does not rule out the possibility of COVID-19.

A false-negative test may be due to poor quality of specimen, or specimen collected late or very early in the course of the disease or the specimen was not handled and shipped appropriately or technical reasons.[20]

Imaging

Chest X-ray: Chest X-ray in a patient with COVID-19 shows bilateral peripheral consolidation. Baseline chest X-ray had a sensitivity of 69%, compared to 91% for initial RT-PCR.[21]

Chest CT scan: The major findings on CT include bilateral ground glass opacity, consolidation or both.[22]

The RT-PCR test has high specificity but low sensitivity (60-70%). Hence, patients may have pneumonia even with an initial negative RT-PCR. CT therefore could be an important modality to detect COVID-19 pneumonia in such patients.[23]

MANAGEMENT

Patients with mild disease or their close contacts can be managed by isolation at home or isolation facility. Patients with severe disease need hospitalization.

There is no specific antiviral treatment recommended for COVID-19.

The "Solidarity trial", to be conducted by the WHO, will compare the safety and effectiveness of four different drugs or drug combinations against COVID-19: Remdesivir; chloroquine, hydroxychloroquine; combination of lopinavir and ritonavir; combination of lopinavir, ritonavir and interferon-beta.

Various drugs used for treatment of COVID-19 are remdesivir (experimental antiviral drug - compassionate use only),[24] combination of lopinavir and ritonavir,[25] hydroxychloroquine and chloroquine.[26,27]

The Central Drugs Standard Control Organization (CDSCO) has approved the "restricted use" of lopinavir-ritonavir combination for treating those affected by novel coronavirus.

The National Task Force for COVID-19 set up by ICMR has recommended hydroxychloroquine for prophylaxis of SARS-CoV-2 infection for high-risk population.

- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals.
- Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals.

Systemic corticosteroids are to be used only if there is another indication such as exacerbation of asthma or chronic obstructive pulmonary disease (COPD), septic shock.[28]

When to Discharge the Patient?

If the person tests positive for COVID-19, the case shall be managed as per the confirmed case management protocol. The treated patient should be discharged only after evidence of chest CT clearance and two samples test negative for the virus within a period of 24 hours.[29]

Some patients with mild COVID-19 may continue to be infectious even when symptoms have resolved. In a study from China, about 50% of patients who had recovered from mild disease continued to shed the virus for up to 8 days despite two consecutive negative RT-PCR tests. This may hamper efforts to control the spread of the infection.[30] Therefore, the recently recovered patients or asymptomatic persons should be treated as carefully as symptomatic patients.

ROLE OF THE GP IN MANAGEMENT OF COVID-19

General practitioners (GPs) are the backbone of medical practice as they are the first point of contact for the patient. Hence, in the current scenario of the national lockdown due to the COVID-19 pandemic, GPs have an important role to play. The first and foremost is timely consultation. This facilitates prompt case detection and its management and thus prevents further spread of infection.

GPs should provide as many teleconsultations as possible at least for the duration of the lockdown. These consultations can be paid similar to the regular in-person consultations. Inform all your patients by SMS or email that no office consultation would be provided. Teleconsultation helps to prevent cross infection of coronavirus-like illnesses among the large number of patients waiting to see the doctor. It also keeps the doctor and the staff safe.

The government has released new telemedicine practice guidelines. Patient consent is necessary for any telemedicine consultation. Four types of telemedicine consults have been identified according to:

- Mode of communication (video, audio, text-based)
- Timing of the information transmitted (real time or asynchronous - accessed as per need or convenience)
- Purpose of the consultation (non-emergency or emergency)
- Interaction between the individuals involved (Registered medical practitioner [RMP]-to-patient/caregiver, or RMP to RMP).

Take a complete medical history including travel history to a country with active COVID-19 transmission or history of close contact with a positive case.

If the person is a suspect case (*as per criteria defined earlier*), prescribe blood tests (complete blood count [CBC], CRP) including test for COVID-19. Check the ICMR list of approved government or private laboratories nearby, which are equipped to test for COVID-19. Or, advise the patient to contact the central or state helpline number for testing.

If there is a positive history of travel to COVID-19 affected countries or if the patient falls under the case definition of COVID-19 (suspect/case), get the self-declaration form (from Health Ministry) filled.

All suspect cases should be informed to the appropriate authority. As per directive from the Health Ministry, Government of India, *"it is obligatory for all hospitals (Government and Private), Medical officers in Government health institutions and registered Private Medical Practitioners including AYUSH Practitioners, to now notify COVID-19 affected person (as defined by MoHFW) to concerned district surveillance unit".*

Assess the patient to categorize the severity of illness: Mild, moderate or severe.

If the person has history of travel in the last 14 days and has symptoms, advise isolation at home or in an isolation facility. For close contacts, advise home quarantine for 14 days. Any person in quarantine who develops symptoms (cough/fever/difficulty in breathing) at any point during the quarantine period should be advised to inform or visit the nearest health center or call the helpline number. Educate them about cough hygiene, hand hygiene, proper use of masks and maintaining distance from others in the family.

It is easy to identify patients who will need hospitalization as they will be breathless. Refer such patients to nodal hospitals.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. Cascella M, Rajnik M, Cuomo A, et al. Features, evaluation and treatment coronavirus (COVID-19) [Updated 2020 Mar 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/.
3. Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? Lancet Infect Dis. 2020 Mar 5. pii: S1473-3099(20)30129-8. [Epub ahead of print]
4. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations, Scientific brief, 29 March 2020, WHO. Available at: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations.
5. Atkinson J, Chartier Y, Pessoa-Silva CL, et al., editors. Natural Ventilation for Infection Control in Health-Care Settings. Geneva: World Health Organization; 2009. Annex C, Respiratory droplets. Available from: https://www.ncbi.nlm.nih.gov/books/NBK143281/.
6. Moriarty LF, Plucinski MM, Marston BJ, Kurbatova EV, Knust B, Murray EL, et al; CDC Cruise Ship Response Team; California Department of Public Health COVID-19 Team; Solano County COVID-19 Team. Public health responses to COVID-19 outbreaks on cruise ships - Worldwide, February-March 2020. MMWR Morb Mortal Wkly Rep. 2020;69(12):347-52.
7. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020 Mar 17. [Epub ahead of print]
8. Detail Question and Answers on COVID-19 for Public. Available at: https://www.mohfw.gov.in/pdf/FAQ.pdf.
9. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med. 2020;382(10):970-1.
10. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809-15.
11. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020 Feb 24. [Epub ahead of print]
12. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020;80(4):388-93.
13. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507-13.
14. AAO-HNS statement. Available at: https://www.entnet.org/content/coronavirus-disease-2019-resources.
15. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Feb 28. [Epub ahead of print]
16. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020 Mar 11. pii: S0140-6736(20)30566-3. [Epub ahead of print]

17. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020;505:190-1.
18. Revised Guidelines on Clinical Management of COVID-19, Government of India, Ministry of Health & Family Welfare, Directorate General of Health Services (EMR Division), March 31, 2020.
19. Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19), CDC. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html
20. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases, Interim guidance, WHO, March 19, 2020.
21. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and distribution of chest radiographic findings in COVID-19 positive patients. Radiology. 2019 Mar 27:201160. [Epub ahead of print].
22. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for Radiologists on COVID-19: An Update-Radiology Scientific Expert Panel. Radiology. 2020 Feb 27:200527. [Epub ahead of print].
23. Lee EYP, Ng MY, Khong PL. COVID-19 pneumonia: what has CT taught us? Lancet Infect Dis. 2020;20(4):384-5.
24. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al; Washington State 2019-nCoV Case Investigation Team. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-36.
25. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020;35(6):e79.
26. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. pii: ciaa237. [Epub ahead of print].
27. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72-7.
28. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance, WHO, March 13, 2020.
29. Discharge Policy of nCoV Case. Ministry of Health & Family Welfare, Government of India.
30. Chang, Mo G, Yuan X, Tao Y, Peng X, Wang F, et al. Time kinetics of viral clearance and resolution of symptoms in novel coronavirus infection. Am J Respir Crit Care Med. 2020 Mar 23. [Epub ahead of print].

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Lactic Acid Bacteria Isolated from a Korean Food Item Activate Vitamin D Receptor-autophagy Signaling Pathways

According to a study published in the *Inflammatory Bowel Diseases* journal, probiotic lactic acid bacteria (LAB) exert anti-inflammatory action and induce autophagy. These effects have been reported to depend on the expression of vitamin D receptor.

In this study, 5 LAB strains were isolated from Korean kimchi. The findings demonstrated benefits of these strains isolated from food in anti-infection and anti-inflammation.

Magnetic Field Exposure *in utero* may Increase Kids' Risk of ADHD

Babies exposed to relatively strong household magnetic fields (MF*) in utero* appeared to have higher odds of developing attention-deficit/hyperactivity disorder (ADHD), reported a longitudinal birth cohort study published in *JAMA Network Open*.

Children whose mothers were exposed during pregnancy to fields of over 1.3 milligauss (mG) during normal activities were more than twofold as likely to develop ADHD as those exposed to lower levels (adjusted HR 2.01, 95% CI 1.06-3.81), reported researchers.

Asthma, Type 1 Diabetes Often Co-occur in Children, Families

Asthma and type 1 diabetes often co-occur in children and their family members, suggests new research.

Siblings with either condition had an increased risk of the other compared with the general population. While individuals diagnosed with asthma first, at an average age of 3 years, had an increased risk for a subsequent diagnosis of type 1 diabetes (at an average age of 5.9 years), the reverse wasn't seen. The findings were published online in *JAMA Network Open*.

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

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ABSTRACT

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

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

THE ENDANGERED STORY OF PREGNANCY

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

THE BURDENED ADAPTATIONS OF PREGNANCY

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

MEASUREMENTS: DO IT THE RIGHT WAY

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

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

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

RIDE ON AN ALREADY TIRED HORSE

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

GESTATIONAL HYPERTENSION

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

THE RENAL MESS

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

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

HAYWIRED END ORGANS: PRE-ECLAMPSIA

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

THE PUPPETS BEHIND THE SCENE

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

NO NEED FOR HURRY

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

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

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

MAGNIFICENT MAGNESIUM

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

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

SUGGESTED READING

1. Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, et al. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2015;31(5):549-68.
2. Ringrose JS, McLean D, Ao P, Yousefi F, Sankaralingam S, Millay J, et al. Effect of cuff design on auscultatory and oscillometric blood pressure measurements. Am J Hypertens. 2016;29(9):1063-9.
3. Spiro L, Scemons D. Management of chronic and gestational hypertension of pregnancy: a guide for primary care nurse practitioners. Open Nurs J. 2018;12:180-3.
4. Smith GN, Pudwell J, Saade GR. Impact of the new American hypertension guidelines on the prevalence of postpartum hypertension. Am J Perinatol. 2019;36(4): 440-2.
5. Hauspurg A, Sutton EF, Catov JM, Caritis SN. Aspirin effect on adverse pregnancy outcomes associated with stage 1 hypertension in a high-risk cohort. Hypertension. 2018;72(1):202-7.
6. Miller MJ, Butler P, Gilchriest J, Taylor A, Lutgendorf MA. Implementation of a standardized nurse initiated protocol to manage severe hypertension in pregnancy. J Matern Fetal Neonatal Med. 2020;33(6):1008-14.
7. Dymara-Konopka W, Laskowska M, Oleszczuk J. Preeclampsia - current management and future approach. Curr Pharm Biotechnol. 2018;19(10):786-96.
8. Yang YY, Fang YH, Wang X, Zhang Y, Liu XJ, Yin ZZ. A retrospective cohort study of risk factors and pregnancy outcomes in 14,014 Chinese pregnant women. Medicine (Baltimore). 2018;97(33):e11748.

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Extreme Heat and Humidity Projected to Affect Areas Home to 1.2 Billion People

Extreme heat and humidity causing heat stress will annually affect areas now home to 1.2 billion people by 2100, according to a new study published in the journal *Environmental Research Letters*.

The figure is more than 4 times the number of people affected currently, and more than 12 times the number who would have been affected without industrial era global warming.

Ibuprofen, a Commonly Prescribed Drug should be Used with Caution

An experimental study suggested that ibuprofen can have an adverse impact on liver health. The changes were different, depending on the gender of the experimental model. In the males, changes occurred in at least 34 metabolic pathways, including those that help regulate some essential components of health like amino acids, hormones, vitamins and the release of reactive oxygen and hydrogen peroxide within cells. On the other hand, in females, administration of ibuprofen increased the activity of some cytochrome P450s…(*Medical News Today*)

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Fresh Look into Current Expanding Indications for Sutureless Repair for Total Anomalous Pulmonary Venous Return

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ABSTRACT

Total anomalous pulmonary venous return (TAPVR) has an incidence of about 5.9-7.1 per 1,00,000 live births. Sutureless repair is a safe and effective procedure to manage TAPVR. The sutureless technique with creation of neoatrium leads to less pulmonary venous obstruction postoperatively and less reoperation rates as well. This article provides an overview of sutureless repair for TAPVR.

Keywords: Sutureless technique, total anomalous pulmonary venous connection or return, classical TAPVC correction, pulmonary vein stenosis, pulmonary vein gradients, extracorporeal membrane oxygenation

Incidence of total anomalous pulmonary venous return (TAPVR) currently is about 5.9-7.1 in 1,00,000 live births.[1] In TAPVR, all the pulmonary veins connect to chambers other than left atrium (LA) necessitating an obligatory right to left shunt for survival. Pulmonary hypertension in situations with right-sided volume overload with oxygenated blood and pulmonary venous obstruction (PVO) at multiple levels are major contributory factors to mortality from the disease.[2,3] A drop in mortality has been noted in high volume centers from 15% to <3%. *In situ* pericardial tissue being used for neo LA creation by sutureless techniques has been increasingly appreciated as an excellent technique for recurrent pulmonary venous stenosis (PVS).[3,4] Safety has been reported by many current meta-analytical studies.[5]

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A meta-analysis of seven leading studies on mortality that compared the two surgical techniques – traditional repair versus sutureless techniques – showed no difference statistically in these two methods.[5] Here native pulmonary venous tissues do not have any suture lines. Reactive intimal proliferation is avoided maintaining optimal flow patterns. Gradients in pulmonary veins, especially after infracardiac type repairs, necessitate support with extracorporeal membrane oxygenation (ECMO) and anastomotic revision by conventional repair techniques.

Avoidance of distortion or narrowing, with optimal flow characteristics have been the two most attractive options with sutureless repair technique. Pulmonary vein scoring is generally done as follows:

PVS: 0 = no stenosis (mean gradient <2 mmHg); 1 = mild stenosis (mean gradient 2.0-6.9 mmHg); 2 = severe stenosis (mean gradient >7 mmHg) and 3 = complete occlusion. The sum of the individual pulmonary vein scores is then used as a subjective measure of the overall degree of PVS ranging from 0 (no stenosis) to a theoretic maximum score of 12.

Echocardiography should focus on right ventricular systolic pressure evaluation using the tricuspid regurgitant jet. Early diastolic velocity of the pulmonary regurgitant jet gives the mean pulmonary artery pressure. Left ventricular ejection fraction (LVEF) should also be measured. Indexed left atrial volume (LAVi) should be also measured. The collecting chamber is

included in the left atrial volumetric measurement post repair. Mean gradients of the individual pulmonary veins should also be calculated.

TECHNIQUE

Using standard cardiopulmonary bypass with bicaval cannulation, unroofing of the coronary sinus is done for cardiac TAPVR and further includes single- or two-sided atriopericardial connection, especially if there is associated vein to confluence orifice stenosis. In case of sutureless repair of infracardiac and supracardiac TAPVR, incisions are made in the venous confluence and then extended separately into both pulmonary veins separately for unobstructed flow. Small pulmonary venous confluences, as in infracardiac TAPVR require incisions into individual pulmonary veins. In sutureless repair atriopericardial anastomosis is fashioned using pericardium close to the pulmonary vein orifice to the pericardium. A neo LA is created allowing free flow of blood from pulmonary veins into LA. The interatrial communication is closed. Operative duration is more often linked to complexity in the anatomy than to type of repair in most cases in high volume centers. Early challenges are related to pulmonary hypertension and lung function while late morbidity is due to PVS. Even small pulmonary gradients can cause significant secondary pulmonary hypertension.

DISCUSSION

Though sutureless repair evolved for cases where ECMO could not be weaned off as salvage procedures, indications to use these are being more liberalized as more technical expertise is being attained in high volume centers. This technique can be safely and confidently applied for all infracardiac types, cardiac types with PVS and also for select cases of supracardiac types with pulmonary vein narrowing. In recent years, this sutureless technique, utilized also for the primary repair of TAPVR, has been expanded for use in patients who had preoperative PVO or were at risk of developing PVO.[6] Mortality figures exponentially rise in procedures for recurrent PVS.

Treatment procedures for recurrent PVS include medical therapy, inhaled nitric oxide, ECMO or surgical revision, or septostomy. In cases with diffuse proliferative fibrosis, the requirement of lung or heart-lung transplantation is a reality. Thrombosis, embolism, rupture, phrenic nerve injuries are points that necessitate discussion with this procedure. Integrity of the pleuropericardial junction is a crucial feature when this technique is adopted. Reoperation rates for PVO are less for sutureless techniques.[7]

CONCLUSIONS

Use of sutureless technique with creation of neoatrium results in less PVO postoperatively and less reoperation rates while having the same postoperative mortality as traditional repair, indicating that it is safe in experienced hands. Better and more complete visualization of pulmonary veins is provided by this technique and suture induced inflammation is completely eliminated. Wide opening ensures obstruction free drainage even with intimal fibroblastic proliferation that occurs later in the disease process naturally.

REFERENCES

1. Seale AN, Uemura H, Webber SA, Partridge J, Roughton M, Ho SY, et al; British Congenital Cardiac Association. Total anomalous pulmonary venous connection: morphology and outcome from an international population-based study. Circulation. 2010;122(25):2718-26.
2. Mueller C, Dave H, Prêtre R. Primary correction of total anomalous pulmonary venous return with a modified sutureless technique. Eur J Cardiothorac Surg. 2013;43(3):635-40.
3. Lacour-Gayet F, Rey C, Planché C. Pulmonary vein stenosis. Description of a sutureless surgical procedure using the pericardium in situ. Arch Mal Coeur Vaiss. 1996;89(5):633-6.
4. Najm HK, Caldarone CA, Smallhorn J, Coles JG. A sutureless technique for the relief of pulmonary vein stenosis with the use of in situ pericardium. J Thorac Cardiovasc Surg. 1998;115(2):468-70.0
5. Wu Y, Wu Z, Zheng J, Li Y, Zhou Y, Kuang H, et al. Sutureless technique versus conventional surgery in the primary treatment of total anomalous pulmonary venous connection: a systematic review and meta-analysis. J Cardiothorac Surg. 2018;13(1):69.
6. Yoshimura N, Fukahara K, Yamashita A, Doi T, Takeuchi K, Yamashita S, et al. Surgery for total anomalous pulmonary venous connection: primary sutureless repair vs. conventional repair. Gen Thorac Cardiovasc Surg. 2017;65(5):245-251.
7. Lo Rito M, Gazzaz T, Wilder T, Saedi A, Chetan D, Van Arsdell GS, et al. Repair type influences mode of pulmonary vein stenosis in total anomalous pulmonary venous drainage. Ann Thorac Surg. 2015;100(2):654-62.

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Sepsis – An Impendence That Needs a Global Solution

Know Safety – No Infection

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ABSTRACT

Sepsis has been called a hidden public health disaster. Sepsis arises from the host response to infection, which is directed to kill the invading pathogens. It is an extreme response to an infection and one of the most common causes of multiorgan failure. The human body sends a flood of chemicals into the bloodstream to fight the threat. This causes widespread inflammation which, over time, can slow blood flow and damage the organs. Sepsis is clinically diagnosed by a combination of clinical signs, laboratory tests and microbiologically confirmed by the detection of bacteria in blood by culture. Early and aggressive management with appropriate antimicrobials and rapid and complete hemodynamic stabilization has been shown to be associated with improved outcomes. Detecting sepsis early and starting immediate treatment is often the difference between life and death.

Keywords: *Staphylococcus aureus* bacteria, septic shock, 25-hydroxyvitamin D, hospital-acquired infection, bloodstream infections, cytokines, anion gap

Saving patients from sepsis is a race against time. Sepsis is a clinical syndrome characterized by a systemic response to infection.

The lungs, kidneys and cardiovascular system are the most affected organs during sepsis and septic shock. It was found that blood glucose levels influence the mechanisms of "tolerance" against infections. In several cases where the disease tolerance fails, the clinical symptoms of sepsis often show more dramatic courses than classical infections.

The term "septic shock" refers to an elevated lactate level of >2 mmol/L. Bloodstream infections remain a major cause of morbidity and mortality despite the availability of potent antimicrobial therapy and advances in supportive care. It is estimated that Gram-negative bacilli are the cause of approximately a quarter to half of all bloodstream infections. Gram-negative sepsis carries a mortality rate of 12-38%.

Sepsis may lead to systemic vasodilation, organ injury, shock and death. Sepsis is a major public health burden in the United States. Interleukin (IL)-10 as an initial biomarker can help clinicians consider more aggressive antimicrobials for rapid bacterial load reduction in high-risk *Staphylococcus aureus* bacteria patients. *S. aureus* virulence is multifactorial, dependent on numerous toxins.

Sepsis is said to be present if a focus has developed from which pathogenic bacteria invade the bloodstream thus causing subjective and objective symptoms.

The hemodynamic, metabolic and immune changes seen in sepsis occur through mediators and cytokines that play a role in intercellular signal transmission. Cytokines show their effects not only by entering the systemic circulation but also by their direct cell-to-cell relationship and by very small concentrations.

Microorganisms do not need to pass into the blood for the development of sepsis. The local or systemic extension of signal products and toxins of the pathogen might initiate sepsis.

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The diagnostic uncertainty may contribute to delays in the initiation of lifesaving therapies and overuse of antimicrobial agents.

The biomarkers and molecular diagnostics are useful for the assessment of the host response and clinical management of sepsis. Bloodstream infections are associated with significant morbidity and mortality risks. Delayed administration of effective antibiotics increases the mortality risk.

There has been a decrease in the incidence of late-onset sepsis (LOS) over the past decade, still 34% of all extremely low birth weight infants develop LOS. The intestinal microbiota has increasingly been considered to play a pivotal role in LOS. Vitamin D plays an integral role in the functioning of the immune system.

Clinical applications of these discoveries are encouraging. An individual-level meta-analysis of randomized, controlled trials demonstrated that vitamin D supplementation reduces the risk of acute respiratory infections.

HISTORY

The term "sepsis" was introduced by Hippocrates in the fourth century BC, and it meant the process of decay or decomposition of organic matter. In the 11th century, Avicenna used the term "blood rot" for diseases linked to the severe purulent process.

The terms "septicemia" and "blood poisoning" referred to the microorganisms or their toxins in the blood and are no longer used.

The currently used terms depend on the microorganism present in blood. It is termed bacteremia if bacteria are present in the blood at abnormal levels, viremia for viruses and fungemia for fungi.

Certain mice have been found to be immune to the endotoxin-induced shock and the genetic locus for the same was found to be lipopolysaccharides. The mice were highly susceptible to infection by Gram-negative bacteria. These observations were later linked in 1998 by the discovery of the toll-like receptor gene 4 (TLR4).

Septic shock is a potential consequence of bacteremia. It is a clinical condition characterized by inadequate tissue perfusion. Most patients with septic shock have infections caused by Gram-negative enteric bacteria, *Pseudomonas aeruginosa* or *Neisseria meningitidis*. It is also associated with disease caused by Gram-positive bacteria, viruses, rickettsiae and fungi.

There was controversy over the use of mouse models in sepsis research. Hence, to continue research, one approach is to focus more on studying biopsies and clinical data from people who have had sepsis, and identify biomarkers and drug targets for intervention.

The pathogenesis of sepsis and septic shock begins with the proliferation of the microorganisms at the infection site. The microorganisms may invade the bloodstream directly or may proliferate locally and release various products into the bloodstream. These products include both structural components of the microorganisms.

"Black Death", one of the most devastating pandemics in human history, was caused by septicemia due to *Yersinia pestis*.

The increase in the number of invasive procedures being performed has led to an increased rate of sepsis. Sepsis arises from the host response to infection, which is directed to kill the invading pathogens.

NEXT-GENERATION OF SEPSIS TRIALS

S. aureus, Escherichia coli, Klebsiella, Proteus, Serratia, Pseudomonas, fecal streptococci, *Candida* are commonly occurring microorganisms in hospital-acquired infections. Respiratory infection-causing organisms are *S. aureus, Streptococcus pyogenes,* Gram-negative bacilli, *Klebsiella, Pseudomonas, Haemophilus influenzae. Streptococcus pneumoniae, Moraxella catarrhalis* and respiratory viruses. Bloodstream infections are caused by *Staphylococcus epidermidis, S. aureus,* enterococci, Gram-negative bacilli, *Candida albicans. Candida, Shigella* spp. and Rotavirus cause gastrointestinal infections. Similarly, urinary tract infections are caused by *E. coli, Klebsiella, Proteus, Serratia, Pseudomonas,* fecal streptococci, *C. albicans.*

Some patients may develop surgical site infections and stitch abscess after discharge from the hospital. Most of the infections are caused by enterococci, other non-hemolytic streptococci, anaerobic cocci, Bacteroides and gas gangrene-producing clostridia. The widespread use of antibiotics, chemotherapeutic agents, antiseptics and aseptic techniques in hospitals have produced selective pressures so that sensitive microorganisms die out and those that are resistant multiply, spread and infect patients and become predominant in patients, hospital staff and hospital environment.

Cellulitis caused by *S. aureus, S. pyogenes* or *Streptococcus agalactiae* can lead to bacteremia in about 2% of patients. Skin breakdown in bed-ridden patients (bed sores) or peripheral vascular disease from diabetes are common

causes of infected skin ulcers, which can provide a portal of entry for bacterial invasion of the bloodstream, often resulting in polymicrobial bacteremia. Some of the most commonly reported offending organisms are *Proteus mirabilis, E. coli, S. aureus, Bacteroides fragilis, Pseudomonas* spp., *Clostridium* spp.

Over the past 30 years, the prognosis for patients with severe sepsis and septic shock has improved substantially, because of the care and use of antimicrobial agents.

In the early stage of sepsis development, the main symptoms are from a decrease in systemic vascular resistance due to vasodilation. The late stage of sepsis development is caused by the body being unable to meet the oxygen demands of tissues. Tissue damage and lactic acidosis can occur, causing a hypovolemic state. Carnitine is an amino acid derivative synthesized endogenously from the essential amino acids lysine and methionine.

L-carnitine is decreased in sepsis. Carnitine is stored mainly in muscles. It has an important role in facilitating medium-chain and long-chain fatty acid transport from the cytosol into the mitochondria for β-oxidation and energy generation. It also stimulates pyruvate dehydrogenase complex activity and the Krebs cycle, increasing branched-chain amino acid oxidation in muscles. Sepsis and endotoxemia cause impaired lipid metabolism and hepatic energy generation from fatty acid oxidation. This could, in infants, lead to l-carnitine deficiency.

THE MECHANISM INVOLVED IN THE DEVELOPMENT OF SEPTIC SHOCK

Disturbances in temperature regulation may be due to direct central nervous system (CNS) effects or in the case of early febrile response, mediated by IL-1 and tumor necrosis factor (TNF) released from macrophages (e.g., IL-1, IL-8 and interferon-γ). There may be direct effects on vascular endothelial function and integrity. There is depression of cardiac muscle contractility by TNF, myocardial depressant factor and other well-defined serum factors and impairment of protein C anticoagulant pathway, resulting in disseminated intravascular coagulation. The resultant alterations in blood flow and capillary permeability lead to progressive organ dysfunction.

LACTATE AND ANION GAP

The lactate exits the cells and moves to the liver, where it is oxidized back to pyruvate and is converted to glucose via the Cori cycle.

Serum lactate measurement is useful in screening sepsis. Elevated lactate will raise the anion gap. This anion gap helps to measure lactate concentration. Lactic acidosis is the common cause of metabolic acidosis. Lactic acidosis results in excess lactic acid production. Increased lactate production obstructs the supply of tissue oxygenation and results in a defect of mitochondrial oxygen utilization. The anion gap is a good but not confirmatory screening test to identify the elevated lactic levels.

The anion gap is calculated by subtracting the serum concentrations of chloride and bicarbonate (anions) from the concentrations of sodium and potassium (cations):

$$= ([Na^+] + [K^+]) - ([Cl^-] + [HCO–3]) = 20 \text{ mEq/L}$$

Lactic acidosis in sepsis and septic shock has traditionally been explained as a result of tissue hypoxia when whole body oxygen delivery fails to meet whole body oxygen requirements.

BIOTECHNOLOGY FOR MOLECULAR DIAGNOSIS OF SEPSIS

Surviving sepsis should be the goal of every physician and survival with a good quality of life is the priority. Advances in the field of molecular biology will lead to interesting therapies and the coming years are going to witness directed therapies against the complex mediators of sepsis and personalized care.

There are many biomarkers that can be used in sepsis, but none has sufficient specificity or sensitivity to be routinely employed in clinical practice.

A combination of several sepsis biomarkers may be more effective, but this requires further evaluation. Molecular diagnostic tests (MDT) have been associated with significant decreases in mortality risk in an American antimicrobial stewardship program (ASP). Significant decrease in mortality risk was also seen for studies including Gram-positive organisms, Gram-negative organisms and multiple organism types. In addition, molecular rapid diagnostic testing (mRDT), which includes tests such as polymerase chain reaction (PCR), matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry and peptide nucleic acid fluorescent *in situ* hybridization (PNA-FISH), has improved on conventional microbiologic methods, reducing time to organism identification, optimizing antimicrobial therapy, and subsequently improving clinical outcomes, including mortality rates.

American ASP guidelines recommended the use of rapid diagnostic testing (RDT) with ASP to improve clinical outcomes.

RESEARCHERS STRUGGLE TO DEVELOP NEW TREATMENT OF SEPSIS

Sepsis should be treated as a medical emergency. Deliver high-flow oxygen. Take blood cultures. Administer intravenous (IV) antibiotics. Measure serum lactate and order a full blood count. Start IV fluid replacement. Commence accurate measurement of urine output.

Antimicrobial agents remain the mainstay of treatment of bacteremia. Broad-spectrum antimicrobial agents are frequently used for initial empiric therapy and a combination of agents may be used to ensure coverage of several possible pathogens. Use the most effective agent against the responsible pathogen while minimizing the potential for adverse reactions and the emergence of antimicrobial resistance.

For infection caused by some pathogens such as *Enterococcus faecium, P. aeruginosa*, etc., a cell wall active agent such as β-lactam is combined with an aminoglycoside, resulting in a synergistic antimicrobial effect and improved clinical outcome. Along with antimicrobial therapy, drainage of infected fluid and removal of an infected intravascular catheter may be essential to achieving cure of the infection. Treatment of comorbid conditions such as diabetes is helpful for gaining control of infection.

Antisepsis therapy is used by aiming at blocking the cascade of events that result in sepsis, shock and death. Antisepsis therapy is used in combination with antimicrobial agents. Unfortunately, even with treatment, 30-50% of patients with sepsis die usually because of underlying illness in addition to sepsis. Resuscitation with IV fluids to maintain tissue perfusion is a fundamental method for the management of the septic patient.

In a patient with septic shock who does not respond to fluid support, along with fluids, respiratory therapy with oxygen is used. Drotrecogin alfa, also known as activated protein C, has been shown in clinical trials to decrease mortality in patients with septic shock. Drotrecogin alfa may also decrease chemotaxis of white blood cells by interfering with the interaction between the leukocytes and endothelium of blood vessels.

Glucocorticoids have long been of interest in the treatment of sepsis. A large number of investigational agents aimed at blocking the action of TNF and other cytokine mediators of sepsis have been studied in the treatment of sepsis.

NEW APPROACHES IN THE DISCOVERY OF NOVEL SEPSIS TREATMENT

The Surviving Sepsis Campaign (SSC) is an international collaboration established in 2002, aimed at improving outcomes in severe sepsis and especially at reducing the relative mortality. It is now firmly established that the earlier patients receive appropriate antimicrobials, the better the outcome, which means that treatment should be discussed with an expert and initiated as soon as possible rather than for instance, left until the next drug round. After recognizing sepsis, administration of 100% oxygen, taking blood cultures administration of IV antibiotics, starting fluid resuscitation, checking the hemoglobin and lactate, and placing and monitoring a urinary catheter must be done. It is with the initial recognition and management of sepsis that greatest gains can be made, and these ideas are now actively promoted by intensive care departments to non-specialist areas.

Manipulation of inflammatory mediators involved in sepsis has been proposed as a therapeutic modality, but laboratory studies have proved it difficult to translate into clinical advances. High dose steroids, antibodies against endotoxin, TNF antagonists and IL-1 receptor antagonists, all of which showed promise in animal models, have failed in clinical trials. However, administration of recombinant human activated protein C has been shown to improve the outcome of sepsis in adult patients, who on clinical grounds, are deemed at a high risk of death.

OPENING THE DEBATE ON THE NEW SEPSIS TREATMENT

The use of corticosteroids as adjunctive therapy in sepsis has been the cause of much controversy. The current recommendation is that steroids given as IV hydrocortisone in a dose of 100 mg twice a day are only used in adult patients requiring escalating catecholamine doses. An important mechanism is that corticosteroids up-regulate androgenic receptors thus augmenting the catecholamine effects. Severe sepsis may be associated with both hypo- and hyperglycemia. Children and malnourished patients are particularly prone to hyperglycemia.

EARLY RECOGNITION AND MANAGEMENT OF SEPSIS

Early recognition of the problem is crucial and management obviously requires considerably more than antimicrobial therapy. Other primary therapeutic measures include maintenance of adequate tissue

perfusion through careful fluid and electrolyte management and the use of vasoactive amines. It is also evident that protein C replacement may ameliorate coagulopathy.

Early effective fluid resuscitation is the key for the correction of sepsis-induced tissue hypoperfusion. Sepsis-induced hypoperfusion may be manifested by acute organ dysfunction and decreased blood pressure and increased serum lactate. A strategy of keeping the mean arterial pressure (MAP) >60 mmHg and ensuring lactate clearance with close hemodynamic monitoring is the goal in the initial resuscitation phase. It is unclear when vasopressors should be started during the resuscitation. The initial management of infection requires forming a probable diagnosis, obtaining cultures and initiating appropriate and timely empirical antimicrobial therapy and source control (draining pus, if appropriate). The speed of administration of appropriate antimicrobials is very important and outcomes are directly dependent on the time of antibiotic administration after the onset of sepsis.

CONCLUSION

Sepsis is one of the most challenging frontiers in internal medicine. With the increased expertise in providing organ support, increased awareness of sepsis, its early recognition and initial management, mortality is showing a downward trend. The focus should disseminate the evidence for early recognition and management of severe sepsis.

Care for critically ill patients requires a frequent reassessment of patient's condition, related treatments and repeated concomitant appreciation of overall condition and treatment goals is crucial. Sepsis, and particularly severe sepsis and septic shock, carry high mortality and merit vigorous and expert treatment. It is important to treat infection appropriately, but antimicrobials are just one among a variety of therapeutic strategies. Experience with immunomodulatory drugs has been disappointing, but further advances in our understanding of this complex condition may reveal new opportunities for intervention.

SUGGESTED READING

1. O'Brien JM Jr, Ali NA, Aberegg SK, Abraham E. Sepsis. Am J Med. 2007;120(12):1012-22.
2. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health. 2018;6(7):e744-e757.
3. Weis S, Carlos AR, Moita MR, Singh S, Blankenhaus B, Cardoso S, et al. Metabolic adaptation establishes disease tolerance to sepsis. Cell. 2017;169(7):1263-75.e14.
4. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med. 2014;2(8):611-20.
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
6. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother. 2005;49(2):760-6.
7. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303-10.
8. Rose WE, Shukla SK, Berti AD, Hayney MS, Henriquez KM, Ranzoni A, et al. Increased endovascular *Staphylococcus aureus* inoculum is the link between elevated serum interleukin 10 concentrations and mortality in patients with bacteremia. Clin Infect Dis. 2017;64(10):1406-12.
9. Kreisel KM, Stine OC, Johnson JK, Perencevich EN, Shardell MD, Lesse AJ, et al. USA300 methicillin-resistant *Staphylococcus aureus* bacteremia and the risk of severe sepsis: is USA300 methicillin-resistant *Staphylococcus aureus* associated with more severe infections? Diagn Microbiol Infect Dis. 2011;70(3):285-90.
10. Cerra FB. The systemic septic response: multiple systems organ failure. Crit Care Clin. 1985;1(3):591-607.
11. Cheng B, Hoeft AH, Book M, Shu Q, Pastores SM. Sepsis: pathogenesis, biomarkers, and treatment. Biomed Res Int. 2015;2015:846935.
12. Rivers EP, McIntyre L, Morro DC, Rivers KK. Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity. CMAJ. 2005;173(9):1054-65.
13. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96.
14. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit Care. 2010;14(1):R15.
15. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect. 2013;19(6): 501-9.

16. Zasowski EJ, Claeys KC, Lagnf AM, Davis SL, Rybak MJ. Time is of the essence: the impact of delayed antibiotic therapy on patient outcomes in hospital-onset enterococcal bloodstream infections. Clin Infect Dis. 2016;62(10): 1242-50.
17. Greenberg RG, Kandefer S, Do BT, Smith PB, Stoll BJ, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Late-onset sepsis in extremely premature infants: 2000-2011. Pediatr Infect Dis J. 2017;36(8):774-9.
18. Tarr PI, Warner BB. Gut bacteria and late-onset neonatal bloodstream infections in preterm infants. Semin Fetal Neonatal Med. 2016;21(6):388-93.
19. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol. 2010;10(4):482-96.
20. Upala S, Sanguankeo A, Permpalung N. Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis. BMC Anesthesiol. 2015;15:84.
21. Marshall JC. Sepsis: rethinking the approach to clinical research. J Leukoc Biol. 2008;83(3):471-82.
22. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840-51.
23. "Bacteremia - Infections - Merck Manuals Consumer Version". The Merck Manuals. Archived from the original on 28 July 2017. Retrieved 25 November 2017.
24. Marshall JC. Sepsis: rethinking the approach to clinical research. J Leukoc Biol. 2008;83(3):471-82.
25. Hazeldine J, Hampson P, Lord JM. The diagnostic and prognostic value of systems biology research in major traumatic and thermal injury: a review. Burns Trauma. 2016;4:33.
26. Willey JM, Sherwood L, Woolverton CJ. Prescott's Microbiology. 9th Edition, New York: McGraw-Hill; 2014.
27. Drancourt M, Aboudharam G, Signoli M, Dutour O, Raoult D. Detection of 400-year-old *Yersinia pestis* DNA in human dental pulp: an approach to the diagnosis of ancient septicemia. Proc Natl Acad Sci U S A. 1998;95(21): 12637-40.
28. Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis and septic shock: current treatment strategies and new approaches. Eurasian J Med. 2017;49(1):53-8.
29. Nathan C. Points of control in inflammation. Nature. 2002;420(6917):846-52.
30. Reddy R. General Microbiology. New Age International Publishers; 2009.
31. Mahon CR, Lehman DC, Manuselis G. Textbook of Diagnostic Microbiology. 5th Edition, Elsevier, Chapter 36; 2015.
32. Mullard A. Drug withdrawal sends critical care specialists back to basics. Lancet. 2011;378(9805):1769.
33. Gardner SL, Carter BS, Enzman-Hines M, Hernandez J. Merenstein & Gardner's Handbook of Neonatal Intensive Care. 8th Edition, St. Louis, MO: Mosby Elsevier; 2015.
34. Eaton S, Pierro A. Carnitine and fatty acid oxidation in sepsis. Monatshefte fuer Chemie/Chem Monthly. 2005;136(8):1483-92.
35. Xi L, Brown K, Woodworth J, Shim K, Johnson B, Odle J. Maternal dietary L-carnitine supplementation influences fetal carnitine status and stimulates carnitine palmitoyltransferase and pyruvate dehydrogenase complex activities in swine. J Nutr. 2008;138(12):2356-62.
36. Gallo LL, Tian Y, Orfalian Z, Fiskum G. Amelioration of popolysaccharide-induced sepsis in rats by free and esterified carnitine. Mediators Inflamm. 1993;2(7):S51-6.
37. Gunnerson KJ, Harvey CE. Lactic Acidosis. Medscape. Available from: https://emedicine.medscape.com/article/167027-overview.
38. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis. 2014;59 Suppl 3:S134-45.
39. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10): e51-77.
40. Ralston SH, Pennmen ID, Strachan MWJ, Hobson RP. Davidson's Principles and Practice of Medicine. 23rd Edition, 2018.
41. Mahon CR, et al. Bacteremia and sepsis (Chap 36). In: Textbook of Diagnostic Microbiology. 6th Edition.
42. Ramasubban S. Sepsis. In: Kamath SA, Shah SN, Nadkar MY, et al (Eds.). API Textbook of Medicine. 11th Edition, Volume 2. API; 2019.

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SARS-CoV-2: People Who do not Yet Display Any Symptoms Transmitted Nearly 10% of Infections

People can transmit the virus even before symptoms begin, a scenario known as presymptomatic transmission. It has been estimated that the proportion of such people who had not yet developed symptoms transmitted around 10% of the cases.

The serial interval (time between one person developing the symptoms of a condition and a second person becoming infected and developing symptoms) for SARS-CoV-2 has been reported to be approximately 4 days… (*Medical News Today*)

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Epidemiology, Clinical Presentation, Lab Diagnosis and Outcome of Scrub Typhus Outbreak in a Tertiary Care Center in Southern Rajasthan

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ABSTRACT

Introduction: Scrub typhus is also known as tsutsugamushi disease or bush typhus. It is a mite-borne acute febrile illness caused by Gram-negative intracellular organism called *Orientia tsutsugamushi*, which belongs to the family of Rickettsiaceae. **Aims and objectives:** To study the epidemiological patterns, different clinical manifestations and complications associated with scrub typhus. **Material and methods:** This was a prospective study which was carried out over a period of 12 months from January 2019 to December 2019 in patients of scrub typhus admitted in various medical wards of MB Govt. Hospital and RNT Medical College, Udaipur, Rajasthan. **Observation and results:** All the patients admitted with history of acute febrile illness suspected to be scrub typhus were assessed in the study. All these patients were evaluated by the set protocol in the form of detailed history, physical examination and relevant systemic examination. A total of 3,814 suspected patients of scrub typhus were tested in our microbiology laboratory and 1,340 patients were reported positive. Out of these, only 480 patients who were admitted in our medical wards were enrolled in our study and evaluated. **Conclusion:** We conclude that in rural Rajasthan, any patient who presents with fever, myalgia, hepatosplenomegaly and multiorgan dysfunction syndrome, a diagnosis of scrub typhus should be suspected.

Keywords: Scrub typhus, Rickettsiaceae, tsutsugamushi

Scrub typhus is also known as tsutsugamushi disease or bush typhus. It is a mite-borne acute febrile illness caused by Gram-negative intracellular organism called as *Orientia tsutsugamushi*, which belongs to the family of Rickettsiaceae. Although the disease has a worldwide distribution, most of the cases are reported from the so called "tsutsugamushi triangle", which is a wide area bounded by Pakistan, India and Nepal in the West, Siberia, Japan, China and Korea in the North and Indonesia, Philippines, Australia and the Pacific islands in the South. There is an estimated 1 million new scrub typhus infections each year and over 1 billion people around the world are at risk. In India, the disease was first noted during World War II in the soldiers posted in the tribal regions of Assam and Bengal and in the 1965 Indo-Pak War. This disease is endemic in the hilly areas of India like Himachal Pradesh and Jammu and Kashmir, but from the last few years a large number of cases has been reported from other parts of India, like Kerala, Pondicherry, Goa, Uttarakhand, West Bengal and Rajasthan. Although the illness is endemic to our country, but it still remains underdiagnosed because of the lack of diagnostic tools and awareness among the treating physicians. The disease is primarily seen in the rural populations and majority of cases are reported during the monsoon/post-monsoon season, that is from July to November.

However, it is not uncommon to find cases during the rest of the year because few case reports have been seen in the summer and winter months.

Scrub typhus may present clinically with a variety of symptoms which ranges from mild non-specific febrile illness to a much severe form of disease

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like cardiovascular, renal, hepatic and neurological involvement.

Very few studies are available from India on scrub typhus with fewer reported from Rajasthan where the disease has shown a resurgence lately. Keeping this current situation in minds, our aim was to conduct an observational prospective study on scrub typhus among the adult patients admitted in the Dept. of General Medicine, RNT Medical College and MB Govt. Hospital, a tertiary care institute located in the city of Udaipur in the state of Rajasthan.

AIMS AND OBJECTIVES

To study the epidemiological patterns, different clinical manifestation and complication associated with scrub typhus.

MATERIAL AND METHODS

This was a prospective study which was carried out over a period of 12 months from January 2019 to December 2019 in patients of scrub typhus admitted in various medical wards of MB Govt. Hospital and RNT Medical College, Udaipur, Rajasthan.

All the patients admitted with history of acute febrile illness suspected to be scrub typhus were taken in the study. All these patients were evaluated by the set protocol in the form of detailed history, physical examination and relevant systemic examination. These patients underwent investigations which included complete blood count, platelet count, urine examination, renal function and liver function tests, including hepatitis viral markers, X-ray chest, ultrasonography and electrocardiography. Cerebrospinal fluid examination and magnetic resonance imaging (MRI) of brain were done whenever required. Specific investigations under fever panel were also done in all these patients which included malarial parasite quantitative buffy coat (MPQBC) test for malaria, immunoglobulin M/G (IgM/IgG) and NS1 antigen testing to rule out dengue fever, Typhidot for typhoid fever, enzyme-linked immunosorbent assay (ELISA) test for Chikungunya. For the diagnosis of scrub typhus, we performed ELISA test to detect IgM antibodies against *O. tsutsugamushi* antigens. A total of 3,814 suspected patients of scrub typhus were tested in our Microbiology laboratory and 1,340 patients were reported positive. Out of these, only 480 patients who were admitted in our medical wards were enrolled in our study and evaluated.

Informed written consents were obtained from all the patients enrolled in our study.

Inclusion Criteria

All the admitted patients who were above the age of 18 years and found positive for scrub typhus by IgM ELISA technique were included in the study.

Table 1. Month-wise Distribution of the Cases

Month	Number of patients found positive	Number of patients enrolled in the study
January 2019	0	0
February 2019	1	1
March 2019	1	0
April 2019	1	0
May 2019	1	0
June 2019	2	1
July 2019	35	10
August 2019	173	68
September 2019	281	93
October 2019	320	103
November 2019	343	135
December 2019	182	69
Total	**1,340**	**480**

Table 2. Distribution of the Patients According to the Age, Gender and Rural vs. Urban

Sex/Age groups	18-40 years	40-60 years	>60 years
Male (n = 292)	122 (41.78%)	114 (39.04%)	56 (19.17%)
Female (n = 188)	86 (45.74%)	58 (30.85%)	44 (23.40%)
Total (480)	**208 (43.33%)**	**172 (35.83%)**	**100 (20.83%)**
Distribution			
Rural vs. Urban	Rural: 376 (78.33%)		Urban: 104 (21.67%)

Table 3. Distribution of Patients According to the Signs and Symptoms

	No. of patients	Percentage (%)
Fever	480	100
Headache	402	83.75
Myalgia	437	91.04
Vomiting	287	59.79
Rashes	92	19.16
Jaundice	302	62.91
Oliguria	184	38.33
Eschar	94	19.58
Altered sensorium	59	12.29
Neck rigidity	47	9.79
Bleeding	18	3.73
Hepatomegaly	284	59.16
Splenomegaly	279	58.12
Hypotension	152	31.66

Exclusion Criteria

Patient with known liver disorders, kidney failure and any cerebrovascular events (stroke, meningitis or meningoencephalitis in recent past).

Patient with concurrent infection with malaria, chikungunya and dengue fever.

All these patients were followed-up during their hospital stay and their outcomes were recorded in the form of primary and secondary outcome. Primary outcomes included death or discharge from hospital and secondary outcomes included duration of stay in hospital, need for ventilator and hemodialysis support.

OBSERVATION AND RESULTS

The maximum number of cases were reported in the months from August to December. The highest number of cases were reported in the month of November, i.e., 135 (28.12%) followed by in the month of October [103 (21.45%) cases] (Table 1). Among the 480 patients studied, 292 were male. About 43.33% patients were in the age group of 18-40 years, followed by 35.83% in the 40-60 years age group (Table 2). About 20.83% were above 60 years of age. Majority of patients belonged to the rural setting (Table 2).

Fever was the most common symptom (100%), followed by myalgia (91.04%). Other common signs and symptoms included headache, jaundice, vomiting, hepatomegaly and splenomegaly. Eschar was noted in 19.58% (Table 3).

More than half of the patients with scrub typhus had anemia. About 37.91% had leukocytosis and 36.25% had leukopenia. Nearly 95% patients had total serum

Table 4. Laboratory Findings in Patients of Scrub Typhus

Parameter	No. of patients	Percentage (%)
Anemia (Hb <12)	265	55.20
Leukocytosis (>11,000)	182	37.91
Leukopenia (<4,000)	174	36.25
Thrombocytopenia (<1,50,000)	289	60.2
Bilirubin (>1.1)	324	67.5
Elevated SGOT and SGPT	426	88.75
Elevated ALP	428	89.16
Serum albumin (<2.5 mg/dL)	442	92.08
Serum total protein (<5.5 mg/dL)	456	95.00
Serum LDH (>480 IU/L)	434	90.41
Serum triglyceride (>150 mg/dL)	438	91.25
Serum cholesterol (>200 mg/dL)	430	89.58
Serum urea (>40 mg/dL)	289	60.2
Serum creatinine (>1.1 mg/dL)	339	70.6

Hb = Hemoglobin; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; ALP = Alkaline phosphatase; LDH = Lactate dehydrogenase.

Table 5. Outcome Observed in the Patients of Scrub Typhus

Recovery and discharge	431 (89.79%)
Need for mechanical ventilation	58 (12.08%)
Weaned off from ventilatory support	27 (5.62%)
Need for dialysis	42 (8.75%)
Average hospital stay	8 days
Death	49 (10.20%)

protein below 5.5 mg/dL. The laboratory findings in patients with scrub typhus are summarized in Table 4.

Overall, 90% patients recovered and were discharged, 12% needed mechanical ventilation and 8.75% needed dialysis. Average hospital stay was for 8 days (Table 5).

DISCUSSION

Scrub typhus is a potentially fatal infection which affects about 1 million people every year. The disease first came into prominence during the World War II when many from the US, Ceylon and Burma army were infected and ultimately succumbed to the illness due to lack of proper antibiotic treatment.

Although a lot of epidemics of scrub typhus have occurred in India, the literature available on this illness is still limited. *O. tsutsugamushi* is the causative agent. It was first identified and studied in Japan in the year 1930. It is an obligate intracellular bacterium transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*. The incubation period varies from 6 to 21 days with an average of 10 days. These larval mites usually feed on the wild rats of the subgenus Rattus. The organism is maintained by transovarian transmission in mites. Although there are several serotypes of *O. tsutsugamushi*, infection with one species gives only a transient cross immunity to another. After a forest is cleared, scrubs grow on those areas over a period of time. These scrubs later get infested by larval mites. When man gets in contact with these scrubs, he becomes infected. The basic pathologic changes are focal vasculitis and perivasculitis of the

small blood vessels in the involved organs. These arise from multiplication of the organisms in the endothelial cells which line the small blood vessels.

In our study, we used IgM ELISA as the diagnostic tool for establishing the diagnosis of scrub typhus infection. Indirect immunofluorescence test is the gold standard diagnostic test for scrub typhus. Weil-Felix agglutination test is also widely available. Though Weil-Felix agglutination test is not a very sensitive test, it has high specificity and positive predictive value. Due to lack of availability of definitive tests in India, IgM ELISA can be a useful tool when used and interpreted in correct clinical context.

The study was conducted in RNT Medical College and MB Govt. Hospital, Udaipur, Rajasthan from January 2019 to December 2019. A total of 480 patients were enrolled in the study and the following observations were made.

In present study, the maximum number of cases were reported in the months from August to December which was 468 patients (97.5%), with the highest number of cases reported in the month of November i.e., 135 (28.12%) followed by in the month of October 103 (21.45%) cases. A study done in 2017-18 in 160 patients of scrub typhus found maximum patients in the month of September and 78% patients were reported in monsoon and post-monsoon season. The results of our study do not match with this study due to the fact that there may be variation of timing of monsoon and degree of rainfall.

Almost all the outbreaks of scrub typhus seem to occur in the rural population particularly seen among farmers, people involved in animal husbandry and those living close to woods and bushes. In the present study, we observed similar results where 376 (78.33%) patients were from rural population.

In the study, males were more frequently affected [292 (60.84%)] as compared to females [188 (39.16%)]. A study showed that among the 59 patients studied, 59% were males and 41% were females. More number of males affected in our study could probably be because of the reason that more number of males were involved in farming and animal husbandry activities. Among the total number of patients enrolled, maximum belonged to the age group of 18-40 years (208 participants). This is in accordance with the study conducted by Jamil et al in North Eastern India, wherein the investigators found that the maximum number of patients belonged to the age group of 18-30 indicating that these groups are more vulnerable to exposure owing to their involvement in more outdoor and recreational activities. The study conducted by Subbalaxmi et al found the mean age group of the affected population as 41 years.

Scrub typhus can cause a wide variety of symptoms ranging from fever, myalgia, headache, vomiting, loose stools to severe complications like acute renal failure, acute respiratory distress syndrome (ARDS), pneumonia, sepsis, meningitis and even death. Among the symptoms noted in this study, the most commonly observed was fever (100%) followed by headache (83.75%), myalgia (91%), vomiting (59.79%), rashes (19.16%), jaundice (62.91%) and oliguria (38.3%). Serious side effects like hypotension, bleeding and altered sensorium were also seen in less than 10% of the population. The characteristic finding of scrub typhus, that is the presence of eschar, was found in 19.58% of the patients. Hepatomegaly and splenomegaly were seen in 59.16% and 58.12% patients, respectively. This finding is in accordance with a study conducted in Rajasthan wherein the researchers found that fever (100%), headache (81.6%), cough, dyspnea (58.4%) and myalgia (48%) were the most common symptoms. Twenty-six (20.80%) patients had altered sensorium, 6 (4.8%) had gastrointestinal bleed and 6 (4.8%) had opisthotonus posturing with muscle spasms. Eschar was found only in 22% of the total population. Hepatomegaly (22%) and splenomegaly (10%) were also noted. From this, we can conclude that fever is seen almost universally in all the cases of scrub typhus making it an important differential diagnosis of any acute febrile illness.

The most common abnormality found in complete blood count analysis was thrombocytopenia (60.2%) followed by anemia (55.20%), leukocytosis (37.91%) and leukopenia (36.25%). The studies conducted by Subbalaxmi et al, Mathai et al and Wu et al also showed similar results. In the study by Subbalaxmi et al, thrombocytopenia was found in around 30% with leukocytosis in around 24% and leukopenia in 10% of the population. The presence of thrombocytopenia probably explains the bleeding manifestations encountered in scrub typhus.

Scrub typhus is one of the many different illnesses that is almost always associated with hepatitis. Liver function tests of the patients enrolled in our study showed that the abnormalities commonly encountered were raised bilirubin (67%) along with derangements in liver enzymes seen in 88% of the population. This was also associated with decrease in both total protein and levels of albumin seen in around 95% and 92% of the total population, respectively. The study conducted by Vivekanandan et al showed that derangement of liver

function test was seen in 95% of the study group while that of Mathai et al showed derangement in 88% of the study group. Thus, any patient who presents with an acute febrile illness with derangements of transaminase with hypoproteinemia should be evaluated for scrub typhus.

Scrub typhus also leads to derangements in renal function test, as noted in our study. The common findings were raised urea (60.2%) and raised creatinine (70.6%) observed among the patients studied. The study conducted by Mathai et al showed that renal failure was observed in 37% of the population while a similar study by Vivekanandan et al showed the derangement was seen in 13% of the population.

Of the total 480 patients studied, 431 recovered and were discharged from the hospital. Fifty-eight patients needed mechanical ventilation. Among these, 27 were weaned off from ventilator support. Forty-two patients had the need for renal replacement therapy in the form of hemodialysis or peritoneal dialysis. Average number of hospital stay was 8 days and 49 patients died. Similar findings were noted by Saluja et al. Of the total 160 patients included in the study, 12 patients had the need for mechanical ventilation. Average duration of hospital stay was 5.4 days and mortality was seen in 6 patients.

CONCLUSION

Scrub typhus is a disease which clinically mimics infections like dengue viral infection, leptospirosis, malaria and pneumonia. This is because all these infections present with sudden onset fever, mild hepatitis and thrombocytopenia. Whenever there is an associated feature suggestive of a multisystem involvement in the form of associated respiratory involvement, gastrointestinal symptoms, altered sensorium and hepatitis, a physician should always keep the diagnosis of scrub typhus in mind while analyzing the illness. Majority of our patients with scrub typhus are from rural parts. Though eschar is pathognomonic of the disease, it was noted in only less than 20% of the study population. This emphasizes that the absence of an eschar does not rule out scrub typhus. Although fever, headache, myalgia are the most predominant symptoms, serious symptoms like altered sensorium, hypotension and bleeding are also noted. Hepatosplenomegaly was also observed in a significant number of the population studied. Thrombocytopenia, raised transaminases, raised bilirubin and hypoproteinemia are the predominant laboratory abnormalities identified in our study. We conclude that in rural Rajasthan, any patient who presents with fever, myalgia, hepatosplenomegaly, multiorgan dysfunction syndrome and hepatitis, a diagnosis of scrub typhus should be suspected. A delay in treatment may lead to complications and higher mortality. That is why empiric treatment with doxycycline or macrolides may be given in cases where scrub typhus is suspected and if facilities for diagnosis are not available.

SUGGESTED READING

1. Blake FG, Maxcy KF, Sadusk JF, Kohls GM, Bell EJ. Tsutsugamushi disease (scrub typhus, mite-borne typhus) in New Guinea. Am J Public Health Nations Health. 1945;35(11):1121-30.
2. Tamura A, Ohashi N, Urakami H, Miyamura S. Classification of *Rickettsia tsutsugamushi* in a new genus, *Orientia* gen. nov., as *Orientia tsutsugamushi* comb. nov. Int J Syst Bacteriol. 1995;45(3):589-91.
3. Chattopadhyay S, Richards AL. Scrub typhus vaccines: past history and recent developments. Hum Vaccin. 2007;3(3):73-80.
4. Singh P. Scrub typhus, a case report: Military and regional significance. Med J Armed Forces India. 2004; 60(1):89-90.
5. Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. J Assoc Physicians India. 2010;58:24-8.
6. Narvencar KP, Rodrigues S, Nevrekar RP, Dias L, Dias A, Vaz M, Gomes E. Scrub typhus in patients reporting with acute febrile illness at a tertiary health care institution in Goa. Indian J Med Res. 2012;136(6):1020-4.
7. Ahmad S, Srivastava S, Verma SK, Puri P, Shirazi N. Scrub typhus in Uttarakhand, India: a common rickettsial disease in an uncommon geographical region. Trop Doct. 2010;40(3):188-90.
8. Mahajan SK, Rolain JM, Kashyap R, Bakshi D, Sharma V, Prasher BS, et al. Scrub typhus in Himalayas. Emerg Infect Dis. 2006;12(10):1590-2.
9. Laskar AR, Suri S, Acharya AS. Scrub typhus: reemerging public health problem in India. J Commun Dis. 2015; 47(3):19-25.
10. Mahajan SK. Scrub typhus. J Assoc Physicians India. 2005;53:954-8.
11. Walsh DS, Myint KS, Kantipong P, Jongsakul K, Watt G. *Orientia tsutsugamushi* in peripheral white blood cells of patients with acute scrub typhus. Am J Trop Med Hyg. 2001;65(6):899-901.
12. Tseng BY, Yang HH, Liou JH, Chen LK, Hsu YH. Immunohistochemical study of scrub typhus: a report of two cases. Kaohsiung J Med Sci. 2008;24(2):92-8.
13. Saah AJ. *Orientia tsutsugamushi* (scrub typhus). In: Mandell GL, Bennett JE, Dolin R (Eds.). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease.

5th Edition, Philadelphia: Churchill Livingstone; 2000. pp. 2056-7.

14. Allen AC, Spitz S. A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other Rickettsial diseases. Am J Pathol. 1945;21(4):603-81.
15. Song SW, Kim KT, Ku YM, Park SH, Kim YS, Lee DG, et al. Clinical role of interstitial pneumonia in patients with scrub typhus: a possible marker of disease severity. J Korean Med Sci. 2004;19(5):668-73.
16. Seong SY, Choi MS, Kim IS. *Orientia tsutsugamushi* infection: overview and immune responses. Microbes Infect. 2001;3(1):11-21.
17. Strickman D, Smith CD, Corcoran KD, Ngampochjana M, Watcharapichat P, Phulsuksombati D, et al. Pathology of *Rickettsia tsutsugamushi* infection in *Bandicota savilei*, a natural host in Thailand. Am J Trop Med Hyg. 1994;51(4):416-23.
18. Bozeman FM, Elisberg BL. Serological diagnosis of scrub typhus by indirect immunofluorescence. Proc Soc Exp Biol Med. 1963;112:568-73.
19. Saluja M, Vimlani H, Chittora S, Sen P, Suman C, Galav V, et al. Scrub typhus: Epidemiology, clinical presentation, diagnostic approach, and outcomes. JIACM. 2019;20(1):15-22.
20. Subbalaxmi MV, Madisetty MK, Prasad AK, Teja VD, Swaroopa K, Chandra N, et al. Outbreak of scrub typhus in Andhra Pradesh - experience at a tertiary care hospital. J Assoc Physicians India. 2014;62(6):490-6.
21. Jamil MD, Lyngrah KG, Lyngdoh M, Hussain M. Clinical manifestations and complications of scrub typhus: a hospital based study from North Eastern India. J Assoc Physicians India. 2014;62:19-23.
22. Mathai E, Rolain JM, Verghese GM, Abraham OC, Mathai D, Mathai M, et al. Outbreak of scrub typhus in southern India during the cooler months. Ann N Y Acad Sci. 2003;990:359-64.
23. Wu KM, Wu ZW, Peng GQ, Wu JL, Lee SY, et al. Radiologic pulmonary findings, clinical manifestations and serious complications in scrub typhus: experiences from a teaching hospital in Eastern Taiwan. Int J Gerontol. 2009;3(4):223-32.

■■■■

COVID-19: Knowing Viral Load has no Significance

Lescure and colleagues have described the first cases of COVID-19 in Europe, reported in France. The clinical features of 5 patients with COVID-19 are aligned with the quantitative SARS-CoV-2 viral RNA load from nasopharyngeal and other sampling sites.

While the authors make a case for COVID-19 presenting as three distinct clinical patterns, a distinction based on such small numbers seems highly speculative. On the basis of the assumption that viral RNA load correlates with high levels of viral replication, insights need to be gained from this time-course analysis.

Our understanding of the relationship between viral RNA load kinetics and disease severity in patients with COVID-19 continued to be disintegrated. Zou and colleagues had reported that patients with COVID-19 with more severe disease requiring ICU admission were found to have high viral RNA loads at 10 days and beyond, after symptom onset.

Contrary to that, Lescure and colleagues reported the viral RNA kinetics of 2 patients who developed late respiratory deterioration despite the disappearance of nasopharyngeal viral RNA. It would be interesting to know whether viral RNA load in lung tissue, or another sample such as tracheal aspirate, mirrors the reduction in nasopharyngeal shedding. It appears that these late, severe manifestations might be immunologically mediated. This observation has significance for the use of immune-modulatory therapies for this subset of patients. This finding is consistent with recent reports that corticosteroids were beneficial for acute respiratory distress syndrome, and possibly those with COVID-19.

Lescure and colleagues noted the implications for transmission from patients with few symptoms but high viral RNA load in the nasopharynx early in the course of disease. Individuals within the community, policy makers and frontline healthcare providers, particularly general and emergency room practitioners, should remain alert and prepare to manage this risk. The persistently high nasopharyngeal viral RNA load, and the detection of viral RNA in blood and pleural fluid, of the older patient (aged 80 years) with severe multi-organ dysfunction is disturbing. (*The Lancet Infectious Diseases*)

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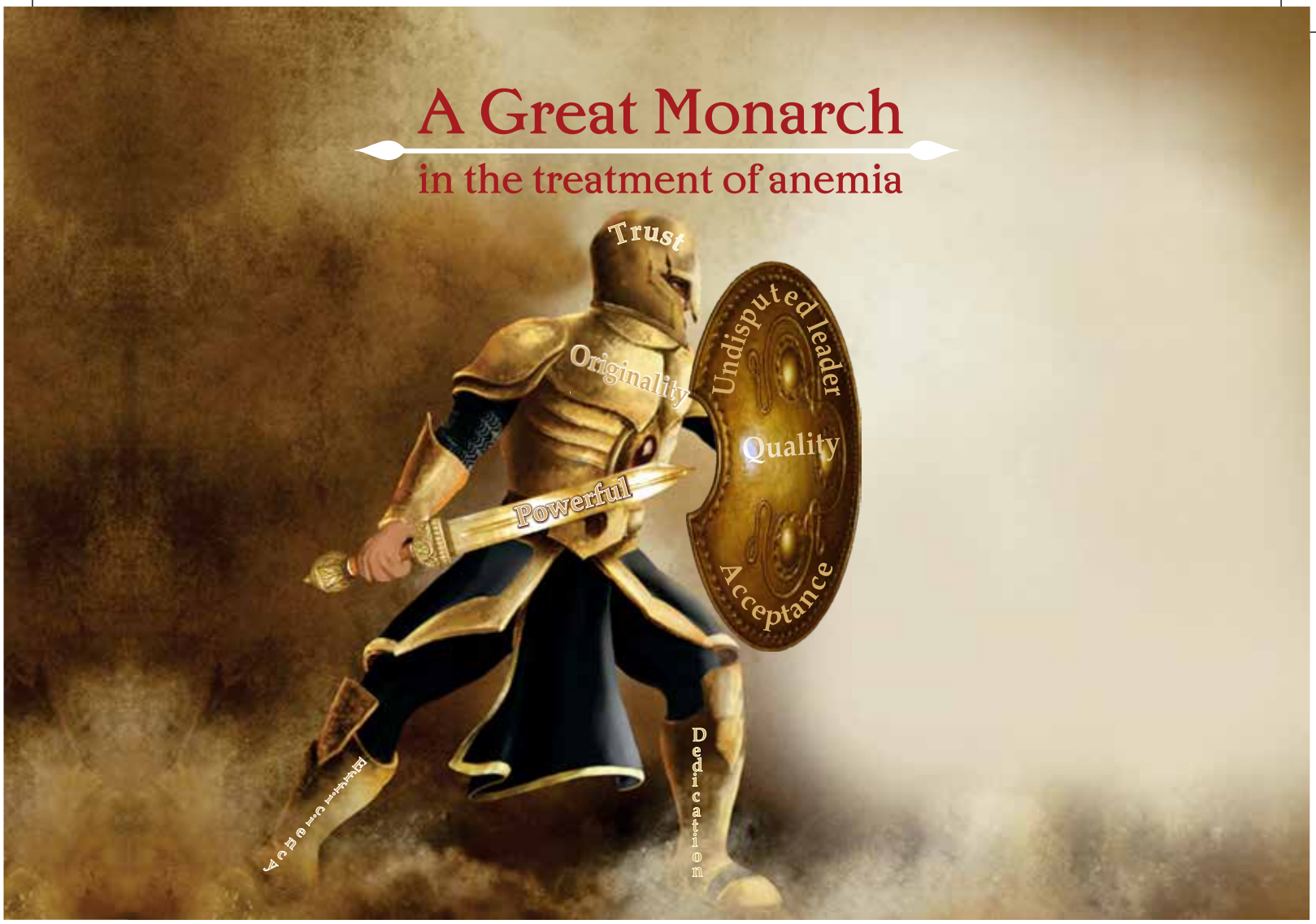

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A Comparative Study of Standard Peripheral Blood Smear and Antigen Detection Test in Diagnosis of Malaria in a Tertiary Care Hospital in Jalandhar

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ABSTRACT

Background: Malaria can cause fatal complications if the diagnosis and treatment are delayed. So, quick detection and early treatment of malaria are the best policies for the management of disease. Microscopy has been the gold standard for malaria diagnosis for decades. Recently, many new rapid diagnostic tests (RDTs) are being widely used. We have made an attempt to compare peripheral smear and rapid antigen detection methods for the diagnosis of malaria. **Material and methods:** A total of 500 blood samples were collected from patients presenting with symptoms of malaria. Thin and thick blood smears were prepared and stained with Leishman's stain. *Plasmodium falciparum* (Pf) HRP-2 antigen and *Plasmodium vivax* (Pv) specific pLDH detection was done using rapid test device for malaria diagnosis. **Results:** Out of the 500 blood samples tested, only 3.4% were positive for malaria. Difference between the positivity for Plasmodium species by both methods was 0.6%. Sensitivity, specificity, positive predictive value and negative predictive values were 85%, 99.6%, 89.5% and 99.4%, respectively with peripheral blood film (PBF) method. **Conclusion:** The study highlights that the RDT, for diagnosis of malaria, is as reliable as microscopy. Microscopy is simple, economical, sensitive and specific but it is time consuming and requires a microscope. In places where such facilities are not available, rapid, simple and easy to interpret antigen detection test can be done.

Keywords: *Plasmodium falciparum*, *Plasmodium vivax*, malaria diagnosis, rapid diagnostic test

Malaria is one of the important vector-borne disease in India and can be fatal if not treated promptly. The early diagnosis and treatment of malaria is essential to prevent complications, especially in cerebral malaria. The disease occurs in over 90 countries worldwide, and over 600 million clinical cases and 3.1 million malaria-related deaths are estimated to occur per year. Malaria is caused by five Plasmodium species with different geographic distribution; *Plasmodium falciparum* (Pf) and *Plasmodium vivax* (Pv) are more common in India. It is important to differentiate between types of malarial parasite causing the illness as treatment of malaria based on assumption would encourage the development and spread of drug-resistant Pf parasites. Conventional peripheral smears, quantitative buffy coat (QBC) and rapid diagnostic tests (RDTs) are commonly available diagnostic tests for malaria.

Changing patterns of accepted morphological appearances of Plasmodium species, possibly due to drug pressure, strain variation or approaches to blood collection, have created diagnostic problems that cannot easily be resolved merely by reference to an atlas of parasitology. Fortunately, new technology provides additional diagnostic options, which can be reviewed and compared to more traditional methods. The various techniques to diagnose malaria are conventional peripheral smear, QBC, antigen-based rapid diagnostic kits and molecular studies (polymerase chain reaction).

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Conventional peripheral blood smear examination for demonstration of malaria parasites is the gold standard method for diagnosing malaria. However, this technique is time consuming and requires skilled personnel. QBC is sensitive but has drawbacks such as high cost, imperfect speciation and is associated with false-positive results due to artifacts, such as cell debris. RDTs detect parasitic antigens like histidine-rich protein-2 (HRP-2), Plasmodium lactate dehydrogenase (pLDH) and pan-specific aldolase. RDTs are easy to perform and yield quick results but they are expensive, associated with false-positive results due to persistent antigenemia, and cross-reactions with autoantibodies such as rheumatoid factor and false-negative result in severe malaria, which could be attributed to immune-complex formation, prozone phenomenon and other causes. All these techniques vary in there sensitivity, specificity, positive and negative predictive values. For this reason, the present study was done to compare the peripheral blood smear test with malaria antigen card test.

MATERIAL AND METHODS

The prospective study was conducted in the Dept. of Pathology in a tertiary care hospital from April 2018 to March 2019. Only 500 blood samples from patients presenting with symptoms of malaria were included in the study. Prior to study, permission from ethical committee was taken.

Thick and thin smears were prepared from finger prick and approximately 5 mL of venous blood was collected in an anticoagulant tube containing ethylenediaminetetraacetic acid (EDTA) from each patient during the peak of fever and transported to the laboratory.

Peripheral Blood Smear

Thick and thin blood smears were prepared and stained with Leishman's stain as per standard method. The slides were examined using light microscope and the average time spent on each slide depended on parasite density. Thick smears were reported negative when no parasite was observed on examination of 200-300 oil immersion fields (OIF) while a thin smear was reported negative when no parasites were observed in 100 OIF. The red blood cells in the tail end of the thin smear were examined for the species identification and stages of the parasites.

Rapid Diagnostic Tests

Pf HRP-2 antigen and Pv specific pLDH detection was done using rapid test device for malaria (Pv/Pf). The kits were all from the same batch and were used before the expiry date and performed according to the instruction manual by the manufacturer.

The test goes by the principle of agglutination of antibodies/antisera with respective antigen in immune-chromatography format using nano gold particles as an agglutination revealing agent.

As the test sample moves through the membrane assembly of the device following the addition of the clearing buffer, the colored colloidal gold conjugates of the agglutinating sera for HRP-2 and the agglutinating sera for Pv specific pLDH complexes the HRP-2/pLDH in the sample. This complex moves ahead on the membrane and reaches the test region and undergoes immobilization by the agglutinating sera for Pan Malaria specific pLDH and/or agglutinating sera for HRP-2 coated on the membrane. This gives rise to the formation of pink-purple colored bands. This validates a positive test result. A band appears under Pf at the test region in falciparum positive samples while a band appears under Pv in vivax malaria positive samples. If a band appears under Pf as well as Pv in the test region, it suggests mixed infection.

If colored band is absent in the test region, it points to a negative test result. The unreacted conjugate and unbound complex move further on the membrane and undergo immobilization by agglutinating sera for rabbit globulin coated on the membrane at the control region, giving rise to a pink-purple band. The control band formation is based on the "Rabbit globulin/agglutinating sera for rabbit globulin" system. This is independent of the analyte detection system.

Therefore, it promotes the formation of a consistent control band signal that does not depend on the analyte concentration. The control band helps validate the test performance.

The procedure and interpretation of test results were conducted according to the manufacturer's literature guideline.

STATISTICAL ANALYSIS

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each method using standard formulae.

Sensitivity = TP/TP+FN, Specificity = TN/TN+FP, PPV = TP/TP+FP, NPV = TN/TN+FN

(TP – True Positive, TN – True Negative, FP – False Positive, FN – False Negative)

RESULTS

Out of the 500 blood samples tested, only 17 (3.4%) were positive for malaria. Out of 17 positive cases, Pv was diagnosed in 15 cases (88.23%), Pf was identified in 1 case (5.88%) and 1 smear (5.88%) showed mixed infection with both Pv and Pf. RDT showed 14 positive cases (2.8%) of malaria, of which 12 (85.71%) cases were of Pv, and 1 case each (7.14%) was of Pf and mixed infection with falciparum and vivax. Difference between the positivity for Plasmodium species by both methods was 0.6% (Table 1).

Sensitivity, specificity, PPV and NPV were 85%, 99.6%, 89.5% and 99.4%, respectively with peripheral blood film (PBF) method (Table 2).

DISCUSSION

Malaria is today one of the major causes of human suffering, both in terms of increasing morbidity/mortality and stunting intellectual/economic growth. Accurate diagnosis and early treatment of malaria is essential to reduce mortality and morbidity. During the last decade, several new rapid diagnostic techniques have been developed and evaluated widely. They aim at prompt and accurate diagnosis of malaria parasite that helps in early initiation of appropriate antimalarial drug to prevent the complications. Leishman's or Giemsa-stained thick smears are considered to be the 'Gold standard' in diagnosis of malaria. In the present study, the PBF positivity for malaria was 3.4% whereas other workers reported it to be 16.84% and 18.28%, respectively. As per Punjab Malaria Elimination Campaign (2017-2021) in Punjab, Annual Parasite Incidence (API) is less than 1 case per 1,000 population at risk and in 2016, API in Jalandhar was reported between 0 to 0.1. In India, 40% of cases are as result of Pv malarial infection, 44.3% are due to Pf malarial infection and 10-15% are due to mixed malarial infection.

In our study, among malaria positive cases by PBF method, 88.23% were due to Pv infection and 5.8% positive cases each were of Pf and mixed infection. Almost similar results were reported by other workers as 98.85% for Pv, 0.57% each for Pf and mixed infection by PBF method. RDT showed 14 positive cases (2.8%) of malaria, of which 12 (85.71%) cases were of Pv and one case each (7.14%) was of Pf and mixed infection with falciparum and vivax. However, other workers with RDT method reported it to be 94.17% for Pv, 2.11% for Pf and 3.7% for mixed infection.

In the present study, we observed 87% sensitivity, 99.6% specificity, 82.35% PPV and 99.58% NPV in antigen card test comparing with the peripheral blood smear (Table 2), whereas other workers have observed 100% sensitivity, 99.5% specificity, 98.59% PPV and 100% NPV in antigen card test comparing with the peripheral blood smear. In the present study, we reported 85% sensitivity for Pf and Pv. It was found that at lower parasitemia, the sensitivity dropped considerably. Sensitivity was 100% at parasitemia level 240 parasites/μL or more. Thick smear provides enhanced sensitivity of blood film technique and seems to be better than thin film to detect low levels of parasitemia and relapse or recrudescence. RDT missed 3 cases of Pv which were positive on microscopy. These false-negative results may be due to the fact that RDT is not sensitive below a parasitic index of 100 parasite/μL and it detects pLDH produced by living parasites. The blood samples judged positive

Table 1. Comparison of Microscopy and Rapid Diagnostic Test Method

	P. vivax (Positive)	*P. falciparum* (Positive)	Mixed infection (Positive)	Negative
PBF (n = 500)	15 (3%)	01	01	483
RDT (n = 500)	12 (2.4%)	01	01	486
Difference between two methods	3 (0.6%)	0	0	

Table 2. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of PBF and RDT Methods for Diagnosis of Malaria

Method of test	Sensitivity	Specificity	PPV	NPV
PBF	85%	99.6%	89.5%	99.4%
RDT	87.5%	99.6%	82.35%	99.58%

by pathologist may have been dead parasites not yet cleared from the host.

CONCLUSION

The study highlights that RDT for diagnosis of malaria is as reliable as microscopy. Microscopy is simple, economical, sensitive and specific but it is time-consuming as one test requires 30-40 minutes and it is subject to bias; results are affected by the skill and workload of the microscopists. RDT is simple, and requires no equipment; however, its drawback is that it is quite expensive and its sensitivity and specificity are debatable at low parasitemia. The rational use of RDTs as a complement to microscopy might give substantial health benefits through earlier treatment, reduction in morbidity and mortality and more rationalized approach for choosing antimalarial drugs, which may prevent drug resistance.

SUGGESTED READING

1. Paul SN, Murmu S, Singh US, Kumar S. A comparative study of peripheral blood smear and rapid diagnostic test for diagnosis of malaria in Jharkhand, India. IJPMR. 2016;4(4):1-2.
2. Yan J, Li N, Wei X, Li P, Zhao Z, Wang L, et al. Performance of two rapid diagnostic tests for malaria diagnosis at the China-Myanmar border area. Malar J. 2013;12:73.
3. Gandhi V, Muley P, Parikh N, Gandhi H, Mehta A. Is rapid diagnostic test (malaria Pv/Pf Ag card test) reliable in diagnosing malaria? Int J Contemp Pediatr. 2018;5(1):92-6.
4. Bhat SK, Sastry AS, Nagaraj ER, Mannur S, Sastry AS. Laboratory diagnosis of malaria by conventional peripheral blood smear examination with Quantitative Buffy Coat (QBC) and Rapid Diagnostic Tests (RDT) - A comparative study. International Journal of Collaborative Research on Internal Medicine & Public Health. 2012;4(10):1746-55.
5. Mendiratta DK, Bhutada K, Narang R, Narang P. Evaluation of different methods for diagnosis of *P. falciparum* malaria. Indian J Med Microbiol. 2006;24(1):49-51.
6. Parija SC, Dhodapkar R, Elangovan S, Chaya DR. A comparative study of blood smear, QBC and antigen detection for diagnosis of malaria. Indian J Pathol Microbiol. 2009;52(2):200-2.
7. Tyagi BK. Vector-borne diseases: Epidemiology and Control. Preface. Jodhpur: Scientific Publishers; 2008.
8. Kumar KR, Sudarshan KS. Clinical evaluation of a rapid diagnostic kit (Paracheck-Pf) for diagnosis of *Plasmodium falciparum* in Karnataka state of India. Indian J Prev Soc Med. 2004;35(1):10-4.
9. Elimination Campaign. 2017-2021. Action Plan & Road Map for Malaria Elimination in Punjab, India. Department of Health and Family Welfare, Punjab. (online) (Cited 2019 July11). Available at: https://www.punjabnvbdcp.in/Download/Punjab%20Malaria%20Elimination%20Campaign%202017-2021.pdf
10. World Health Organization, Regional Office for South-East Asia. (2000). Implementation of collaborative actiities on roll back malaria in the South-East Asia Region: report of an intercountry meeting, New Delhi, 4-6 May 1999. WHO Regional Office for South-East Asia. Available at: https://apps.who.int/iris/handle/10665/205327
11. Kulkarni P, Varna I. Rapid diagnostic tests versus peripheral smear in malaria: a comparative study. Trop J Pathol Microbiol. 2016;2(3):179-82.
12. Cooke AH, Chiodini PL, Doherty T, Moody AH, Ries J, Pinder M. Comparison of a parasite lactate dehydrogenase-based immunochromatographic antigen detection assay (OptiMAL) with microscopy for the detection of malaria parasites in human blood samples. Am J Trop Med Hyg. 1999;60(2):173-6.

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COVID-19: Presence of Viral RNA in Specimens Always Correlates with Viral Transmissibility

No, in a ferret model of H1N1 infection, the loss of viral culture positivity but not the absence of viral RNA corresponded to the end of the infectious period. Real-time reverse transcriptase PCR results continued to be positive 6-8 days after the loss of transmissibility. (*Lancet Infectious Diseases*)

In SARS, Live Virus was Detected for 4 Weeks

No, for SARS coronavirus, viral RNA can be detected in the respiratory secretions and stool of some patients after onset of illness for more than 1 month, but live virus could not be detected by culture after Week 3. (*Lancet Infectious Diseases*)

It's Easy to Differentiate Between Infective and Non-infective Virus

The inability to differentiate between infective and non-infective (dead or antibody-neutralized) viruses is a huge limitation of nucleic acid detection. However, given the difficulties in culturing live virus from clinical specimens during a pandemic, using viral RNA load as a surrogate is reasonable for generating clinical hypotheses. (*Lancet Infectious Diseases*)

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Effectiveness of Video-assisted Teaching Program on Learning Disabilities of School Children Among Primary School Teachers in Selected Schools of Palvoncha

B RAJESH

ABSTRACT

This study was aimed to assess the effectiveness of video-assisted teaching program on learning disabilities of school children among primary school teachers in selected schools. Quantitative research approach with one group pre-test and post-test research design was adopted for this study. Multistage cluster sampling technique was used to select the participants (n = 60). Primary school teachers of selected schools at Palvoncha were selected for the study. Self-structured questionnaire was administered as a tool and the collected data was analyzed. The results revealed that in the pre-test, among 60 subjects, 53 (88.3%) of the teachers had inadequate knowledge, 5 (8.3%) had moderate level of knowledge and 2 (3.3%) had adequate level of knowledge regarding learning disabilities. After video-assisted teaching program, post-test was conducted. In that, majority 50 (83.3%) had moderate level of knowledge and 10 (17%) had adequate level of knowledge regarding learning disabilities. This shows definite gain of knowledge after video-assisted teaching program. The mean obtained for pre-test knowledge on learning disabilities was 10.00 and standard deviation was 4.43. The mean for post-test knowledge was 21.00 and standard deviation was 2.04. This inference clearly shows that there was an improvement in knowledge on learning disabilities among primary school teachers. So, conducting video-assisted teaching program brought an improvement in the primary school teachers' knowledge on learning disabilities. The gained knowledge will help them with early identification of learning disabilities among school children and they would be able to provide better remediation for the children who are learning disabled as well as they can guide the parents too.

Keywords: Learning disabilities, primary school teacher, video-assisted teaching

Learning is an important and significant mental functions of humans, animals and artificial cognitive systems. It relies on the acquisition of different types of knowledge supported by perceived information. It leads to the development of new capacities, skills, values, understanding and preferences. Its goal is to enhance the individual and group experience. Learning functions can be performed by various brain learning processes, which are dependent upon the mental capacities of the learning subject, the type of knowledge, and the socio-cognitive and environmental situation.

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Learning disabilities refer to problems that impact the brain's ability to receive, process, analyze or store information in a way that these problems make it difficult for a student to learn as fast as someone who is not affected by such disabilities.

Eight to ten percent of American children below 18 years of age have been shown to have some type of learning disability. Learning disabilities can be lifelong conditions. Some people may have an isolated learning problem that has little impact on their lives.

Learning disabilities make up the most prevalent and urgent medical problems of school children in the developed countries, so they need special attention and appropriate interventions to prevent the related problem and improve the academics.

The types of learning disorders that are most conspicuous usually involve reading, writing or math. The common types of learning disabilities are dyslexia,

dyscalculia, dysgraphia, dyspraxia, auditory or visual processing disorder and slow learner.

Learning disorder refers to a heterogeneous group of disorders characterized by significant difficulties in acquiring and using skills such as listening, speaking, reading, reasoning, writing or mathematical skill. Learning disorders are intrinsic to the individual and occur as a result of central nervous system dysfunction. Movies like "Taare Zameen Par" have enlightened on the subject of learning disorders. The movie tells the story of an 8-year-old, Ishaan Awasthi, who suffers greatly until his teacher identifies him as a dyslexic.

It is estimated that there are 2,86,000 children (1,80,000 boys, 1,06,000 girls) age 0-17 in the UK with a learning disability. Approximately 2,00,000 children in England are at the School Action Plus stage of assessment of Special Education Needs (SEN) or have a statement of SEN and have a primary SEN associated with a learning.

In India, the incidence rates of learning disability are as follows:

- Learning disabilities - 2.8 million
- Speech/Language disorders - 1.1 million
- Cognitive disabilities - 57 million
- Emotional and/or Behavioral disorders - 48 million
- Other health impairments - 45 million.

In India, nearly 13-14% of all school children have some form of learning disorder. Most schools fail to lend a sympathetic ear to their problems. These children are therefore often tagged as failures.

The role of teachers in education goes way beyond the responsibility of simply passing along information. The principal function of the teacher is to teach several facts and skills to students. A teacher's role also involves a multifaceted sense of purpose that is aimed at encouraging a child's social development. The role that a teacher plays in different aspects of education is guided by the age and grade level of the students. The important role of the teacher in education delivery is highly beneficial for children and parents, including students with special needs.

Video-assisted teaching has become a realistically straight forward proposition with the moving images as a delivery medium that they have tended to dominate all the discussion of its use.

MATERIAL AND METHODS

The quantitative research approach with one group pre-test and post-test research design was adopted for this study. Multistage cluster sampling technique was used to select the participants (n = 60). The tool used for the study was self-structured Questionnaire, organized as Section I - Socio-demographic data and Section II - Questionnaire on Learning disabilities. All the items in the Questionnaire were prepared by the researcher based on reviews, previous studies, journals, magazines and research articles of learning disabilities. Eleven experts constituting 3 psychiatrists, 2 psychologists and 6 mental health nursing personnel validated the Tool. The reliability of the tool was computed by using test-re-test method by using Karl Pearson's coefficient correlation reliability method. The calculated 'r' value was 0.92, indicating that the tool taken by the researcher was reliable, valid and predictable of the desired objective. The data was analyzed by using descriptive and inferential statistics.

RESULTS

Table 1 depicts that in the pre-test, majority (88.3%) of the teachers had inadequate knowledge, 8.3% had moderate knowledge and 3.3% had adequate level of knowledge regarding learning disabilities. In the post-test, 83.3% had moderate level of knowledge and 17% had adequate level of knowledge regarding learning disabilities.

Table 2 depicts the difference between mean pre-test knowledge score and the mean post-test score regarding learning disabilities. The calculated 't' value (25.69) was greater than tabulated value.

It shows that there was a high significance at the level of $p \leq 0.05$ level. Hence, the research hypothesis was accepted. So, it was concluded that there was improvement in the knowledge levels of teachers after structured teaching program regarding learning disabilities.

Table 1. Frequency and Percentage Distribution of Pre- and Post-test Level of Knowledge on Learning Disabilities Among Primary School Teachers (n = 60)

Level of knowledge	Pre-test		Post-test	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Inadequate knowledge	53	88.3	-0-	-0-
Moderate knowledge	05	8.3	50	83.3
Adequate knowledge	02	3.3	10	17

Table 2. Mean, Standard Deviation and Paired 't' Test of Pre- and Post-test Level of Knowledge Among Primary School Teachers (n = 60)

Level of knowledge	Pre-test	Post-test
Mean	10	21
Standard deviation	4.43	2.04
Paired 't' test	-	t = 25.69

DISCUSSION

The results denote that in the pre-test, majority (88.3%) of teachers had inadequate knowledge, 8.3% had moderate knowledge and 3.3% had adequate level of knowledge regarding learning disabilities of children. After giving video-assisted teaching program, post-test was conducted. In the post-test, 83.3% had moderate level of knowledge and 17% had adequate level of knowledge. This shows the definite gain of knowledge after video-assisted teaching program. Hence, the hypothesis stated was accepted.

The implications drawn from the present study are of vital significance to school children in order to prevent learning disabilities. There is a need for the provision of health education program. The findings of the study have implications in various areas like nursing service, nursing education, nursing administration and nursing research. It is recommended to do same study with a large sample in different settings.

Informational booklet is a strong weapon. Hence, nurses working in community will have the opportunity to give appropriate health education to the parents and public to prevent learning disabilities. In the community, nurses should take part in health education program on prevention of learning disabilities, and early identification of children with learning disabilities and by bringing awareness through different health educational methods like psychodrama, role play and mime shows, etc. Teachers and parents can play a key role in preventing and reducing learning disabilities.

In psychiatric hospitals, nurses can play a key role in identifying learning disabilities and are encouraged to provide patients and parents with information about the manifestations and consequences of learning disabilities, and assisting them in seeking better treatment. The teaching faculty should plan for using various teaching strategies and special education skills to students and encourage them to maximize their efforts towards the learning disabled children and improving their quality of life.

In nursing colleges and other educational institutions, it is important to adequately prepare the students to provide incidental and planned health education to parents and teachers which is helpful for them in early identification of learning disorders. Nursing students should be trained in planning and implementing health education program, depending on the need, with good communication skills.

To conduct these programs, efficient team work strategies for optimization of resources and focus on cost-effective methods are to be planned properly.

Nursing administration should have a health education cell with adequately trained nurses with good communication skills to develop and provide health education to teachers, parents and other individuals.

CONCLUSION

The present study revealed that 53 (88.3%) primary school teachers had inadequate knowledge on learning disabilities of school children. So, video-assisted teaching program imparted to primary school teachers can bring about an improvement in the knowledge on learning disabilities. The gained knowledge will help them with early identification of learning disabilities among school children and they will also be able to provide better remediation for the children who are learning disabled as well as they can guide the parents too.

The implications drawn from the present study are of vital significance to school children in order to prevent learning disorders and promote healthy ways of controlling learning disorders and for close supervision of parents regarding good learning habits in homes. Encourage educational institutions to offer student benefit teacher assistance programs, various prescribed teaching strategies, counseling sessions to students and parents, interaction programs between parents and teachers on learning disabilities and confidential referral to treatment.

SUGGESTED READING

1. Barker P. Basic Child Psychiatry. Blackwell Scientific Publications, Oxford; 1988. pp. 533-66.
2. Kapoor B. Textbook of Psychiatric Nursing. 1st Edition, New Delhi: Kumar Publications; 1994. pp. 150-80.
3. Blackwell's Neurology and Psychiatry Access series. Edited by S. B. Sexson. pp. 100-30.
4. Polit DF, Hungler BP. Nursing Research: Principles and Methods. 5th Edition, Philadelphia, Lippincott Williams and Wilkins; 1995. pp. 141-50.

5. Abrams JC, Kaslow FW. Learning disability and family dynamics: A mutual interaction. J Clin Child Psychol. 1976;5(1):35-40.
6. Bakwin H. Reading disability in twins. Dev Med Child Neurol. 1973;15(2):184-7.
7. Sajitha B. Achievement performance at the primary level in public and private schools of Tamil Nadu. Indian Education Rev. 1994;29(3-4): July- Oct.
8. Bhargava S, Garg OP, Singhi S, Singhi P, Lall KB. Prevalence of behaviour problems in Ajmer school children. Indian J Pediatr. 1988;55(3):408-15.
9. Bryan T, Barstein K, Bryan J. Students with learning disabilities: Homework problems and promising practices. Educational Psychologists. 2001;36(3):167-80.
10. Lindsay P. Dyslexia in Primary Schools. BDA, London; 1996. pp. 122-90.
11. Boyd MA. Psychiatric Nursing: Contemporary Practice. 4th Edition, Lippincott Williams & Wilkins; 2006. p. 524.
12. Mercer CD, Mercer AR. Teaching Students with Learning Problems. Merrill, New Jerssey; 1994. pp. 90-899.
13. Ahuja N. A Short Textbook of Psychiatry. 6th Edition, Jaypee Brothers Medical Publishers; 2008. pp. 35-55.
14. Vyas JN, Ahuja N. Textbook of Postgraduate Psychiatry. 2nd Edition, Jaypee Brothers Medical Publishers; 2008. pp. 76-140.
15. Payne T, Turner E. Dyslexia - A Parents and Teachers Guide. Clevedon, UK: Multilingual Matters Ltd; 1988. pp. 340-876.
16. Prabhakara GN. Biostatistics. New Delhi: Jaypee Brothers Medical Publishers; 2006. pp. 11-24.
17. Selikowitz M. Dyslexia and Other Learning Difficulties – The Facts. Oxford University Press, Oxford; 1993. pp. 600-875.
18. Cooper H, Valentine JC, Nye B, Lindsey JJ. Relationship between five after school activities and academic achievement. J Educat Psychol. 1999;91(2):369-78.
19. DeFries JC. Gender ratios in children with reading disability and their affected relatives: a commentary. J Learn Disabil. 1989;22(9):544-5.
20. Dyson LL. The experiences of families of children with learning disabilities: parental stress, family functioning, and sibling self-concept. J Learn Disabil. 1996;29(3): 280-6.
21. Fergusson DM, Lynskey MT. Early reading difficulties and later conduct problems. J Child Psychol Psychiatry. 1997;38(8):899-907.
22. Gajria M, Salend SJ. Homework practices of students with and without learning disabilities: a comparison. J Learn Disabil. 1995;28(5):291-6.
23. Gittelman R, Mannuzza S, Shenker R, Bonagura N. Hyperactive boys almost grown up. I. Psychiatric status. Arch Gen Psychiatry. 1985;42(10):937-47.
24. Handwerk ML, Marshall RM. Behavioral and emotional problems of students with learning disabilities, serious emotional disturbance, or both conditions. J Learn Disabil. 1998;31(4):327-38.
25. Janaki. A study of poor school performance in school children. Dissertation for M.Phil degree in Clinical Psychology Deemed University, NIMHANS, Bangalore. 1986.
26. Jogi I, Kulkarni SY, Kulkarni VV. Dynamics of behavioural problems care of selected primary school. Maharashtra J Exten Educ. 1992;11:130-8.
27. John A, Kapur M. Scholastic backwardness in a child guidance population: a preliminary report. NIMHANS J. 1986;4(1):55-9.
28. Lane SE, Lewandoswski L. Oral and written compositions of students with and without learning disabilities. J Psycho-Educat Assess. 1994;2:142-53.
29. Maag JW, Reid R. Depression among students with learning disabilities: assessing the risk. J Learn Disabil. 2006;39(1):3-10.

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CMAAO Coronavirus Facts and Myth Busters

Aerial spraying should work

It is not possible to fight the virus through aerial spraying or by dousing the public drinking water with some potion.

We have not been able to trace patient zero

A shrimp seller at the wet market in the Chinese city of Wuhan, could possibly be the first person to have tested positive for the disease.

The London-based Metro newspaper stated that the 57-year-old woman, named by the Wall Street Journal as Wei Guixian, was selling shrimp at the Huanan Seafood Market when she developed what she believed was a cold last December. Chinese digital news outlet, *The Paper*, stated that she may be 'patient zero'.

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Comparison of Myoinositol and Metformin in Women with Polycystic Ovarian Syndrome

SHAYISTA NABI*, RAKA GULERIA†

ABSTRACT

Objective: The aim of the study was to compare the effects of 16-week treatment with two insulin-lowering therapies on the clinical, endocrine-metabolic and ovulatory parameters in women affected by polycystic ovarian syndrome (PCOS). **Material and methods:** A total of 70 patients attending the Gynecology OPD of Holy Family Hospital, Okhla, New Delhi, with clinical features of PCOS in the age group of 17-35 years, between June 2015 and May 2016, were selected. Patients were randomly distributed into two groups with 35 patients each. Group 1 received myoinositol (MYO) 2 g/day, while Group 2 received metformin 500 mg/day twice-daily. Baseline anthropometry, biochemical investigations and pelvic ultrasonography were done and repeated after 16 weeks. **Results:** Modified Ferriman-Gallwey (mFG) score was reduced from 4.66 ± 4.06 SD to 3.56 ± 3.29 SD in Group 1 and 4.94 ± 4.05 SD to 3.87 ± 3.24 SD in Group 2; the fall in Group 1 was more significant than Group 2. Fasting insulin decreased from 13.90 ± 6.88 SD to 11.66 ± 6.05 SD in Group 1 and from 12.85 ± 4.46 SD to 11.78 ± 4.39 SD in Group 2; reduction was highly significant in Group 1 than Group 2. Results for luteinizing hormone (LH) were not significant. Free testosterone decreased from mean of 1.47 ± 0.37 SD to 1.37 ± 0.37 SD in Group 1 and from 1.43 ± 0.37 SD to 1.36 ± 0.36 SD in Group 2; the fall in Group 1 was more significant than Group 2. **Conclusion:** Metformin is effective in reducing the metabolic and hormonal parameters and improves fertility. MYO not only improves all the above parameters but also decreases insulin resistance significantly. Thus, MYO supplementation is essential in the management of PCOS to improve insulin sensitivity.

Keywords: Polycystic ovarian syndrome, myoinositol, metformin, fasting insulin

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, affecting 5-10% of women worldwide. It is defined as a heterogeneous syndrome complex characterized by hyperandrogenism (clinical and/or bio-clinical), ovarian dysfunction (oligo- and/or anovulation) and polycystic ovaries, with exclusion of related disorders. This is with the recognition that forms of PCOS may occur without overt incidence of hyperandrogenism.[1]

Initially defined by Stein and Leventhal in 1953, this syndrome has changed in definition over the years and is briefly defined in Table 1.

In 2003, Rotterdam proposed a revised criterion for PCOS that included ultrasound morphology of ovaries as potential criteria to define PCOS:[2]

- Menstrual irregularity (due to oligo- and/or anovulation)
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (by ultrasound).

Table 1. Definition of PCOS

National Institute of Health (NIH) - 1990	Androgen Excess Society (AES)
Evidence of clinical or biochemical hyperandrogenism	Androgen excess (clinical and/or biochemical hyperandrogenism)
Chronic anovulation	Ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology on ultrasonography)

All criteria require exclusion of other causes of hyperandrogenism such as adult onset congenital adrenal hyperplasia, hyperprolactinemia and androgen secreting tumors.

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In addition, other etiology must be excluded (congenital adrenal hyperplasia, androgen secreting tumors, thyroid dysfunction, Cushing's syndrome).

In young women with PCOS, insulin resistance may occur with higher frequency of about 30-40%. Additionally, a defect in insulin signalling pathway seems to be implicated in the pathogenesis of insulin resistance. The exact cause of insulin resistance observed in PCOS women is not known; however, a post-receptor defect that could affect glucose transport has been proposed.[3] The importance of insulin resistance in PCOS is suggested by the fact that insulin-sensitizing drugs such as metformin, pioglitazone, troglitazone and myoinositol (MYO) have been proposed as treatment to resolve hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins, metformin being the oldest drug in use whilst MYO being the recent development in insulin-sensitizing drugs. The focus of this study is primarily based on these two insulin-sensitizing drugs, i.e, MYO and metformin.

MYO is one of the nine stereoisomeric forms of a C6 sugar alcohol that belongs to vitamin B-complex group.[4] Studies have suggested that impairment in insulin pathway could be due to a defect in inositol phosphoglycans (IPGs) second messenger. In PCOS, defect in tissue availability or altered metabolism of inositol or IPGs mediators may contribute to insulin resistance.[5] Therefore, supplying MYO can accelerate glucose disposal and decrease circulating insulin, serum testosterone and enhance ovulation. The commonly used dose is 200-4,000 mg once-daily before breakfast in PCOS. Very high doses of MYO can cause gastrointestinal side effects like nausea, diarrhea, dizziness, insomnia and possible worsening of bipolar disorder. No toxicity has been reported. There is no evidence for MYO drug interaction till date.

Metformin is an oral biguanide antihyperglycemic drug. It lowers blood glucose by inhibiting hepatic glucose production (by decreasing gluconeogenesis), enhancing peripheral glucose uptake by skeletal muscles and adipose tissue and reduces intestinal glucose absorption. It enhances insulin sensitivity at the post-receptor level and stimulates insulin mediated glucose disposal without producing hypoglycemia in PCOS women. It has been used to treat anovulatory infertility, insulin resistance and hyperandrogenism in PCOS patients. The action of metformin is limited due to low levels of inositol in PCOS. Dose of metformin can vary from 500 to 2,500 mg/day. Metformin causes a significant increase in nausea, vomiting and gastrointestinal distress in women with PCOS. There are; however, no published reports of lactic acidosis with metformin therapy in women with PCOS.

MATERIAL AND METHODS

This study was carried out at Holy Family Hospital, New Delhi, from June 2015 to May 2016. The patients attending Gynecological OPD, with clinical features suggestive of PCOS (menstrual abnormalities, infertility, obesity, acne, hirsuitism), were selected. It was a randomized comparative study with sample size of 70. Patients were defined as having PCOS according to Rotterdam criteria (2003). The patients would have to satisfy a minimum of two criteria listed below in order to be diagnosed as PCOS:

- Oligo- and/or anovulation: Oligomenorrhea would be defined if menses occurred less than 9 times a year or if 3 cycles more than 36 days long occurred during the last year.
- Clinical and/or biochemical signs of hyperandrogenism: Clinical hyperandrogenism would be diagnosed if the modified Ferriman-Gallwey (mFG) score is 8 or greater or the patient has moderate-to-severe acne, defined by the presence of inflammatory lesions and their extension.
- Polycystic ovaries (by ultrasound): Presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 mL, calculated using the formula 0.5 × length × width × thickness). Single ovary fitting this definition is enough to define PCOS.

The inclusion and exclusion criteria are mentioned in Table 2.

Table 2. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Women with PCOS, diagnosed in accordance with Rotterdam consensus conference criteria 2003 in the age group of 17-35 years.	• Pregnancy • Thyroid disorders • Significant liver or renal impairment • Unstable mental illness • Diagnosis of diabetes mellitus or impaired glucose tolerance • Use of drugs able to interfere with glucoinsulinemic metabolism for at least 3 months prior to entering the study • Hypersensitivity to MYO

Patients were randomly allocated to two groups; Group 1 (MYO) and Group 2 (metformin). At the beginning of the study, baseline levels of various study variables were recorded. Patients were subjected to anthropometry - body weight, body mass index (BMI), waist-hip ratio (WHR) - and biochemical investigations which included fasting blood sugar (FBS), post-meal blood sugar (PMBS), fasting insulin, luteinizing hormone (LH), LH/follicle-stimulating hormone (FSH) ratio, free testosterone, prolactin (PL). Hirsutism was scored by mFG using 9 body sights - lip, chin, chest, upper abdomen, lower abdomen, upper arm, upper back, lower back and thigh. Each body area was visually scored on a scale of 0 to 4, where "0" indicated no terminal hair growth and "4" indicated full male pattern terminal hair growth. Cut-off was taken as score of "8" or more. Ovulatory activity was monitored with serum progesterone. It was recorded at the baseline and repeated every month in the mid-luteal phase. The peak value during the study was taken as final value. Cut-off was taken as 8 ng/mL. In addition, a baseline ultrasonography was done for noting down the number of follicles and/or ovarian volume.

Participants of Group 1 received 2 g MYO daily and those of Group 2 received 500 mg metformin twice-daily. Patients were called for follow-up after 16 weeks of drug therapy and tests for all the study variables were repeated and compared with the baseline findings. Patients who conceived after treatment were noted. The side effects experienced in each study group were noted down. Outcome was studied in terms of regularization of cycle, reduction in mFG score, improvement in anthropometric, biochemical and ultrasonographic parameters before and after the treatment in the two groups. The summary of the findings has been described in tables below.

RESULTS

In all, 70 patients were enrolled for the study within the age group of 17-35 years. Patients were randomly distributed into two groups with 35 patients each. Two patients were lost during follow-up from Group 2 and 5 patients conceived during early stages of the study (3 from Group 1 and 2 from Group 2). The final study was based on 63 patients - 32 patients in Group 1 and 31 in Group 2. Since the age distribution of patients was from 17 to 35 years, the study covers the mean population age of 26.62 ± 5.38 in Group 1 and 26.23 ± 4.58 in Group 2. It is noteworthy that race, ethnicity, socioeconomic factors were almost similar in both the groups.

The most common complaint was irregular cycles (53.1% in Group 1 and 64.5% in Group 2) followed by scanty flow, secondary amenorrhea, weight gain, hirsutism and infertility. After treatment, in Group 1 53.1% of patients achieved regular cycles whilst in Group 2, 41.9% of patients achieved regular cycles (Table 3).

The fall in body weight and WHR was significant in both groups, but on comparing the two, it was more significant in Group 1 than Group 2. The fall in BMI was more significant in Group 2 than Group 1 (Table 4).

The fall in mFG score was more significant in Group 1 as compared to Group 2. While LH results were not significant, the fall in LH/FSH ratio was more significant in Group 2 than Group 1. The reduction in fasting insulin was highly significant in Group 1 than Group 2. Free testosterone decrease was more significant in Group 1 than Group 2. FBS was normal in all patients; the fall in Group 2 was more significant than Group 1. For postprandial blood sugar (PPBS), fall was more significant in Group 1 (Table 5).

In Group 1 serum, progesterone changed from mean of 3.73 ± 1.44 SD to 6.73 ± 1.90 SD and in Group 2 from mean of 3.76 ± 1.57 SD to 5.82 ± 2.03 SD. Change in serum progesterone value was more significant in Group 1 than Group 2. In Group 1, 36.1% of patients ovulated, 8.6% conceived and in Group 2, 27.6% ovulated and 5.7% conceived. The reduction in number of follicles was more significant in Group 1 than Group 2 whilst decrease in ovarian volume (mean ovarian volume of >10 mL) was almost same in both groups (Table 6).

Table 3. Regularization of Cycles

	Group 1		Group 2		P value
	Frequency	%	Frequency	%	
Improved (I)	17	53.1	13	41.9	
Not improved (N)	15	46.9	18	58.1	0.374
Total	**32**	**100**	**31**	**100**	

Table 4. Anthropometry Findings

Item description	Body weight			BMI			WHR		
	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	65.99 ± 10.12	66.37 ± 7.84	0.869	22.26 ± 2.71	23.04 ± 2.94	0.272	0.80 ± 0.06	0.80 ± 0.07	0.907
After	63.25 ± 9.06	64.47 ± 7.05	0.556	20.82 ± 2.37	21.35 ± 2.70	0.410	0.77 ± 0.05	0.78 ± 0.06	0.557
Mean difference ± SD	-2.74 ± 2.24	-1.91 ± 1.91	0.116	-1.44 ± 0.80	-1.69 ± 1.27	0.338	-0.03 ± 0.04	-0.02 ± 0.03	0.443
P value	<0.001	<0.001		<0.001	<0.001		<0.001	<0.001	

Table 5. Biochemical Parameters

Item description	mFG score			LH			LH/FSH ratio			Fasting insulin		
	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	4.66 ± 4.06	4.94 ± 4.05	0.786	3.21 ± 3.01	5.13 ± 2.14	0.254	1.97 ± 1.03	2.04 ± 0.96	0.768	13.90 ± 6.88	12.85 ± 4.46	0.479
After	3.56 ± 3.29	3.87 ± 3.24	0.709	5.13 ± 2.14	5.95 ± 3.24	0.241	1.79 ± 0.96	1.84 ± 0.86	0.829	11.66 ± 6.05	11.78 ± 4.39	0.928
Mean difference ± SD	-1.09 ± 1.03	-1.06 ± 0.10	0.909	-1.08 ± 3.31	-1.19 ± 3.53	0.899	-0.17 ± 0.18	-0.20 ± 0.26	0.664	-2.24 ± 2.09	-1.07 ± 1.51	0.013
P value	<0.001	<0.001		0.060	0.070		<0.001	<0.001		<0.001	<0.001	

Item description	Free testosterone			Prolactin			FBS			PPBS		
	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	1.47 ± 0.37	1.43 ± 0.37	0.717	14.31 ± 4.39	13.85 ± 3.53	0.653	89.81 ± 8.32	89.23 ± 11.04	0.812	115.97 ± 12.03	111.13 ± 13.25	0.134
After	1.37 ± 0.37	1.36 ± 0.36	0.895	14.09 ± 4.17	13.35 ± 2.94	0.421	88.50 ± 7.79	87.81 ± 10.32	0.764	113.03 ± 12.00	109.84 ± 11.76	0.291
Mean difference ± SD	-0.10 ± 0.10	-0.08 ± 0.08	0.339	-0.22 ± 1.73	-0.50 ± 2.23	0.574	-1.31 ± 1.66	-1.42 ± 2.01	0.818	-2.94 ± 4.01	-1.29 ± 3.24	0.078
P value	<0.001	<0.001		0.484	0.221		<0.001	<0.001		<0.001	0.034	

Table 6. Ultrasonographic Parameters

Item description	Reduction in no. of follicles			Mean ovarian volume		
	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	14.59 ± 2.69	14.08 ± 1.84	0.382	13.51 ± 2.02	12.81 ± 2.35	0.213
After	12.19 ± 1.69	12.05 ± 1.75	0.749	11.93 ± 1.91	11.65 ± 1.96	0.575
Mean difference ± SD	-2.41 ± 1.49	-2.03 ± 1.66	0.350	-1.58 ± 0.98	-1.58 ± 0.98	0.057
P value	<0.001	<0.001		<0.001	<0.001	

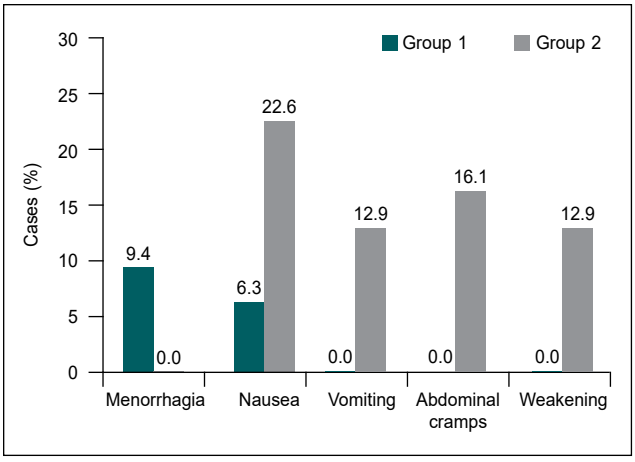

Figure 1. Side effects.

In the study, only 15.6% of patients experienced side effects in Group 1. Menorrhagia was a complaint seen only in Group 1. In Group 2, 64.5% experienced side effects. P value was significant only for abdominal cramps. Details of the side effects have been described in Figure 1.

DISCUSSION

PCOS is one of the most common endocrine disorders in women of reproductive age. Its etiology remains unclear. In young women with PCOS, insulin resistance is intrinsic to the syndrome and affects 30-40% of patients with PCOS. Studies have shown that insulin resistance in PCOS may be linked to abnormal ovarian steroidogenesis by means of altered insulin signal transduction.

The age distribution of patients in this study was 17-35 years. Mean age of patients was 26.62 ± 5.38 in Group 1 and 26.23 ± 4.58 in Group 2 which is similar to studies conducted by Immediata et al[6] and Costantino et al.[7]

In the study, 53.1% of patients achieved regular cycles in Group 1 (MYO) compared to 41.9% in Group 2 (metformin), which is similar to results obtained by Leo et al.[8]

Our results are supported by the study carried out by Awalekar et al.[9] They studied the effect of MYO, metformin and lifestyle modification in PCOS patients. In their study, BMI in the metformin group was reduced from a mean of 29.64 ± 3.49 to 27.13 ± 3.49 after 3 months of treatment, which is highly significant (p = 0.0000) and in MYO group, BMI changed from mean of 25.40 ± 6.53 to 24.40 ± 5.91 (p = 0.009). Similar results were seen in studies done by Le Donne et al,[10] and Cheang et al.[11] Immediata et al[6] conducted a crossover study in which metformin was able to decrease body weight ($p < 0.05$), improve menstrual cycle (<0.001) and mFG score (0.05). None of these clinical changes were observed during MYO administration. These results are not in concordance with our study.

In the study by Leo et al,[8] fall in mFG score in MYO group from 11.7 ± 2.7 to 7 ± 3.9 (p = 0.001) was significant than metformin group, as in our study. Similar results were seen in a study by Zacche et al.[12] Genazzani et al[13] studied 20 overweight patients of PCOS. In MYO group, LH, PL, testosterone (T), insulin levels and LH:FSH significantly decreased along with improved insulin sensitivity. Similarly, in our study, there was highly significant decrease in fasting insulin and free testosterone in Group 1. Our results are further supported by Angik et al.[14] They studied 100 patients in a randomized controlled trial (RCT) (50 in each group). MYO decreased FBS, PPBS, fasting and post-meal insulin, homeostasis model assessment (HOMA), T levels, LH:FSH, ovarian volume significantly; whereas in metformin group, significant improvement occurred in FBS, PPBS, T, LH:FHS and ovarian volume but not in fasting insulin and HOMA index. Fasting insulin decreased from 16.51 ± 13.95 to 14.58 ± 9.79 in MYO group. This result was significant, but in metformin group, the reduction was not significant. Similar results were seen in the study by Awalekar et al.[9] In contrast, in the study by Gerli et al,[15] no change in fasting glucose concentrations, fasting insulin or insulin responses to glucose challenge was recorded after MYO therapy. In a study by Minozzi et al[16] fasting insulin changed from 12.2 to 8.3 with mean difference of -3.9 ± 1.8; results were not significant.

Raffone et al[17] studied 120 patients with PCOS and 14-16 months of infertility. The study demonstrated a statistically significant difference in restoration of spontaneous ovulation in patients receiving MYO. Though there was a higher overall rate of pregnancy in the MYO group, the effect was not significant. In our study also, there was higher ovulation (36.1%) and conception rate (8.6%) in Group 1 compared to Group 2 (27.6% and 5.7%). Our results are in contrast to the study by Papaleo et al[18] in which 88% restored at least one spontaneous menstrual cycle, of which 72% maintained normal ovulatory activity during the follow-up period and 40% pregnancies were achieved after MYO administration. Similar contrast results were seen in studies by Palomba et al[19] and Abdelhamid et al.[20]

In the study by Angik et al,[14] the number of follicles decreased from 11.40 ± 3.00 to 11.60 ± 2.13 (p = 0.001) in

MYO group and in metformin group from 10.20 ± 2.31 to 10.18 ± 2.0 (p = 0.001) and ovarian volume decreased from 14.45 ± 3.8 to 12.35 ± 2.83 (p = 0.001) in MYO group and in metformin group from 14.53 ± 3.44 to 12.24 ± 2.83 (p = 0.001), which is similar to our study.

CONCLUSION

Metformin is effective in improving the metabolic and hormonal parameters and improves fertility. But MYO not only improves all the above parameters but also decreases insulin resistance significantly. MYO also has better patient compliance and is better tolerated than metformin. These beneficial effects of inositol support a future therapeutic role in women with PCOS. Inositol deficiency is the basic pathophysiology for PCOS and thus MYO supplementation is essential in the management of PCOS. MYO improves insulin sensitivity and thus, should be the first-line of therapy in PCOS.

REFERENCES

1. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al; Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456-88.
2. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41-7.
3. Baillargeon JP, Nestler JE. Commentary: polycystic ovary syndrome: a syndrome of ovarian hypersensitivity to insulin? J Clin Endocrinol Metab. 2006;91(1):22-4.
4. Bizzarri M, Carlomagno G. Inositol: history of an effective therapy for polycystic ovary syndrome. Eur Rev Med Pharmacol Sci. 2014;18(13):1896-903.
5. Baillargeon JP, Diamanti-Kandarakis E, Ostlund RE Jr, Apridonidze T, Iuorno MJ, Nestler JE. Altered D-chiro-inositol urinary clearance in women with polycystic ovary syndrome. Diabetes Care. 2006;29(2):300-5.
6. Immediata V, Romualdi D, De Cicco S, Tagliaferri V, Di Florio C, Cirella E, et al. Metformin versus myoinositol: which one is better in obese PCOS patients? A crossover study on clinical, endocrine and metabolic effects.
7. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci. 2009;13(2):105-10.
8. Leo VD, Musacchio MC, Cappelli V, Sabatino AD, Tosti C, Piomboni P. A combined treatment with myo-inositol and monacolin K improve the androgen and lipid profiles of insulin-resistant PCOS patients. J Metabolic Synd. 2013;2:127.
9. Awalekar JC, Awalekar C, Jadhav VM, Chivate CG, Patwardhan MH. Effect of metformin & myoinositol & life style modification in patients of polycystic ovarian disease (PCOD). Int J Biomed Res. 2015;6(09):698-704.
10. Le Donne M, Alibrandi A, Giarrusso R, Lo Monaco I, Muraca U. Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: effects on body composition. Minerva Ginecol. 2012;64(1):23-9.
11. Cheang KI, Huszar JM, Best AM, Sharma S, Essah PA, Nestler JE. Long-term effect of metformin on metabolic parameters in the polycystic ovary syndrome. Diab Vasc Dis Res. 2009;6(2):110-9.
12. Zacchè MM, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynecol Endocrinol. 2009;25(8):508-13.
13. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol. 2008;24(3):139-44.
14. Angik R, Jajoo SS, Hariharan C, Chimote A. A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: a randomised controlled trial. Int J Reprod Contracept Obstet Gynecol. 2015;4(1):189-94.
15. Gerli S, Papaleo E, Ferrari A, Di Renzo GC. Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. Eur Rev Med Pharmacol Sci. 2007;11(5):347-54.
16. Minozzi M, D'Andrea G, Unfer V. Treatment of hirsutism with myo-inositol: a prospective clinical study. Reprod Biomed Online. 2008;17(4):579-82.
17. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. Gynecol Endocrinol. 2010;26(4):275-80.
18. Papaleo E, Unfer V, Baillargeon JP, De Santis L, Fusi F, Brigante C, et al. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. Gynecol Endocrinol. 2007;23(12):700-3.
19. Palomba S, Orio F Jr, Falbo A, Manguso F, Russo T, Cascella T, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90(7):4068-74.
20. Abdelhamid AMS, Ismail Madkour WA, Borg TF. Inositol versus metformin administration in polycystic ovarian disease patients: a case–control study. Evid Based Women's Health J. 2015;5(2):61-6.

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

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

About Sameer Malik Heart Care Foundation Fund

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

Objectives

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

Activities of the Fund

Financial Assistance

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

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

Drug Subsidy

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

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

Who is Eligible?

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

Important Notes

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

Check List of Documents to be Submitted with Application Form

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

Free Diagnostic Facility

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

Free Education and Employment Facility

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

Laboratory Subsidy

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

Help Us to Save Lives

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

Donate Now...

About Heart Care Foundation of India

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

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

Objectives

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

Heart Care Foundation Blood Donation Camps

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

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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.

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An Assessment of Knowledge Level on Insulin Therapy Among Nurses Before and After Educational Workshop

P KASTHURI*, SONIA*

ABSTRACT

Objective: This study was conducted to compare the difference between the pre-test and post-test knowledge level on insulin therapy among nurses. **Methods:** The study included 100 participants (newly joined nurses), at Apollo Hospitals, Chennai, Tamil Nadu. The knowledge scores of the participants were assessed before and after the workshop. **Results:** The mean knowledge score for all the participants improved significantly after attending the workshop, irrespective of age. More than 90% participants reported having knowledge on insulin therapy in post-test compared to about 58% in the pre-test. About 85% participants showed having adequate knowledge, and about 10% of the participants had moderately adequate knowledge. The remaining 5% of the nurses possessed inadequate knowledge in post-test. **Conclusion:** The current study demonstrated that mean knowledge score improved significantly for all the participants after attending the workshop. To provide quality diabetes care and education, the nurses should obtain continuing professional education.

Keywords: Diabetes, insulin, knowledge, education

More than 425 million people currently have diabetes. Most of these are cases of type 2 diabetes. This condition can be prevented through regular physical activity, healthy and balanced diet and healthy living environments. Families have a significant role to play in addressing the modifiable risk factors for type 2 diabetes and in using appropriate guidelines, which promptly reverse hypoglycemia.

It is important to prevent, recognize and manage hypoglycemia secondary to the use of insulin or insulin secretagogues. It is always better and more effective to prevent hypoglycemia rather than treating it once it occurs.

Therefore, it becomes important to identify and counsel people with diabetes who are at high risk for hypoglycemia about the ways to prevent it. The treatment for hypoglycemia is aimed at detecting and treating low blood glucose promptly using an intervention/strategy/guideline/protocol/algorithm that can help eliminate the risk of injury and relieves symptoms quickly.

We conducted a study at Apollo Hospitals, Chennai, India to ascertain the difference in knowledge level on insulin therapy among nurses before and after a workshop.

A workshop was designed to tackle the everyday concerns, issues and enhance problem solving when treating insulin-dependent patients through didactic presentation, small groups and in-house style formats, which would refine understanding and ensure confidence towards diabetes management using various real-life scenarios.

OBJECTIVE/AIM OF THE STUDY

- To compare the difference between the pre-test and post-test knowledge level on insulin therapy among nurses.
- To link the significant association between the selected demographic variables and knowledge level on insulin therapy among nurses.

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METHODOLOGY

Study Participants

The study included 100 participants (newly joined nurses), at Apollo Hospitals, Chennai, Tamil Nadu.

The knowledge scores of the participants were assessed before and after the workshop.

ANALYSIS AND RESULTS

The mean knowledge score of all the participants improved significantly after attending the workshop, irrespective of age. There was an increase in mean knowledge score in post-test when compared to pre-test score (Fig. 1). More than 90% participants reported having knowledge on insulin therapy in post-test compared to about 58% in the pre-test. About 85% participants showed having adequate knowledge (>75%), and about 10% of the participants scored between 50% and 75%, suggesting that they had moderately adequate knowledge. The remaining 5% of the nurses scored <50%, which means that they possessed inadequate knowledge in post-test (Fig. 2).

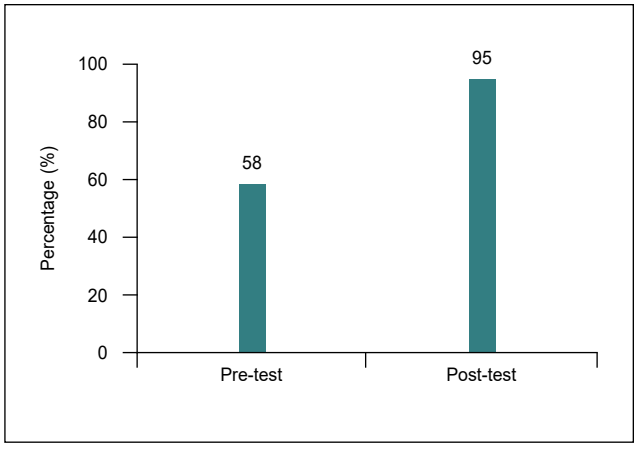

Figure 1. Percentage distribution of participants with knowledge on insulin therapy on pre- and post-test among nurses.

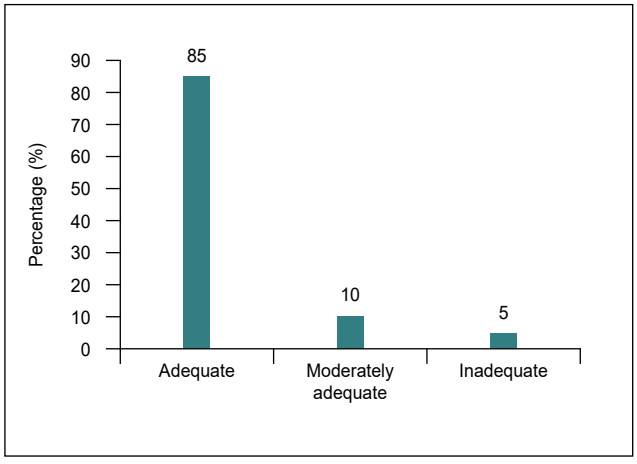

Figure 2. Percentage distribution of post-test knowledge level on insulin therapy among nurses.

DISCUSSION

Some people with diabetes do not show the early warning signs of low blood glucose. This is termed as hypoglycemia unawareness. Seen most often in type 1 diabetes, people with type 2 diabetes can also have the condition. These people are required to check their blood glucose level more often so that they can identify when hypoglycemia is about to occur.

A change in medications, meal plan or physical activity routine may also be needed. Hypoglycemia unawareness develops when frequent episodes of hypoglycemia cause changes in the way the body reacts to low blood glucose levels.

Education plays a vital role in diabetes care; however, it is still in an evolving state in developing countries like India. It is essential for care of people with diabetes who want to achieve positive outcomes.

Education is an important part of nursing care. Since it is important to provide quality information to the diabetic patients, it is essential for all nursing personnel to keep updating their knowledge.

Hypoglycemia can be addressed by multidisciplinary team approach involving physicians, nurses, dietician, diabetic educators and physiotherapists, who treat from the perspective of patient education, and also consider altering the medications. None of the patients should be treated without proper evaluation of the etiology of hypoglycemia.

CONCLUSION

The current study demonstrated that mean knowledge score improved significantly for all the participants after attending the workshop. Therefore, education plays a key role in improving care of diabetes patients. Nursing personnel should be regularly updated about all that is new in diabetes care. To provide quality diabetes care and education, the nurses should obtain continuing professional education.

Implementation Process

Education is not only a part of treatment but it is the treatment in diabetes. Therefore, nurses need to identify the needs of diabetes patients, as health education is an integral part of nursing care.

Cost of Implementation: Expected cost for charts for workshop/study is ₹ 5,000/14 charts for all wards.

Challenges/Difficulties: To monitor and assess the impact of the study, after implementation, as a trial, over a period of 3 months from December 2019 to February 2020.

Project Impact/Outcome of the Study

There are considerable gaps in knowledge on insulin therapy among nurses. This led us to conduct the sessions and seminars for nurses to teach them the basic knowledge regarding the management of diabetes focusing mainly on inpatient component. Subsequently, standardized protocols and algorithm (both hand written and computerized) have been designed for management of inpatient hypoglycemia based on latest published guidelines for guidance among nurses. In addition, online education courses for nurses are planned to be introduced to fill the gap in diabetes education.

SUGGESTED READING

1. Dunn SM. Rethinking the models and modes of diabetes education. Patient Educ Couns. 1990;16(3):281-6.
2. Thompson A, Gibbon C. Setting standards in diabetes education. Nurs Stand. 1993;7(43):25-8.
3. Ruby KL, Blainey CA, Haas LB, Patrick M. The knowledge and practices of registered nurse, certified diabetes educators: teaching elderly clients about exercise. Diabetes Educ. 1993;19(4):299-306.
4. Anderson RM, Funnell MM, Barr PA, Dedrick RF, Davis WK. Learning to empower patients. Results of professional education program for diabetes educators. Diabetes Care. 1991;14(7):584-90.

■■■■

COVID-19: The R_0 is an Intrinsic Feature of the Virus

The pandemic seems to be guided by direct, human-to-human transmission. As a result, people have been told to practice social distancing, which seems to be a simple but effective way to drive down the virus's reproductive number — i.e., R_0 (R naught). This represents the average number of new infections generated by each infected person.

R_0 is not an intrinsic feature of the virus. It can be reduced by means of containment, mitigation and herd immunity.

For the epidemic to begin to end, the reproduction rate has to come down to below 1.

In the early days of the outbreak in China, before extreme travel restrictions were imposed in Wuhan and nearby areas, and before everyone could realize the exact impact that the epidemic might have, the R_0 was 2.38, as per a study published in the journal *Science*. This means a highly contagious disease.

On January 23, China imposed intense travel restrictions and put hundreds of millions of people into a sort of lockdown as authorities aggressively limited social contact. The R_0 declined below 1, and the epidemic has been controlled in China, at least for now.

The virus does have an innate infectivity, as it appears from the way it binds to receptors in cells in the respiratory tract and then takes over the machinery of the cells to multiply. Its ability to spread depends also on the susceptibility of the human population, including the density of the community.

If someone has a seriously infectious virus and is sitting by himself in a room, the R_0 is zero. He/she can't give it to anybody. This is also the basis of lock down. (*Excerpts from The Washington Post*)

- Allergic Cough
- Cough with RTI
- Smoker's Cough
- Cough with Bronchial Asthma and Bronchitis
- Drug Induced Cough
- Cough with LPRD/GERD*

Free From Cough Discomfort

In Dry and Allergic Cough

℞ Grilinctus® Syrup

(Dextromethorphan HBr 5 mg, Chlorpheniramine Maleate 2.5 mg, Guaifenesin 50 mg and NH_4Cl 60 mg/ 5 ml)

℞ Grilinctus®-L Syrup

(Levocloperastine Fendizoate Eq. to Levocloperastine HCl 20 mg /5ml)

In Productive Cough

℞ Grilinctus®-BM Syrup

(Terbutaline Sulphate - 2.5 mg and Bromhexine HCL - 8 mg/5ml)

Grilinctus®-LS Syrup

(Levosalbutamol 1 mg + Ambroxol Hydrochloride 30 mg + Guaiphenesin 50 mg / 5ml)

2020

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

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To Deduce Optimal Fentanyl Infusion Dose for Effective Analgesia with Minimal Side Effects and Maximum Hemodynamic Stability

ANUJ MALIK*, GAURAV GUPTA†, KAMAL BAGDI*, RANJEET SINGH VIRK‡, UMA RATHI‡

ABSTRACT

Objective: To deduce optimal fentanyl infusion dose for effective analgesia with minimal side effects and maximum hemodynamic stability. **Material and methods:** In our prospective study, we compared three groups (of 30 patients each) namely group 2, 3, 4 receiving three different doses of fentanyl (20 μg, 30 μg, 40 μg), respectively with control group (Group 1) receiving conventional analgesics through intramuscular or intravenous route. Effective analgesia was rated on linear visual analog scale (VAS) with minimum side effects and most stable hemodynamic parameters. **Results:** The VAS scores, at rest, were significantly lower for epidural fentanyl groups as compared to control group. Mean blood pressure and pulse rate in all groups were comparable at all times. The incidence of side effects was similar in the three fentanyl groups as compared to control group. **Conclusion:** Fentanyl dose of 40 μg is the optimal epidural dose of background infusion along with patient on demand analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects in patients undergoing unilateral total knee replacement.

Keywords: Fentanyl infusion, analgesia, optimal dose, unilateral total knee replacement

"The greatest evil is physical pain" —Saint Augustine

Adequate relief of postoperative pain is the cornerstone of any acute pain management service in the modern era. Introduction of new pain management standards by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and recognition of the untoward consequences of uncontrolled postoperative pain have led to a greater appreciation for the importance of acute postoperative pain control. Inadequate control of postoperative pain may result in a higher incidence of chronic postsurgical pain, increased postoperative morbidities and worsened patient-oriented outcomes such as quality of life.

In the past, postoperative pain experienced by patients was treated conventionally with boluses of intramuscular or intravenous analgesics either on demand or at fixed intervals, which provided inadequate analgesia for inappropriate length of time. These two routes are least desirable because while intramuscular route is painful, both routes produce unpredictable blood levels due to erratic absorption. Patient dissatisfaction is common because of delays in drug administration and incorrect dosing. Cycles of sedation, analgesia and inadequate analgesia are common.

After knee surgery, poorly managed pain may inhibit the early ability to mobilize the knee joint. This, in turn, may result in adhesions, capsular contracture and muscle atrophy, all of which may delay or permanently impair the ultimate functional outcome, increased complications and diminished patient oriented outcomes such as quality of life and satisfaction. Early mobilization results in shorter hospital stay and cost containment and better resource utilization.

Postoperative epidural analgesia has been used in orthopedic surgeries and reported to expedite the achievements in postoperative rehabilitative milestones, reduce postoperative morbidity and decrease the length of hospital stay, compared with general anesthesia.

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Since there is lack of availability of sufficient data on "dose response" studies done with epidural fentanyl and a lack of consensus on its efficacy as compared to the traditional analgesic modalities, we planned this study to compare the analgesic effects of various doses of epidural fentanyl (background infusion) along with "on demand" boluses to determine the "optimal dose" postoperatively in patients undergoing unilateral total knee replacement.

MATERIAL AND METHODS

After obtaining informed consent from each and every patient, 120 (American Society of Anesthesiologists [ASA] physical status I or II) patients of either sex, scheduled for elective unilateral knee replacement were enrolled in the study. Their age ranged from 20 to 70 years.

Adult patients who were to undergo unilateral total knee replacement under spinal anesthesia were divided randomly into four groups of 30 patients each for the purpose of this study. Patients were randomly assigned to one of the four groups to receive either none (Group 1 receiving traditional intravenous or intramuscular analgesics referred to as "control" group) or 20 μg/hr (Group 2), 30 μg/hr (Group 3), 40 μg/hr (Group 4) dose of background epidural fentanyl infusion along with "on demand" dose of 20 μg fentanyl.

Combined spinal epidural set: The combined spinal epidural set consisted of -

- Sponge holding forceps
- Sterile gauze pieces
- Sterile towel
- Glass syringe (10 and 20 mL)
- Epidural Kit
- Spinal needle 26G
- Sterile dressing.

Visual Analog Scale

The linear visual analog scale (VAS) was used to assess the pain and pain relief of the patients. It consists of a straight line with 0.5 cm segments. One end having a mark 'O' represented "no pain" and the other having mark '10' represented "worst imaginable pain".

Interpretation of the VAS was explained to each and every patient during pre-anesthetic check-up and was explained for the second time after surgery in the recovery room before starting the background infusion of fentanyl. It was thus ascertained that every patient is able to aptly correlate his pain and accurately report it when asked about the same. The surgery was performed under spinal anesthesia. In the postoperative recovery room, before starting the individual background infusion, return of active toe movements was confirmed.

Any "breakthrough pain" before the return of active toe movements was treated likewise with epidural bolus dose of 20 μg but the background infusion was started only after the return of active toe movements and on confirmation of catheter position. Patients experiencing severe breakthrough pain and requiring analgesia even after loading epidural dose of 20 μg fentanyl, before return of active toe movements were excluded from the study. All patients were monitored before starting infusion (0 hour) and for up to 36 hours at 4 hours, 8 hours, 12 hours, 24 hours and 36 hours, respectively after starting epidural fentanyl infusion.

Blood pressure, pulse rate, respiratory rate, SpO_2, pain (as per sedation score), nausea/vomiting (as per nausea, vomiting score), adverse effects (e.g., pruritus, skin allergy, urinary retention respiratory depression) - noted and treated with naloxone/ondansetron. The Duncan's mean test was used to compare the four groups for demographic variables, hemodynamic parameters, VAS scores, analgesia quality, received demand doses and quantifying side effects each time of the study i.e., at 0, 4, 8, 12, 24, 36 hours, respectively. The data were compiled and analyzed to compare the analgesic efficacy of various doses of epidural fentanyl and to determine the optimal dose in terms of effective pain control, minimal number of additional demands made by patient, minimum sedation, maximum hemodynamic stability and minimum side effects.

OBSERVATION AND RESULTS

Hemodynamic parameters were in normal range during entire perioperative period and there was no serious concern.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34, in Group 3 was 1.42 ± 0.31 and in Group 4 was 0.97 ± 0.27. The difference of mean VAS was statistically significant in Group 1 vs. 2, Group 1 vs. 3, Group 1 vs. 4 (Table 1).

The analgesic efficacy in the four groups of patients at 0, 4, 8, 12, 24, 36 hours has been defined as (i) Excellent if mean VAS was between 0 and 3; (ii) Good if mean VAS was between 4 and 6 and (iii) Poor if mean VAS was between 7 and 10. This shows that there was significant reduction in pain score (VAS) as the background infusion dose of fentanyl increased from 20 μg/hr in Group 2 to 40 μg/hr in Group 4 (Table 2).

Table 1. VAS Score in the Groups 1 to 4

G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
Mean	SD	Mean	SD	Mean	SD	Mean	SD		370.80
3.62	0.39	2.48	0.34	1.42	0.31	0.97	0.27	G-2 vs. G-1 G-3 vs. G-1 G-4 vs. G-1 G-3 vs. G-2 G-4 vs. G-2 G-4 vs. G-3	

Table 2. Analgesic Efficacy in the Four Groups of Patients at 0, 4, 8, 12, 24, 36 Hours

VAS Group	G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
VAS0	2.10	0.60	1.83	0.38	1.80	0.61	1.86	0.62	-	1.73
VAS4	4.43	1.04	3.03	0.85	1.33	0.60	0.97	0.61	G-4 vs. G-1 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	121.08
VAS8	4.13	1.19	2.73	0.64	1.37	0.61	0.97	0.56	G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	98.12
VAS12	4.23	0.81	2.80	0.76	1.46	0.73	0.80	0.66	G-4 vs. G-3 G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1	124.75
VAS24	3.60	0.72	2.33	0.54	1.37	0.67	0.60	0.56	G-4 vs. G-3 G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	126.74
VAS36	3.23	0.81	2.17	0.46	1.20	0.96	0.63	0.67	G-4 vs. G-3 G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	69.45

DISCUSSION

Postoperative pain is the most common form of pain encountered by the anesthesiologist. The associated morbidity and severity requires adequate management of postoperative pain. Besides the humanitarian cause, the effective management of postoperative pain is mandatory also for prevention of complications like nausea and vomiting, negative nitrogen balance, deep vein thrombosis, lung atelectasis and other respiratory complications. Ureteral and bladder hypomobility, which may delay recovery and prolong hospitalization.

When an opioid is administered to the chief site of action, the substantia gelatinosa of the dorsal horn, it produces a highly selective depressing action on nociceptive pathway in the rexed laminae of the dorsal horn without effecting motor sympathetic or proprioceptive pathways thus allowing pain relief without sympathetic or motor blockade.

The cardiovascular and hemodynamic effects of fentanyl have usually been relatively small and limited to minimal depression in the heart rate, blood pressure and right ventricular work with a compensatory increase in stroke volume.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34. There was no statistically significant difference in the mean VAS scores in the four groups at 0 hours. The mean VAS scores at 4, 8, 12, 24 and 36 hours post-fentanyl infusion along with on demand rescue analgesia were least in Group 4 followed by Group 3, 2 and 1. This shows the analgesic efficacy of 40 μg/hr fentanyl infusion dose in Group 4. Thus, in terms of analgesic efficacy, 40 μg/hr epidural fentanyl dose is the 'optimal dose' along with 'on demand' 20 μg bolus dose of fentanyl. The analgesic efficacy of fentanyl can be attributed to supraspinal and spinal mechanisms.

The results support a segmental spinal effect of epidural fentanyl bolus administration and a nonsegmental dual spinal and supraspinal effect of epidural fentanyl infusion. They also provide evidence of clinical benefits from its predominant spinal action, notably improved analgesia, with a reduction in central side effects. The study thus provides support for a spinal mechanism of action of bolus administration of epidural fentanyl.

CONCLUSION

We thus conclude that epidural fentanyl dose of 40 μg/hr (Group 4) as "background infusion" is the most efficacious dose in terms of pain relief (analgesic efficacy) followed by 30 μg/hr (Group 3) and 20 μg/hr (Group 2), respectively along with patient's "on demand" rescue analgesia bolus dose of 20 μg in patients undergoing unilateral total knee replacement. Epidural fentanyl dose of 40 μg/hr is the "optimal dose" of background infusion along with patient control analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects, in patients undergoing unilateral total knee replacement.

SUGGESTED READING

1. Practice guidelines for acute pain management in the perioperative setting. A report by the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section. Anesthesiology. 1995;82(4):1071-81.
2. Lubenow TR, lvankovich AD, McCarthy RJ. Management of Acute Postoperative Pain. Lippincott, Raven: Philadelphia; 1997. pp. 1305-38.
3. Egbert AM, Parks LH, Short LM, Burnett ML. Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. Arch Intern Med. 1990;150(9):1897-903.
4. Sandler AN, Stringer D, Panos L, Badner N, Friedlander M, Koren G, et al. A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for postthoracotomy pain relief. Analgesic, pharmacokinetic, and respiratory effects. Anesthesiology. 1992;77(4):626-34.
5. Lutz LJ, Lamer TJ. Management of postoperative pain: review of current techniques and methods. Mayo Clin Proc. 1990;65(4):584-96.
6. Walmsley RHN, Colclough GW, Mazloom Doost M, et al. Epidural PCA/infusion for postoperative pain. Anaesthesiology. 1989;71:A684.
7. Bonica JJ. Postoperative pain. In Bonica JJ (Ed.). The Management of Pain. 2nd Edition, Philadelphia: Lea and Febiger; 1990. pp. 461-80.
8. Ilahi OA, Davidson JP, Tullos HS. Continuous epidural analgesia using fentanyl and bupivacaine after total knee arthroplasty. Clin Orthop Relat Res. 1994;(299):44-52.
9. Kehlet H. Surgical stress: the role of pain and analgesia. Br J Anaesth. 1989;63(2):189-95.
10. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth. 1995;42(10):891-903.
11. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology. 1995;82(6):1474-506.
12. Wheatley RG, Schug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. Br J Anaesth. 2001;87(1):47-61.
13. Scott DA, Beilby DS, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1,014 patients. Anesthesiology. 1995;83(4):727-37.
14. Ready LB. Acute pain: lessons learned from 25,000 patients. Reg Anesth Pain Med. 1999;24(6):499-505.

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Acute Intermittent Porphyria: A Frequently Misdiagnosed Chameleon!

ARVIND VYAS*, DIVYA GOEL†

ABSTRACT

Acute intermittent porphyria (AIP) is an inborn disorder of heme biosynthesis, autosomal dominant in inheritance. It is a frequent occurrence in young females of reproductive age group. While abdominal pain is the most frequent presentation of this disorder, it can present with a myriad of clinical and biochemical features, frequently leading to misdiagnosis of this condition. We present a case of a 17-year-old young female who presented with an acute onset weakness in all four limbs along with absent deep tendon reflexes but characteristically preserved ankle jerks, who was initially diagnosed as Guillain-Barré syndrome (GBS), treated with intravenous immunoglobulin (IVIg), succumbed to a chronic progressive course of weakness and put on oral steroids. Lack of improvement and subsequent development of abdominal pain led us to investigate her for urine for porphobilinogen which came out to be positive, thus leading to a final diagnosis of AIP.

Keywords: Acute intermittent porphyria, abdominal pain, Guillain-Barré syndrome

Porphyrias are a group of relatively uncommon metabolic disorders produced by defective biosynthesis of heme. There are broadly two categories, i.e., hepatic and erythroid and clinically they can be classified as neurovisceral, cutaneous or mixed. Acute intermittent porphyria (AIP) is the most common of all and results from partial deficiency of porphobilinogen deaminase enzyme. Being an easily missed entity, it should be looked for with high index of suspicion in any patient presenting with acute onset weakness and abdominal pain. There have been case reports on misdiagnosis of AIP mostly as Guillain-Barré syndrome (GBS) due to acute presentation of the disease. We report a case here with acute presentation of weakness of all four limbs, subsequently attaining a progressive form of weakness and wasting, mimicking chronic inflammatory demyelinating polyneuropathy (CIDP). Based on our literature search, this transition from acute to chronic phase in AIP has not been described before.

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CASE REPORT

A 17-year-old young female presented with history of subacute onset weakness of all four limbs in the form of difficulty in carrying out overhead activities and performing fine activities, along with difficulty in rising from sitting position, for the last 4 months. There was no associated sensory complaint, difficulty swallowing, bowel or bladder involvement. She was treated 4 months back as a case of acute motor axonal neuropathy (AMAN) variant of GBS with intravenous immunoglobulin (IVIg) on the basis of her neurophysiological study, which revealed pure motor axonal affection of the tested nerves. She developed acute abdominal pain during hospital stay along with vomiting and was treated as a case of acute cholecystitis. After 15 days, as no significant improvement was found, she was subjected to nerve biopsy and started on oral corticosteroid treatment thinking of CIDP. She had minimal improvement with steroids; her nerve biopsy report was inconclusive and after 4 months, she presented to our institute with residual and static weakness. On asking about her family, she revealed that her younger sister suffered with fever, abdominal pain and seizures last year, which lasted for a month, followed by her sad demise.

On examination, the patient was tachypneic and had resting tachycardia. On neurological examination, there was wasting of posterior fibers of deltoid; both anterior and posterior compartments of arms and

Figure 1. Bilateral wrist drop.

Figure 2. Urine sample turned cola-colored on exposure to sunlight.

forearms bilaterally; interossei, chiefly the first dorsal interosseous; anteromedial compartment of thighs and calf muscles. Generalized hypotonia was present along with bilateral wrist drop (Fig. 1). Power was 4/5 in upper limbs at shoulder and elbow joints, 0/5 at dorsiflexors of wrists, 4/5 in lower limbs at hip and knee joints, 5/5 at ankle bilaterally. Deep tendon reflexes were absent, except ankle jerk which was 2+ bilaterally. Sensory and cerebellar examination was unremarkable. Her urine sample was sent for porphobilinogen and a sample was also kept in sunlight to see for change in its color (Fig. 2) considering the past history of acute abdominal pain, vomiting, neuropathy along with suspected positive family history. The report came out to be positive and patient was advised high carbohydrate diet and avoidance of all the drugs that precipitate porphyria. Thus, after a great diagnostic odyssey, the patient was finally labeled as AIP and advised high carbohydrate diet. On follow-up after 2 months, the patient has shown marked improvement in her functional status.

DISCUSSION

Porphyrias are heme biosynthetic disorders leading to accumulation of toxic porphyrin precursors and porphyrin itself, the excess of which accumulates in various tissues giving rise to a myriad of clinical features. There are eight main varieties of hepatic and erythroid porphyrias, amongst which AIP is the most common. It is caused by the deficiency of porphobilinogen deaminase leading to excessive accumulation and urinary excretion of porphobilinogen. AIP is most prevalent in young females of reproductive age group and crises mostly occur after puberty. This disease is manifested by acute gastrointestinal manifestations like abdominal pain, nausea, vomiting, constipation; neurological manifestations like neuropathy involving both motor and sensory nerves, psychiatric symptoms, seizures; cardiovascular manifestations like arrhythmias and autonomic disturbances.

The symptoms can range from acute crisis to chronic progressive neurological weakness, thus making it difficult to be diagnosed timely. AIP can mimic many other illnesses like in our case, the patient was initially thought to have GBS with co-existent cholecystitis. Subsequently, when she attained a chronic progressive course of weakness, she was treated as CIDP but all in vain. Misdiagnosis of GBS in a case of porphyria has been reported previously, highlighting the fact that muscular weakness progressing to quadriparesis can mimic GBS in a case of porphyria.

CONCLUSION

This case establishes the fact that AIP can be a great masquerader and thus easily misdiagnosed in clinical settings. Thus, a high index of suspicion is required when confronted with a blend of gastrointestinal and neurological manifestations in a patient in order to prevent a delayed diagnosis and grave outcomes.

SUGGESTED READING

1. Foran SE, Abel G. Guide to porphyrias. A historical and clinical perspective. Am J Clin Pathol. 2003;119 Suppl:S86-93.
2. Thadani H, Deacon A, Peters T. Diagnosis and management of porphyria. BMJ. 2000;320(7250):1647-51.
3. Kauppinen R. Porphyrias. Lancet. 2005;365(9455):241-52.
4. Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, Pimstone NR, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005;142(6):439-50.
5. Oomman A, Gurtoo A. Acute intermittent porphyria as a cause of acute respiratory failure. J Indian Med Assoc. 2002;100(1):44, 46.
6. Suarez JI, Cohen ML, Larkin J, Kernich CA, Hricik DE, Daroff RB. Acute intermittent porphyria: clinicopathologic correlation. Report of a case and review of the literature. Neurology. 1997;48(6):1678-83.
7. González-Arriaza HL, Bostwick JM. Acute porphyrias: a case report and review. Am J Psychiatry. 2003;160(3):450-9.

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Chondrosarcoma of Right Upper Limb: Largest of Its Kind Operated in Our Institute

VIJAY JAGAD*, MUNISH MAHAJAN*, AMITABH KUMAR UPADHYA†, SEEMA CHABBRA‡

ABSTRACT

Chondrosarcoma of extremities is the second most common site for this particular bone tumor. Neoadjuvant chemoradiotherapy is frequently used to down stage tumor for limb-sparing surgery in locally advanced tumor, but chondrosarcoma is relatively resistant to chemotherapy and radiotherapy, and hence sometimes mutilating surgery like forequarter amputation has to be performed. In this case also, patient presented with locally advanced chondrosarcoma of right upper extremity and we had to perform forequarter amputation to achieve adequate clearance.

Keywords: Chondrosarcoma, forequarter amputation

CASE REPORT

A 56-year-old man, presented to our Surgical Oncology OPD with complaints of massive swelling of right upper limb for past 2 years. To begin with, patient had noticed the swelling just below the right shoulder joint that gradually progressed to attain the present size. Patient had visited many oncology centers and he was offered multiple treatments consisting of combination of chemotherapy and radiotherapy, but all were fruitless. He then approached our institute. On examination, the whole of the upper extremity and the right shoulder was engulfed by the tumor (Fig. 1). Confirmation of the type of tumor was done by core cut biopsy, which revealed chondrosarcoma intermediate grade. Computed tomography (CT) scan of chest with upper abdominal cuts was done that revealed large tumoral mass involving the right humerus and scapula with involvement of shoulder girdle muscles. Pectoral muscles were also involved by the tumor. There was no evidence of metastasis in chest as well as in abdomen. According to the Enneking staging, it was Stage IIB. As the patient had already received neoadjuvant chemotherapy and radiotherapy but the tumor size was still increasing, he was planned for forequarter amputation. Patient tolerated the procedure well and the final histopathology report revealed evenly placed anaplastic chondrocytes within lacuna in a chondroid background suggestive of intermediate grade chondrosarcoma with all resection margins free of tumor (Fig. 2). On follow-up after 14 days, stitches

Figure 1. Preoperative figure of the tumor involving whole of the right upper limb and the right shoulder.

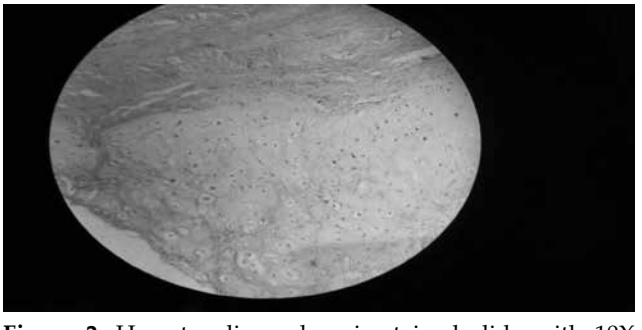

Figure 2. Hematoxylin and eosin-stained slide with 10X power showing evenly placed anaplastic chondrocytes in lacuna within chondroid background.

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Figure 3. Postoperative photograph of the patient after stitch removal.

were removed (Fig. 3), and he was kept on close follow-up to look for recurrence or metastasis. After 1½ years, the patient is still on follow-up and he is disease-free locally as well as in terms of distant metastasis.

DISCUSSION

Chondrosarcoma is a malignant cartilaginous matrix-producing tumor with diverse morphologic features. The peak age of occurrence is between 40 and 70 years. The most common primary sites include the pelvis followed by femur and humerus. Most common presenting symptoms are pain and swelling at the site of tumor. About 90% of chondrosarcomas are primary bone tumors, but around 10% develop from pre-existing osteochondromas, enchondromas or fibrous dysplasia. Chondrosarcomas are graded on a scale from 1 to 3, based upon nuclear size, staining pattern (hyperchromasia), mitotic activity and degree of cellularity. Histological grade is one of the most important indicators of clinical behavior and prognosis. Metastasis in chondrosarcoma depends upon the grade of the tumor. Patients with Grade II and III have higher chances of metastasis compared to Grade I and that can range from 60% to 70%.

Chondrosarcomas are relatively resistant to chemotherapy and radiotherapy and therefore treatment depends upon the completeness of surgical resection. En-bloc resection of the tumor has shown to improve the survival of the patient. Surgical resection margin and the grade of the tumor have been found to be independent prognostic marker for survival of the patient.

This patient who presented to our institute had already received neoadjuvant chemotherapy and radiotherapy to downstage the disease but there was no change. Complete right upper limb along with scapula and shoulder girdle muscle was involved. CT scan revealed no evidence of distant metastasis. Complete en-bloc removal of the tumor, i.e., forequarter amputation was required. Pros and cons of the surgery were discussed and with due consent patient underwent surgery. Now the patient has been kept on follow-up, as the final histopathology revealed intermediate grade chondrosarcoma. Patient has been explained about the risk of distant metastasis. Patient is being followed according to the National Comprehensive Cancer Network (NCCN) guidelines with physical examination, complete blood count and chest as well as local imaging every 3 months for the first 2 years, every 4 months during year 3, every 6 months for years 4 and 5, then annually. It has also been explained that routine post-treatment surveillance has to be extended up to 10 years, as late recurrences can occur.

CONCLUSION

Chondrosarcomas are usually low-grade tumors affecting mainly the pelvic region and the extremities. Complete surgical excision with negative margins is the best treatment to be offered to improve survival. As these tumors are relatively resistant to radiotherapy and chemotherapy, downstaging of the tumor for limb preservation surgery is not possible and patients in locally advanced stage disease have to undergo mutilating surgeries with functional compromise.

SUGGESTED READING

1. Van Oosterom AT, Dirix LY. Chondrosarcoma and other rare bone sarcomas. Curr Opin Oncol. 1990;2(3):495-9.
2. Spjut HJ, Ayala AG. Skeletal tumors in children and adolescents. Hum Pathol. 1983;14(7):628-42.
3. Garrison RC, Unni KK, McLeod RA, Pritchard DJ, Dahlin DC. Chondrosarcoma arising in osteochondroma. Cancer. 1982;49(9):1890-7.
4. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer. 1977;40(2):818-31.
5. Sheth DS, Yasko AW, Johnson ME, Ayala AG, Murray JA, Romsdahl MM. Chondrosarcoma of the pelvis. Prognostic factors for 67 patients treated with definitive surgery. Cancer. 1996;78(4):745-50.
6. Pring ME, Weber KL, Unni KK, Sim FH. Chondrosarcoma of the pelvis. A review of sixty-four cases. J Bone Joint Surg Am. 2001;83-A(11):1630-42.
7. Marcove RC, Miké V, Hutter RV, Huvos AG, Shoji H, Miller TR, et al. Chondrosarcoma of the pelvis and upper end of the femur. An analysis of factors influencing survival time in one hundred and thirteen cases. J Bone Joint Surg Am. 1972;54(3):561-72.
8. Giuffrida AY, Burgueno JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. J Bone Joint Surg Am. 2009;91(5):1063-72.

Operational Costs: Think Beyond Healthcare Providers and Incentives

AMIT AGRAWAL*, LUIS RAFAEL MOSCOTE-SALAZAR†, SAGAR GALWANKAR‡

Healthcare delivery, maintenance and sustenance require finances to support infrastructure and human resources and financial resources. The studies have observed substantial reduction in operational costs (3%-first year to about 7%-fifth year) after the transition to the more sophisticated cost-measurement approach.[1] It is expected that "Electronic health record (EHR) systems" shall provide the clinical and operational data to allow us to capture cost data.[1] EHR data is tip of the iceberg as the operational costs of the healthcare system involve much more than clinical care related expenses (e.g., administrative, infrastructure, maintenance costs, etc.). We need to further expand the breakup of operational costs, which operational costs were reduced, were they uniform across the hospitals, their impact on clinical outcomes and patient satisfaction. It will be interesting to know the share of "Incentives for Healthcare Providers" as "Incentives" do not translate into improved values or better outcomes.[2,3] Inappropriate incentive policies can potentially make the healthcare unaffordable, erode medical ethics and the results may be short lived.[4]

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REFERENCES

1. Ederhof M, Ginsburg PB. "Meaningful use" of cost-measurement systems - incentives for health care providers. N Engl J Med. 2019;381(1):4-6.
2. Doran T, Maurer KA, Ryan AM. Impact of provider incentives on quality and value of health care. Annu Rev Public Health. 2017;38:449-65.
3. Lavergne MR. Financial incentives for physicians to improve health care. CMAJ. 2017;189(49):E1505-E1506.
4. Yip WC, Hsiao W, Meng Q, Chen W, Sun X. Realignment of incentives for health-care providers in China. Lancet. 2010;375(9720):1120-30.

■■■■

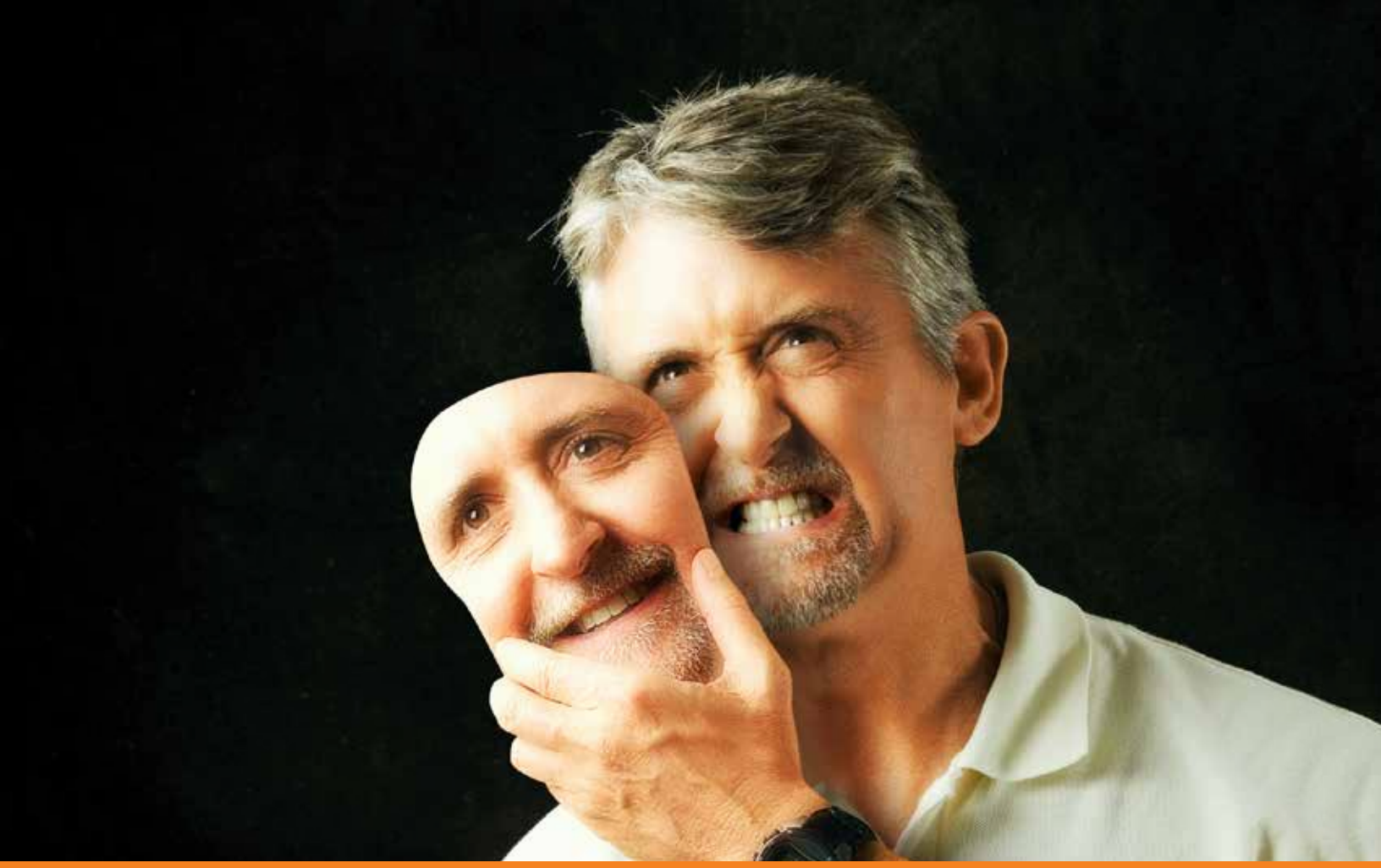
CMAAO Coronavirus Facts and Myth Busters

In hospitals, virus can infect up to 3 hours

WHO: No. An experimental study published in the *New England Journal of Medicine* assessed virus persistence of the COVID-19 virus. In this study, aerosols were generated using a three-jet Collison nebulizer and fed into a Goldberg drum under controlled conditions. This high-powered machine does not reflect normal human cough conditions. Further, the finding of COVID-19 virus in aerosol particles up to 3 hours does not mirror a clinical setting in which aerosol-generating procedures are performed. This means that this was an experimentally induced aerosol-generating procedure.

WHO has no final recommendation

WHO continues to emphasize the significance of frequent hand hygiene, respiratory etiquette and environmental cleaning and disinfection, besides the importance of maintaining physical distance and avoidance of close, unprotected contact with people with fever or respiratory symptoms. (*WHO*)



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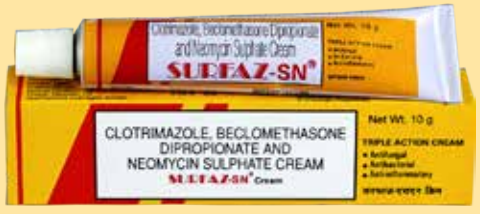

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Indian Journal of Clinical Practice, Vol. 30, No. 11, April 2020

Containment Plan for Large Outbreaks: Novel Coronavirus Disease 2019 (COVID-19)

1. INTRODUCTION

1.1. Background

On 31st December 2019, the World Health Organization (WHO) China Country Office was informed of cases of pneumonia of unknown etiology (unknown cause) detected in Wuhan City, Hubei Province of China. On 7th January 2020, Chinese authorities identified a new strain of Coronavirus as the causative agent for the disease. The virus has been renamed by WHO as SARS-CoV-2 and the disease caused by it as COVID-19. The disease since its first detection in China has now spread to over 200 countries/territories, with reports of local transmission happening in more than 160 of these countries/territories. As per WHO (as of 1st April, 2020), there has been a total of 823626 confirmed cases and 40598 deaths due to COVID-19 worldwide.

In India, as on 2nd April, 2020, 1965 confirmed cases (including 51 foreign nationals) and 50 deaths reported from 29 States/UTs. Large number of cases has been reported from Delhi, Karnataka, Kerala, Maharashtra, Rajasthan, Tamil Nadu, Telangana and Uttar Pradesh.

1.2. Risk Assessment

COVID-19 was declared a pandemic by WHO on 11th March, 2020. While earlier the focus of spread was centered on China, it has now shifted to Europe and North America. WHO has advised countries to take a whole-of-government, whole-of-society approach, built around a comprehensive strategy to prevent infections, save lives and minimize impact.

In India also, clusters have appeared in multiple States, particularly Kerala, Maharashtra, Rajasthan, Uttar Pradesh, Delhi, Punjab, Karnataka, Telangana and UT of Ladakh. 211 districts are now reporting COVID-19 cases and the risk of further spread remains very high.

Ministry of Health and Family Welfare, Government of India

1.3. Epidemiology

Coronaviruses belong to a large family of viruses, some causing illness in people and others that circulate among animals, including camels, cats, bats, etc. Rarely, animal coronaviruses may evolve and jump species to infect people and then spread between people as witnessed during the outbreak of Severe Acute Respiratory Syndrome (SARS, 2003) and Middle East Respiratory Syndrome (MERS, 2014). The etiologic agent responsible for current outbreak of SARS-CoV-2 is a novel coronavirus closely related to SARS-Coronavirus.

In humans, the transmission of SARS-CoV-2 can occur via respiratory secretions (directly through droplets from coughing or sneezing, or indirectly through contaminated objects or surfaces as well as close contacts). Nosocomial transmission has been described as an important driver in the epidemiology of SARS and MERS and has also been documented in COVID-19.

Current estimates of the incubation period of COVID range from 2-14 days, and these estimates will be refined as more data become available. Most common symptoms include fever, fatigue, dry cough and breathing difficulty. Upper respiratory tract symptoms like sore throat, rhinorrhoea, and gastrointestinal symptoms like diarrhoea and nausea/vomiting are seen in about 20% of cases.

Due to paucity of scientific literature based on community based studies, the available data on host factors is skewed towards cases requiring hospitalization. As per analysis of the biggest cohort reported by Chinese CDC, about 81% of the cases are mild, 14% require hospitalization and 5% require ventilator and critical care management. The deaths reported are mainly among elderly population particularly those with co-morbidities.

At the time of writing this document, many of the crucial epidemiological information particularly source of infection, mode of transmission, period of infectivity, etc. are still under investigation.

2. STRATEGIC APPROACH

India would be following a scenario based approach for the following possible scenarios:

i. Travel related case reported in India

ii. Local transmission of COVID-19

iii. Large outbreaks amenable to containment

iv. Wide-spread community transmission of COVID-19 disease

v. India becomes endemic for COVID-19.

2.1. Strategic Approach for Scenario: "Travel Related Cases Reported from India"

(i) Inter-Ministerial coordination (Group of Ministers, Committee of Secretaries) and Centre-State co-ordination been established.

(ii) Early detection through universal screening of all International passengers at Points of Entries (PoEs).

(iii) Surveillance and contact tracing through Integrated Disease Surveillance Programme (IDSP) for tracking travellers in the community who have travelled from affected countries.

(iv) Early diagnosis through testing samples of suspect cases.

(v) Buffer stock of Personal Protective Equipment (PPE) maintained.

(vi) Risk communication for creating awareness among public to follow preventive public health measures.

2.2. Local Transmission of COVID-2019 Disease

Local transmission will lead to clustering of cases in time and space, epidemiologically linked to a travel related case or a positive case that has links to a travel related case. The cluster containment strategy will be:

- Extensive contact tracing and active search for cases in containment zone
- Testing all suspect cases and high risk contacts
- Isolating all suspect/confirmed cases and providing medical care.
- Quarantining contacts
- Implementing social distancing measures.
- Intensive risk communication.

2.3. Large Outbreaks Amenable to Containment

The strategy will remain the same as explained in para 2.2 as above but vary in extent depending upon spread and response to be mounted to contain it. Geographic quarantine and containment strategy will include:

- Defining the area of operation
- Active surveillance for cases and contacts in the identified geographic zone.
- Expanding laboratory capacity for testing all suspect cases, high risk contacts and SARI cases.
- Operationalize surge capacities created for isolation (COVID-19 hospitals/COVID-19 dedicated blocks) to hospitalize and manage all suspect/confirmed cases.
- Implementation of social distancing measures with strict perimeter control.
- Provide chemoprophylaxis with Hydroxychloroquine to all asymptomatic healthcare workers and asymptomatic household contacts of laboratory confirmed cases.
- Further intensification of risk communication through audio, social and visual media.

3. SCOPE OF THIS DOCUMENT

In alignment with strategic approach, this document provides action that needs to be taken for containing a large outbreak. The actions for mitigation phase will be dealt separately under a mitigation plan.

4. OBJECTIVE

The objective of this plan is to stop the chain of transmission thus reducing the morbidity and mortality due to COVID-19.

5. CONTAINMENT FOR LARGE OUTBREAKS THROUGH GEOGRAPHIC QUARANTINE

5.1. Geographic Quarantine

Geographic quarantine (cordon sanitaire) strategy calls for near absolute interruption of movement of people to and from a relatively large defined geographic area where there is single large outbreak or multiple foci of local transmission of COVID-19. In simple terms, it is a barrier erected around the focus of infection.

Geographic quarantine shall be applicable to such areas reporting large outbreak and/or multiple clusters of COVID-19 spread over multiple blocks of one or more districts that are contiguous.

5.2. Cluster Containment Strategy

The Cluster Containment Strategy would be to contain the disease within a defined geographic area by early detection of cases, breaking the chain of transmission and thus preventing its spread to new areas. This would include geographic quarantine, social distancing measures, enhanced active surveillance, testing all suspected cases, isolation of cases, quarantine of

contacts and risk communication to create awareness among public on preventive public health measures.

5.3. Evidence for Implementing Geographic Quarantine

In 2009, during the H1N1 Influenza pandemic it was observed that well connected big cities with substantive population movement were reporting large number of cases, whereas rural areas and smaller towns with low population densities and relatively poor road/rail/airway connectivity were reporting only few cases.

The current geographic distribution of COVID-19 mimics the distribution of H1N1 Pandemic Influenza. This suggests that while the spread of COVID-19 in our population could be high, it's unlikely that it will be uniformly affecting all parts of the country. This calls for differential approach to different regions of the country, while mounting a strong containment effort in hot spots.

Large scale measures to contain COVID-19 over large territories have been tried in China. Mathematical modeling studies have suggested that containment might be possible especially when other public health interventions are combined with an effective social distancing strategy.

5.4. Factors Affecting Large Outbreak Cluster Containment

A number of variables determine the success of the containment operations through geographic quarantine. These are:

(i) Number and size of the cluster/s.

(ii) Effectiveness of geographic quarantine.

(iii) How efficiently the virus is transmitting in Indian population, taking into account environmental factors especially temperature and humidity.

(iv) Public health response in terms of active case finding, testing of large number of cases, immediate isolation of suspect and confirmed cases and quarantine of contacts.

(v) Geographical characteristics of the area (e.g. accessibility, natural boundaries).

(vi) Population density and their movement (including migrant population).

(vii) Ability to ensure basic infrastructure and essential services.

6. ACTION PLAN FOR GEOGRAPHIC QUARANTINE

6.1. Legal framework

The Central Government/State Government should review the existing legal instruments that provide legal support to implement the containment plan. Some of the Acts/Rules for consideration could be (i) Disaster Management Act (2005) (ii) Epidemic Act (1897) (iii) Cr.PC and (iv) State Specific Public Health Act.

The Home Ministry has delegated the powers under DM Act, 2005 [Section 10 sub-section 2 clauses (i) and (l)] to Secretary (Health and Family Welfare) to act in such a way to contain or control the outbreak. States may invoke the provisions under DM Act, 2005 or under the Epidemic Act, 1897 to delegate powers to identified authority to act in such a manner to control or contain the outbreak.

Indian Penal Code under sections 270 provides power to act against those indulging in spread of disease. Section 144 of the Code of Criminal Procedure, when invoked, prohibits gathering of people.

6.1. Institutional Mechanisms and Inter-sectoral Co-ordination

At the Union Government level

6.1.1 The Group of Ministers (GoM) under the Chairmanship of Union Health Minister will be the apex body to take policy decisions. The GoM will have Ministers of External Affairs, Civil Aviation, Shipping, Pharmaceuticals, Home Ministry and option for co-opting any other Ministry. The Union Health Minister will have an advisory Group that will advise him on way forward. The Public Health Working Group under Secretary (H) and Joint Monitoring Group under DGHS will provide technical inputs.

6.1.2. At the national level, the Cabinet Secretary/ National Crisis Management Committee (NCMC)/ Committee of Secretaries (CoS) will review the situation across the country and continue to direct the concerned Ministries to implement its directions . The co-ordination with health and non-health sectors will be managed by NCMC/CoS, on issues, flagged by Ministry of Health.

The scale of arrangement within the Ministry of Health will be expanded with additional areas among the core capacities assigned to various officers. If need be, there will be empowered group taking decisions for the core areas of work (planning-co-ordination, surveillance, laboratory support, hospital preparedness, human resource, logistics and data analysis).

At the State level

6.1.3. The Concerned State will activate State Crisis Management Committee or the State Disaster Management Authority, as the case may be to manage the clusters of COVID-19.

Institutional arrangement at the operational level

6.1.4. District Collector would be the nodal person for all preparedness and response activities within his jurisdiction. District Collector will hold regular meetings with health functionaries, DDMA, Revenue, PWD, Forest, Education and Panchayati Raj/Local Self Governance Departments where the containment plan will be finalized and operationalized. These officials will issue directions to their ground level staff in all aspects of preparedness, control and containment in accordance with the Containment Plan and Guidelines.

District Collector would need to identify key issues (logistics, legal, technical and resources) and address them for implementing containment operations. He/she will keep ready all administrative orders for social distancing, restriction of rail/road/air transport, perimeter control and continuity of essential services.

In addition, a compendium of all the administrative orders required for enforcing the nonpharmaceutical interventions would be prepared well in advance and kept ready to be executed during response phase.

6.2. Trigger for Action

Epidemiological intelligence on increase in the incidence of a COVID-19 cases occurring within a defined geographic area will be trigger for action. This will be provided by IDSPs early warning and response (EWAR) system. Routine laboratory based surveillance of SARI cases is another trigger for action.

6.3. Deployment of Rapid Response Teams (RRT)

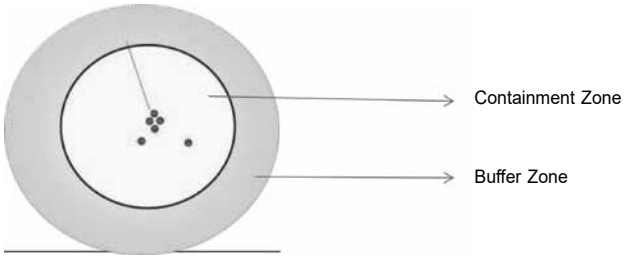
Emergency Medical Relief (EMR) division, Ministry of Health and Family Welfare will deploy the Central Rapid Response Team (RRT) to support and advice the State. The State will deploy its own State RRT and District RRT.

6.4. Identify Area Under Geographic Quarantine

6.4.1 A large outbreak is defined as localized increase in the incidence of a COVID-19 cases occurring within a defined geographic area e.g., in a village, town, or city. This could also imply progression of a small cluster, earlier noticed for which cluster management action is under implementation, into multiple clusters.

6.4.2. Defining containment and buffer zones: The area under geographic quarantine will be defined. There shall be (i) containment zone, surrounded by (ii) buffer zone.

Boundary for geographic quarantine will be defined based on: (i) geospatial distribution of each cluster contained within, (ii) largest administrative unit containing all clusters occurring within a state (with a minimum of 1 district), (iii) feasibility to implement strict interruption of movement of people, (iv) joint assessment by State and Central RRTs.



6.4.3. Buffer Zone

The adjoining blocks of the affected district or rural districts of the affected city will be considered as the buffer zone.

6.4.4. Perimeter

Perimeter of the geographically quarantined will be decided by the State administration based on criteria defined in Para 6.4.1. Clear entry and exit points will be established. The perimeter controls that need to be applied is in para 7.4.

7. SURVEILLANCE

7.1. Surveillance in containment zone, including contact listing, tracking and follow up shall be carried out as detailed in Cluster Containment Plan. Contact tracing shall be as per IDSP guidelines on the same.

7.2. Precise mapping of the outbreak shall be carried out.

7.3. Passive Surveillance shall be enhanced all throughout the area under geographic quarantine and districts surrounding it for ILI and SARI cases. All hospitalized patients with Severe Acute Respiratory Illness shall also be tested for COVID-19.

7.4. Perimeter Control

The perimeter control will ensure that there is no unchecked outward movement of population from the containment zone except for maintaining essential services (including medical emergencies) and government business continuity. Thermal screening, IEC shall be carried out at all entry and exit points.

All vehicular movement, movement of public transport and personnel movement will be stopped. All roads including rural roads connecting the containment zone will be guarded by Police. For personnel and vehicles requiring regular movement, a pass/ID card may be issued with details recorded and communicated.

The District administration will post signs and create awareness informing public about the perimeter control. Health workers posted at the exit point will perform screening (e.g. interview travelers, measure temperature, record the place and duration of intended visit and keep complete record of intended place of stay).

Details of all persons moving out of perimeter zone for essential/emergency services will be recorded and they will be followed up through IDSP. Those entering such geographically quarantined areas shall be given a chemoprophylactic dose of hydroxychloroquine. All vehicles moving out of the perimeter control will be decontaminated with sodium hypochlorite (1%) solution.

8. LABORATORY SUPPORT

8.1. Designated Laboratories

The identified VRDL network laboratories and designated private laboratories nearest to the affected area, will be further strengthened to test samples. The other available Govt. laboratories and private laboratories (BSL 2 following BSL 3 precautions) shall also be engaged to collect/test samples, after ensuring quality assurance by ICMR/VRDL network. If the number of samples exceeds its surge capacity, samples will be shipped to other nearby laboratories or to NCDC, Delhi or NIV, Pune or to other ICMR lab networks depending upon geographic proximity.

All test results should be available within 12-24 hours of sampling. ICMR along with the State Government will ensure that there are designated agencies for sample transportation to identified laboratories. The contact number of such courier agencies shall be a part of the micro-plan.

The designated laboratory will provide daily update (daily and cumulative) to District, State and Central Control Rooms on:

i. No. of samples received

ii. No. of samples tested

iii. No. of samples under testing

iv. No. of positive samples

8.2. Testing Criteria

Laboratory/s will undertake testing of: (i) All symptomatic individuals who have undertaken international travel in the last 14 days, (ii) All symptomatic contacts of laboratory confirmed cases, (iii) All symptomatic health-care workers, (iv) All hospitalized patients with SARI and (v) Asymptomatic direct and high-risk contacts of a confirmed case should be tested once between day 5 and day 14 of coming in his/her contact.

The testing will continue till 14 days from the date the last confirmed case is declared negative by laboratory test.

9. HOSPITAL CARE

All suspect/confirmed COVID-19 cases will be hospitalized and kept in isolation in dedicated COVID-19 hospitals/hospital blocks. Persons testing positive for COVID-19 will remain hospitalized till such time as two of their samples are tested negative as per discharge policy. About 15% of the patients are likely to require hospitalization, and an additional 5% will requires ventilator management.

A three tier arrangement for managing suspect/confirmed cases will be implemented to decrease burden on the COVID Block/hospital.

(i) The mild cases will be kept in temporary makeshift hospital facilities by converting hotels/hostel/guest houses/stadiums near a COVID-19 hospital. The existing quarantine facility may also be converted. This will be identified near an existing COVID hospital/COVID block.

(ii) Dedicated COVID-19 hospitals/dedicated blocks in large hospitals will be identified and operationalized. Moderate to severe cases, who require monitoring of their clinical status (patients with radiological evidence of pneumonia) will be admitted to COVID hospital.

(iii) Some of the severe cases may progress respiratory failure and/or progress to multi-organ failure and hence critical care facility/dialysis facility/ and Salvage therapy [Extra Corporeal Membrane Oxygenator (ECMO)] facility for managing the respiratory/renal complications/multi-organ failure shall be required. If such facilities are not available in the containment zone, nearest tertiary care facility in Government/private sector needs to be identified, that becomes a part of the micro-plan.

In every hospital fever clinics with triage, holding areas, sampling stations and individual doctor's chambers

where patients with fever/cough/breathing difficulty will be attended will be established.

9.1. Surge Capacity

Based on the risk assessment, if the situation so warrants (if data suggests an exponential rise in the number of cases), the surge capacity of the identified hospitals will be enhanced, private hospitals will be roped in and sites identified for temporary hospitals will be operationalized.

Surge capacity will also need enhancement in terms of laboratory testing capacity as detailed in para 8.1 above.

9.2. Pre-hospital Care (Ambulance Facility)

Ambulances need to be in place for transportation of suspect/confirmed cases. Such ambulances shall be manned by personnel adequately trained in Infection Prevention and Control (IPC), use of PPE and protocol that needs to be followed for disinfection of ambulances (by 1% sodium hypochlorite solution using knapsack sprayers).

For any further guidance Standard Operating Procedure (SOP) for transporting a suspect/confirmed case of COVID-19 may be referred to (Available at: https://www.mohfw.gov.in/pdf/StandardOperatingProcedureSOPfortransportingasuspectorconfirmedcaseofCOVID19.pdf)

9.3. Infection Prevention Control Practices

Healthcare associated infections among attending healthcare personnel are well documented in the current COVID-19 outbreak. There shall be strict adherence to Infection Prevention Control (IPC) practices in all health facilities. IPC committees would be formed (if not already in place. The designated hospitals will ensure that all healthcare staff is trained in washing of hands, respiratory etiquettes, donning/doffing & proper disposal of PPEs and biomedical waste management.

At all times doctors, nurses and para-medics working in the clinical areas will wear three layered surgical mask and gloves. The medical personnel working in isolation and critical care facilities where aerozolisation is anticipated, will wear full complement of PPE (including N95 masks).

The support staff engaged in cleaning and disinfection will also wear full complement of PPE. Environmental cleaning should be done twice daily and consist of damp dusting and floor mopping with Lysol or other phenolic disinfectants and cleaning of commonly touched surfaces with sodium hypochlorite solution.

Detailed guidelines available MoHFW's website on (i) Infection prevention and control in healthcare facilities, (ii) Rational use of Personal Protective Equipment, may be referred to.

All healthcare workers must be advised to self-monitor their health and report any breach in IPC practices or occurrence of any illness.

10. CLINICAL MANAGEMENT

10.1. Clinical Management

The hospitalized cases may require symptomatic treatment for fever. Paracetamol is the drug of choice. Suspect cases with co-morbid conditions, if any, will require appropriate management of co-morbid conditions.

For patients with Severe Acute Respiratory Illness (SARI), having respiratory distress may require, pulse oxymetry, oxygen therapy, non-invasive and invasive ventilator therapy.

Detailed guidelines available on MoHFW's website and updated from time to time, may be followed.

Doctors managing severe COVID cases may contact AIIMS, Delhi (helpline - 9971876591) or through tele-medicine network to seek guidance for management of severe cases.

10.2. Discharge Policy

Discharge policy for suspected cases of COVID-19 tested negative will be based on the clinical assessment of the treating physician. For those tested positive for COVID-19, their discharge from hospital will be based on consecutive two samples tested negative and the patient is free from symptoms.

11. PSYCHOSOCIAL SUPPORT

Quarantine, isolation and being affected by a new disease, all can be very stressful for those involved and for their family members. Social distancing measures that force one to stay at home and resulting social isolation can be frustrating. This apart, the healthcare workers working under the fear of an unknown disease, under stressful and demanding situations, impact their mental well-being. A guidance note on dealing with various mental issues is available at: https://www.mohfw.gov.in/pdf/MindingourmindsduringCoronaeditedat.pdf.

The National Institute of Mental Health and Neuro Sciences (NIMHANS) will be the nodal agency to plan and execute psychosocial support. NIHMANS will

prepare a Psychosocial Support plan and implement the same in the COVID affected areas.

12. PHARMACEUTICAL INTERVENTIONS

As of now there is no approved specific drug or vaccine for cure or prevention of COVID-19.

However Hydroxychloroquine has been recommended as chemoprophylaxis drug for use by asymptomatic healthcare workers managing COVID-19 cases and asymptomatic contacts of confirmed COVID-19 cases (advisory issued by ICMR in this regard is available at: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf).

In addition a combination of Hydroxychloroquine and Azithromycin has been advocated for use in severe cases of COVID-19 under medical supervision. (Guideline on clinical management protocol of COVID-19 is available at: https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf).

Contacts and healthcare workers receiving Hydroxycholoroquine as chemoprohylaxis will be informed to report any untoward health event to nearest health facility.

13. NON-PHARMACEUTICAL INTERVENTIONS

In the absence of proven drug or vaccine, non-pharmaceutical interventions will be the mainstay for containment of COVID-19 cluster.

13.1. Preventive Public Health Measures

There will be intensive social mobilization among the population in geographic quarantine zone for adoption of community-wide practice of frequent washing of hands and respiratory etiquettes. The community will also be encouraged to self-monitor their health and report to the ASHA/Anganwadi worker visiting home or to nearest health facility.

13.2. Quarantine and Isolation

Quarantine and Isolation are important mainstay of cluster containment. These measures help by breaking the chain of transmission in the community.

13.2.1. Quarantine

Quarantine refers to separation of individuals who are not yet ill but have been exposed to COVID-19 and therefore have a potential to become ill. There will be home quarantine/facility quarantine of contacts of suspect/confirmed cases. The guideline on home quarantineavailable on the website of the Ministry provides detailed guidance on home quarantine.

The contacts advised quarantine will undergo risk profiling. Those above 60 or with comorbidities will be shifted to designated quarantine facility. This will help identify early development of symptoms among them, their testing and shifting to isolation facility under para 9.

13.2.2. Isolation

Isolation refers to separation of individuals who are ill and suspected or confirmed of COVID-19. There are various modalities of isolating a patient. Ideally, patients can be isolated in individual isolation rooms or negative pressure rooms with 12 or more air-changes per hour.

In resource constrained settings, all positive COVID-19 cases can be cohorted in a ward with good ventilation. Similarly, all suspect cases should also be cohorted in a separate ward. However, under no circumstances these cases should be mixed up. The COVID hospital/COVID block in an identified hospital or the make shift temporary hospitals mentioned under para 9 will all have separate facilities to keep suspect and confirmed cases.

A minimum distance of 1 meter needs to be maintained between adjacent beds. All such patients need to wear a triple layer surgical mask at all times.

13.3. Social Distancing Measures

For the cluster containment, social distancing measures are key interventions to rapidly curtail the community transmission of COVID-19 by limiting interaction between infected persons and susceptible hosts. The following measures would be taken:

13.3.1. Closure of schools, colleges and work places

Administrative orders will be issued to close schools, colleges and work places in containment and buffer zones. Intensive risk communication campaign will be followed to encourage all persons to stay indoors for an initial period of 28 days, to be extended based on the risk assessment. Based on the risk assessment and indication of successful containment operations, an approach of staggered work and market hours may be put into practice.

13.3.2. Cancellation of mass gatherings

All mass gathering events and meetings in public or private places, in the containment and buffer zones shall be cancelled/banned till such time as the area is

declared to be free of COVID-19 or the outbreak has increased to such scales to warrant mitigation measures instead of containment.

13.3.3. Advisory to avoid public places

The public in the containment and buffer zones will be advised to avoid public places and only, if necessary, for attending to essential services. The administration will ensure supply of enough triple layer masks to the households in the containment and buffer zones to be distributed through visiting surveillance teams.

13.3.4. Cancellation of public transport (bus/rail)

There will be prohibition for persons entering the geographic quarantine and on persons exiting the geographic quarantine zone. To facilitate this, if there are major bus transit hubs or railway stations in the containment zone, the same would be made dysfunctional temporarily. Additionally, irrespective of the fact that there is a rail/road transit hub, the perimeter control will take care of prohibiting people exiting the containment zone including those using private vehicles and taxies.

As a significant inconvenience is caused to the public by adopting these measures in the containment zone, State government would proactively engage the community and work with them to make them understand the benefits of such measures.

13.3.5. Enforcement of Geographic quarantine

The perimeter control and movement of vehicles within the containment zone will be prohibited except for those (identified through special passes) earmarked for providing essential services. Police check-posts at prominent locations will check vehicles and give necessary guidance by police. Those found defaulting of Government orders will be prosecuted.

14. MATERIAL LOGISTICS

14.1. Personal Protective Equipment

The type of personal protective equipment for different categories of:

S. No.	Name of the item	Category of personnel
1	PPE Kit, N95 Mask, Gloves, Goggles, cap and shoe cover	• Doctors and nurses attending to patients in isolation, ICU/critical care facilities of hospitals in the containment zone. • Para-medical staff in the back cabin of ambulance performing interventional lifesaving maneuvers. • Those working in laboratories or collecting sample
2	N-95 Mask and gloves	• Supervisory doctors verifying a suspect case • Doctors/nurses attending patients in Screening fever clinics/respiratory clinics/ primary healthcare facilities
3	Triple Layer Surgical mask	• To be used by Field workers doing surveillance work • Staff providing essential services. • Suspect cases and care giver/ by stander of the suspect case • Security staff • Ambulance drivers

The State Government has to ensure adequate stock of Personal Protective Equipment (PPE). The quantity required for a containment operation will depend upon the size and extent of the cluster and the time required for containing it. States will also ensure that the PPE are being used in accordance with the guidelines on rational use of PPE.

14.2. Transportation

A large number of vehicles will be required for mobilizing the surveillance and supervisory teams. The vehicles will be pooled from Government departments. The shortfall, if any, will be met by hiring of vehicles.

14.3. Stay Arrangements for the Field Staff

The field staff brought in for the surveillance activities and that for providing perimeter control need to be accommodated within the containment zone. Facilities such as schools, community buildings, etc. will be identified for sheltering. Catering arrangement will have to be made at these locations.

14.4. Bio-medical Waste Management

A large quantity of bio-medical waste is expected to be generated from containment zone. Arrangement would also be required for such bio-medical waste (discarded PPEs, etc.), preferably by utilizing the bio-medical waste management services at the designated hospital.

15. RISK COMMUNICATION

15.1. Risk Communication Material

Risk communication materials [comprising: (i) posters and pamphlets (ii) audio only material (iii) AV films

(prepared by PIB/MoHFW)] will be prepared and kept ready for targeted roll out in the entire geographic quarantine zone.

15.2. Communication Channels

15.2.1. Interpersonal communication

During house to house surveillance, ASHAs/other community health workers will interact with the community for: (i) reporting symptomatic cases (ii) contact tracing (iii) informationon preventive public health measures.

15.2.2. Mass communication

Awareness will be created among the community through miking, distribution of pamphlets, mass SMS and social media. Also use of radio and television (using local channels) will ensure penetration of health messages in the target community.

15.2.3. Dedicated helpline

A dedicated helpline number will be provided at the Control Room (District Headquarter) and its number will be widely circulated for providing general population with information on risks of COVID-19 transmission, the preventive measures required and the need for prompt reporting to health facilities, availability of essential services and administrative orders on perimeter control.

15.2.4. Media Management

At the Central level, only Secretary (H) or representative nominated by her shall address the media. At the State level, only Principal Secretary (H), his/her nominee will speak to the media. At the District level DM/DC will address the media.

There will be regular press briefings/press releases to keep media updated on the developments and avoid stigmatization of affected communities. Every effort shall be made to address and dispel any misinformation circulating in media including social media.

16. INFORMATION MANAGEMENT

16.1. Control Room at State & District Headquarters

A Control Room (if not already in place) shall be set up at State and District headquarters. This shall be manned by State and District Surveillance Officer (respectively) under which data managers (deployed from IDSP/NHM) responsible for collecting, collating and analyzing data from field and health facilities. Daily situation reports will be put up.

The state will provide aggregate data on daily basis on the following (for the day and cumulative):

i. Total number of suspect cases

ii. Total number of confirmed cases

iii. Total number of critical cases on ventilator

iv. Total number of deaths

v. Total number of contacts under surveillance.

16.2. Control Room in the Geographic Quarantine Zone

A Control Room shall be set up inside the geographic quarantine zone to facilitate collection, collation and dissemination of data from various field units to District and State Control Rooms. This shall be manned by an epidemiologist under which data managers (deployed from IDSP/NHM) will be responsible for collecting, collating and analyzing data from field and health facilities.

This Control Room will provide daily input to the District Control Room for preparation of daily situation report.

16.3. Alerting the Neighboring Districts/States

The Control Room at State Government Headquarters will alert all neighboring Districts. There shall be enhanced surveillance in all such Districts for detection of clustering of symptomatic illness. Awareness will be created in the community for them to report symptomatic cases/contacts.

Also suitable provisions shall be created for enhancing horizontal communication between adjacent districts, especially for contact tracing exercise and follow up of persons exiting the containment zone.

17. CAPACITY BUILDING

It is expected that in such circumstances, large human resource requirement will be there to manage: (i) Field activities including surveillance, (ii) Clinical care at hospitals, (iii) laboratory testing and (iv) support staff to provide support services.

17.1. Training Content

Trainings will be designed to suit requirement of each and every section of healthcare worker involved in the containment operations. These trainings for different target groups shall cover:

1. Field surveillance, contact tracing, data management and reporting

2. Surveillance at designated exit points from the containment zone
3. Sampling, packaging and shipment of specimen
4. Hospital infection prevention and control including use of appropriate PPEs and bio-medical waste management
5. Clinical care of suspect and confirmed cases including ventilator management, critical care management
6. Risk communication to general community and health service providers.

17.2. Target Trainee Population

Various sections of healthcare workforce (including specialist doctors, medical officers, nurses, ANMs, Block Extension Educators, MHWs, ASHAs) and workforce from non-health sector (security personnel, Anganwadi Workers, support staff, etc.). Trainings will be tailored to requirements of each of these sections.

Prepare Training plan and calendar for undertaking training of non-health workers (including trainee ANM), volunteers from Red Cross, Civil Defence, NCC, NSS, Nehru Yuva Kendra volunteers, Panchayati Raj functionaries (rozgar sewaks) on community surveillance (self-protection, brief questionnaire interview and reporting to supervisors).

Train all available clinical resources (respiratory physicians, anaesthetists, intensivists, MBBS doctors who have handled ventilators, including DNB and MD students) on clinical and ventilatory management.

The training resources available at IGOT platform of GoI may be utilized.

The training will be conducted by the RRT a day prior to containment operations are initiated.

17.3. Replication of Training in Other Districts

The State Govt. will ensure that unaffected Districts are also trained along the same lines so as to strengthen the core capacities of their RRTs, doctors, nurses, support staff and non-health field formations. These trainings should be accompanied with functional training exercises like mock-drills.

18. FINANCING OF CONTAINMENT OPERATIONS

The fund requirement would be estimated taking into account the scale of operations and funds will be made available to the district collector from NHM flexi-fund. The SDRF funds can also be used as per notification issued by Ministry of Home Affairs.

19. SCALING DOWN OF OPERATIONS

The operations will be scaled down if no secondary laboratory confirmed COVID-19 case is reported from the geographic quarantine zone for at least four weeks after the last confirmed test has been isolated and all his contacts have been followed up for 28 days. The containment operation shall be deemed to be over 28 days from the discharge of last confirmed case (following negative tests as per discharge policy) from the designated health facility i.e. when the follow up of hospital contacts will be complete.

The closing of the surveillance for the clusters could be independent of one another provided there is no geographic continuity between clusters. However the surveillance will continue for ILI/SARI.

However, if the containment plan is not able to contain the outbreak and large numbers of cases start appearing, then a decision will need to be taken by State administration to abandon the containment plan and start on mitigation activities.

■■■■

Biologics for RA Safe with Nonelective Surgery

Patients with rheumatoid arthritis (RA) who were being treated with biologic therapies and underwent nonelective surgery had outcomes no worse than those who were treated with methotrexate, revealed a large retrospective cohort study.

Among patients being administered a tumor necrosis factor (TNF) inhibitor who needed surgery, the adjusted odds ratios (OR) for 90-day mortality were 0.83 (95% CI 0.67-1.02), and 0.86 (95% CI 0.75-0.933) for 30-day readmission, suggested researchers. They noted that even low-dose glucocorticoid use was associated with worse outcomes, with adjusted OR of 1.41 (95% CI 1.08-1.82) for 90-day mortality and 1.26 (95% CI 1.05-1.52) for 30-day readmission. The findings were published online in *Annals of the Rheumatic Diseases*.

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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Busters

CDC Recommends People Wear Cloth Masks to Block the Spread of COVID-19

Fact: Yes. Surgical masks and N95 respirators should be set aside for healthcare workers.

The Centers for Disease Control and Prevention (CDC) has released guidelines to recommend that US people should wear homemade face coverings to prevent the spread of the novel coronavirus.

The CDC has also advised simple cloth coverings to prevent people who may have the virus and are unaware, from transmitting it to others.

The White House Task Force and the CDC were re-evaluating the mask recommendations over the past few days. Research has suggested that people who do not have symptoms can infect others, and the virus may spread when people speak or breathe. It is not merely by coughing or sneezing. Considering the new evidence, the CDC and the task force recommend that people wear cloth face coverings in public settings where it might be difficult to maintain other distancing measures. If people cover their faces with a cloth mask or another such barrier, it may decrease the amount of virus-laden particles they release.

While there is limited evidence to suggest that these substitute masks prevent the spread of disease, some research suggests that they limit the amount of particles a person wearing them spreads. Some experts say that it is better to use these makeshift masks than nothing. The CDC further states that people should remain 6 feet apart when in public as much as possible, even if they're wearing masks.

Some cities and states, like Colorado and New York City, had already advised people to cover their faces when out in public. (*Source: The Verge*)

There are Groups at Higher Risk for Severe Illness

Fact: According to what is known, those at high-risk for severe illness from coronavirus disease (COVID-19) include:

- People ≥65 years of age
- People residing in a nursing home or long-term care facility.

People of all ages with underlying medical conditions have increased risk of severe illness, more so, if the underlying medical conditions are not well controlled. This includes individuals with:

- Chronic lung disease or moderate-to-severe asthma
- Serious heart conditions
- Conditions that can predispose a person to be immunocompromised, including cancer treatment, smoking, bone marrow or organ transplantation, immune deficiencies, poorly controlled human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), and prolonged use of corticosteroids and other immune weakening medications.
- Severe obesity (body mass index [BMI] ≥40)
- Diabetes
- Chronic kidney disease and those who are undergoing dialysis
- Liver disease.

(*Source: CDC*)

Younger People can be Serious

Fact: Yes. In Italy, with one of the largest outbreaks of COVID-19 in the world, 10-15% of all people in intensive care are under 50.

In Korea, one in six deaths have been reported in people below the age of 60.

World health officials highlighted a study in China that assessed 2,143 cases of children with confirmed or suspected COVID-19 that were reported to the Chinese Centers for Disease Control and Prevention from January 16 to February 8. Over 90% of the cases were asymptomatic, mild or moderate cases. Around 6% of the children's cases were severe or critical, compared with 18.5% for adults. (*Source: CNBC*)

Stability of SARS-CoV-2 in Different Environmental Conditions

Fact: According to a study published in *The Lancet Microbe*, severe acute respiratory syndrome-coronavirus

2 (SARS-CoV-2) can be highly stable in a favorable environment, but it is also susceptible to standard disinfection methods.

Alex WH Chin, University of Hong Kong, Hong Kong, China, and colleagues conducted various experiments to test the stability of SARS-CoV-2 at different temperatures, on various surfaces and its susceptibility to disinfection methods.

SARS-CoV-2 in virus transport medium (final concentration ~6.8 log unit of 50% tissue culture infectious dose [$TCID_{50}$] per mL) was incubated for up to 14 days and was then tested for its infectivity.

Results showed that SARS-CoV-2 is highly stable at 4°C, but has sensitivity to heat. At 4°C, only around 0.7 log-unit reduction of infectious titer was noted on Day 14. As the incubation temperature increased to 70°C, the time for virus inactivation decreased to 5 minutes.

Researchers then assessed the stability of the virus on varying surfaces, including paper, tissue paper, wood, cloth, glass, banknotes, stainless steel, plastic and surgical masks. A 5 μL droplet of virus culture (~7.8 log unit of $TCID_{50}$ per mL) was pipetted on a surface and left at room temperature (22°C) with a relative humidity of around 65%. The inoculated objects retrieved at desired time-points were soaked with 200 μL of virus transport medium for a span of 30 minutes to elute the virus.

No infectious virus was recovered from printing and tissue papers after a 3-hour incubation, while no infectious virus could be detected from treated wood and cloth on Day 2. On the contrary, the virus was more stable on smooth surfaces. No infectious virus could be detected from treated smooth surfaces on Day 4 (glass and banknote) or Day 7 (stainless steel and plastic).

Of note, a detectable level of infectious virus was still present on the outer layer of a surgical mask on Day 7 (~0.1% of the original inoculum).

[Source: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30003-3/fulltext]

Can Povidone-iodine Kill the Virus

Yes; in a study published in *The Lancet Microbe*, researchers assessed the virucidal effects of disinfectants by adding 15 μL of the virus culture (~7.8 log unit of $TCID_{50}$ per mL) to 135 μL of various disinfectants at working concentration.

Disinfectants included household bleach, hand soap, ethanol, povidone-iodine, chlorhexidine and benzalkonium chloride. With the exception of a 5-minute incubation with hand soap, no infectious virus was detectable after a 5-minute incubation at room temperature.

[Source: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30003-3/fulltext]

Can the Virus Survive in Waste Water

In an article, published in *The Lancet Gastroenterology & Hepatology*, researchers have reported the detection of SARS-CoV-2 in wastewater.

From February 17, 2020, onwards, Willemijn Lodder and Ana Maria de Roda Husman, of Centre for Infectious Disease Control, Bilthoven, the Netherlands, took samples once a week from human wastewater collected at Amsterdam Airport Schiphol, Haarlemmermeer, the Netherlands. Samples tested positive for virus RNA as per quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) methodology 4 days after the first cases of COVID-19 were identified in the Netherlands.

This could be attributed to virus excretion from potentially symptomatic, asymptomatic or pre-symptomatic individuals passing through the airport.

Human wastewater sampled near the first Dutch cases in Tilburg, Netherlands, had also tested positive for the presence of viral RNA within a week of the first day of disease onset.

This suggests that wastewater could serve as a sensitive surveillance system and early warning tool, as was previously shown for poliovirus.

[Source: https://www.thelancet.com/journals/langas/article/PIIS24681253(20)30087-X/fulltext]

Feco-oral Transmission

Fact: It is not yet clear if the SARS-CoV-2 is viable under environmental conditions that could promote fecal-oral transmission. However, the possibility of fecal-oral transmission has implications, particularly in areas with poor sanitation where diagnostic capacity might be limited, such as Africa. Wastewater surveillance, particularly in areas with limited data, might provide information, as has been previously shown in monitoring antibiotic resistance on a global scale.

[Source: https://www.thelancet.com/journals/langas/article/PIIS24681253(20)30087-X/fulltext]

Can you Convert Anesthesia Machines into Ventilators

American Society of Anesthesiologists (ASA) has published guidance on how to safely and effectively convert anesthesia into life-sustaining mechanical

ventilation for patients during the COVID-19 pandemic, when there is scarcity of ICU ventilators.

Although guidance is available from the manufacturers, the guidance may not convey all of the clinical considerations. Anesthesia professionals will be needed to put these machines into service and to manage them while in use. Safe and effective use requires an understanding of the capabilities of the machines available, the differences between anesthesia machines and ICU ventilators, and how to set anesthesia machine controls to mimic ICU-type ventilation strategies. [*American Society of Anesthesiologists*]

You cannot Transmit the Disease Before the Symptoms

Myth: A study published by the US CDC has stated that people infected with COVID-19 can transmit the infection one-to-three days before symptoms start appearing.

The study emphasized on the importance of social distancing to fight the COVID-19 pandemic. Overall, 243 cases of COVID-19 reported in Singapore from January 23 to March 16 were assessed. Seven clusters were identified where presymptomatic transmission was likely. In four such groups, where the date of exposure could be determined, presymptomatic transmission was found to occur one-to-three days before symptoms appeared in the source patient.

Of the cases in Singapore, 157 were locally acquired and 10 of these were likely transmitted before symptoms started appearing. The findings thus point that it might not be enough for people having symptoms to limit contact to control the pandemic, noted the investigators in the CDC's *Morbidity and Mortality Weekly Report*.

Public health officials carrying out contact tracing need to consider including a period before symptom onset to account for the possibility of this type of transmission. Transmissions might take place through respiratory droplets or even speech and other vocal activities like singing. The rate of emission corresponds to voice loudness. (*Excerpts from Reuters*)

You cannot Die If Your Age is Less Than One

Myth: A baby in Connecticut died from COVID-19. An infant who passed away in Connecticut tested positive for COVID-19. The 7-week-old girl hailed from Hartford. The first infant death in the United States from COVID-19 was in Chicago, the Illinois Dept. of Public Health reported on March 28. The infant was less than a year old.

Children constitute a small number of coronavirus-related cases. A study published in the *New England Journal of Medicine* had reported that children accounted for fewer than 1% of COVID-19 cases in China. As of March 8, there was one death, that of a 10-month-old baby. The child had bowel blockage and multi-organ failure and succumbed 4 weeks following hospital admission.

NYC Ambulances Won't Take Cardiac Arrest Patients to Hospitals

Fact: Medical first responders in New York City have been told not to take patients in cardiac arrest to a hospital if they fail to restart the patient's heart in the field, according to the *New York Post*.

Differentiate the Population into Five Groups and Treat Accordingly

Fact:

1. We need to know who is infected
2. Identify who is presumed to be infected, i.e., those with signs and symptoms consistent with infection who initially test negative
3. Who has been exposed?
4. Who is not known to have been exposed or infected?
5. Who has recovered from infection and has adequate immunity.

It is required to take action on the basis of symptoms, examinations, tests (polymerase-chain-reaction assays to detect viral RNA), and exposures to recognize those who belong to each of the first four groups.

Those with severe disease or at high risk must be hospitalized. Infirmaries need to be established making use of empty convention centers, to care for those with mild or moderate disease and at low risk; an isolation infirmary for all patients will decrease transmission to family members.

Convert hotels that are vacant now into quarantine centers to accommodate those who have had exposure to the novel coronavirus, and separate them from the general population for 2 weeks. This quarantine method will remain practical until and unless the epidemic has exploded in a particular city or region.

Being able to identify the fifth group of people requires development, validation and deployment of antibody-based tests. [*NEJM*]

Facts

Healthcare workers carrying out aerosol-generating procedures on COVID-19 patients in the ICU setting

must use fitted respirator masks such as N95 respirators, FFP2 or equivalent, in comparison with surgical/ medical masks, **besides using other personal protective equipment** (e.g., gloves, gown and eye protection such as a face shield or safety goggles).

Perform aerosol-generating procedures on COVID-19 patients in the ICU in a **negative-pressure room.**

Healthcare personnel involved in providing usual care for nonventilated patients with COVID-19 must use surgical/medical masks, as compared to respirator masks **besides using other personal protective equipment**.

Endotracheal intubation is recommended in patients with COVID-19, to be performed by healthcare workers with experience in airway management, in order to minimize the number of attempts and risk of transmission.

For intubated and mechanically ventilated adults suspected to have COVID-19, it is suggested to obtain **endotracheal aspirates, over bronchial wash** or bronchoalveolar lavage samples.

For adults with COVID-19 and acute hypoxemic respiratory failure, use **high-flow nasal cannula [HFNC]** over noninvasive positive pressure ventilation [NIPPV].

For adults with COVID-19 given NIPPV or HFNC, monitor closely for worsening of respiratory status and perform early intubation in a controlled setting if worsening occurs.

For mechanically ventilated adults with COVID-19 and moderate-to-severe acute respiratory distress syndrome [ARDS], go for **prone ventilation** for 12-16 hours over no prone ventilation.

For mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), don't **use systemic corticosteroids on a routine basis.**

Healthcare workers carrying out nonaerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19 should use surgical/medical masks, as compared to respirator masks, besides using other personal protective equipment.

Healthcare workers performing endotracheal intubation on patients with COVID-19 should use video-guided laryngoscopy, over direct laryngoscopy, if available.

[Recommendations issued by the European Society of Intensive Care Medicine (ESICM), to be published in *Intensive Care Medicine*.]

Non-shedders cannot Happen

Non-shedder: Both asymptomatic and symptomatic patients, but do not shed the virus

Shedder (normal spreader and silent spreaders): Both asymptomatic and symptomatic patients and shed the virus.

Super spreader: Both asymptomatic and symptomatic patients and shed high volume and high distance of viruses in micro droplets.

WBC Account Provides Accurate Information

No. White blood cell (WBC) count can vary. It does not provide precise information about COVID-19.

[*Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni. Yu Hu, W. Liang, C. Ou, J. He, L. Liu*]

Lymphopenia is Seen in 100% Cases

Leukopenia, leukocytosis and lymphopenia have been reported, with lymphopenia being more common, seen in more than 80% of patients.

[*Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni. Yu Hu, W. Liang, C. Ou, J. He, L. Liu*]

Thrombocytopenia is Seen in All Cases

Mild thrombocytopenia is common. But thrombocytopenia is a poor prognostic sign.

[*Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu; Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen*]

Serum Procalcitonin has No Value

No, serum procalcitonin is often normal at the time of admission, but increases in patients who require ICU care.

D-dimer is not Linked to Low Lymphocytes Counts

A study noted that high D-dimer and lymphopenia are associated with poor prognosis.

[*Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni. Yu Hu, W. Liang, C. Ou, J. He, L. Liu; Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen*]

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Annual Conference of Endocrine Society of India (ESICON 2019)

21ST-24TH NOVEMBER, 2019 | HOTEL LE MERIDIEN, NAGPUR

PPAR TARGETS: FUTURE OF GLITAZONES/ GLITAZARS

Brig (Dr) Narendra Kotwal, New Delhi

- Peroxisome proliferator-activated receptor (PPAR) agonists work as integrators of inflammatory and metabolic signaling networks; work as lipid sensors; repress pro-inflammatory gene expression; fine-tune post-translational modifications and exert antiatherogenic effects.
- Potential of PPAR agonists is well-established in therapeutic areas related to lipid and glucose metabolism and inflammation such as type 2 diabetes mellitus, obesity, dyslipidemia and NAFLD and/or NASH.
- PPAR-γ ligand may prevent loss of β-cell mass.
- PPAR-γ activation reduces insulin resistance, preserves pancreatic β-cell function, improves cardiovascular risk profile.

PPAR agonists play significant roles in several diseases including primary biliary cholangitis, gout, non-small cell lung cancer, neurological diseases and ulcerative colitis.

ALPHA BETA CROSSTALK: BETA TO ALPHA CELLS AND BACK!

Dr Madhukar Mittal, Jodhpur, Rajasthan

- Biological crosstalk – Components of one signal transduction pathway affect another in a number of ways, most common form being crosstalk between proteins of signaling cascades.
- There is a crosstalk between cells that control body's response to sugar and understanding the conversation can help us understand and treat diabetes.
- In type 1 diabetes mellitus, there is almost complete destruction of β-cells; α-cells are present but their function is impaired. In type 2 diabetes mellitus, β-cell number reduction is progressive and α-cell numbers may actually be increased.
- Artemisinins inhibit ARX function and impair α-cell identity. Artemisinins increase β-cell mass in zebrafish and rodent models. They target $GABA_A$ receptor signaling.
- Glucagon-like peptide-1 (GLP-1) receptor agonists exert some of their glycemic effects through reduction in endogenous glucagon. GLP-1 treatment reduces glucagon secretion: by action on pancreatic α-cells, and by stimulation of β-cells, and the paracrine effects of the secreted insulin on adjacent α-cells.
- There are significant structural and functional differences in rodent islets and human islets.
- Structure of human islets permits greater role of paracrine and autocrine interactions in regulating islet cell function.
- This is an ever-expanding area of research with knowledge gaps, and has a potential role in the management of diabetes.

Deciphering α-β crosstalk has potential for curative therapies for diabetes.

SOLITARY THYROID NODULE: WHAT'S NEW IN APPROACH?

Dr Bipin Kumar Sethi, Hyderabad, Telangana

- High resolution ultrasound can detect thyroid nodules in 19-68% individuals. Approximately 1 in 2 people may have incidental thyroid nodules.
- The frequency is higher in the elderly and in females.
- Indeterminate nodules continue to challenge and tease those who wish to separate the chaff from the grain.
- There remains a significant percentage of nodules with ambiguity.
- Commercially available molecular markers: *Afirma* – relies on mRNA microarray sequencing and has high sensitivity/NPV and low specificity/ PPV; *ThyroSeq GC* is a DNA- and RNA-based next-generation sequencing (NGS) with high specificity/ PPV and high sensitivity/NPV; *ThyGenX + ThyraMIR combination* – overall performance is moderate.

- Artificial intelligence algorithms decrease the subjectivity of medical image interpretation.
- More often one "errs" in favor of surgery than uncertainty.

Newer techniques refine the accuracy but do not entirely eliminate the uncertainty and are currently in "not for you" category.

ADRENAL INSUFFICIENCY: CHANGING CONCEPTS IN MANAGEMENT

Prof (Dr) Paul M Stewart, UK

- Morbidity and increased mortality in patients with adrenal insufficiency is unacceptable. Management of adrenal crisis is currently inadequate.
- Morbidity is related, in part, to excessive daily doses of glucocorticoids.
- Glucocorticoid replacement in the treatment of adrenal insufficiency – Current practice: According to a survey of current practice in glucocorticoid replacement therapy in patients with adrenal insufficiency, glucocorticoid replacement therapy consisted primarily of hydrocortisone.
- Patients with adrenal insufficiency are not sufficiently equipped with emergency kits. Recent studies show that subcutaneous administration of drug is effective and patient acceptance is high.
- Subcutaneous administration of 100 mg hydrocortisone shows excellent pharmacokinetics for emergency use; it has a good safety profile and is preferred by patients over intramuscular injection (Hahner S, et al. *Eur J Endocrinol*. 2013;169(2):147-54).
- Adrenal suppression after glucocorticoid treatment is dose- and duration-dependant. Suppression of the adrenal response is common after short-term, high-dose glucocorticoid treatment (Henzen C, et al. *Lancet*. 2000;355(9203):542-5).
- Evidence suggests that circadian rhythm is important. There are deleterious consequences of 'late pm' excess. Elevated evening levels of cortisol are associated with glucose intolerance, abdominal obesity, coronary atherosclerosis, insomnia and reduced sleep quality.
- Management of adrenal suppression is challenging and more studies are required.

Newer preparations mimicking physiology are highly desirable. Endocrinologists need to take ownership of iatrogenic adrenal insufficiency.

CAH: NEWER INSIGHTS IN ETIOLOGY AND MANAGEMENT

Prof (Dr) Richard Auchus, US

- 11-oxygenated 19-carbon ($11oxC_{19}$) steroids are elevated in both men and women with classic 21-hydroxylase deficiency (21OHD). $11oxC_{19}$ steroids are specific biomarkers of adrenal-derived androgen excess (Turcu AF, et al. *Eur J Endocrinol*. 2016;174(5):601-9).
- Potential therapies for management of congenital adrenal hyperplasia (CAH) – Modified-release hydrocortisone; Hydrocortisone subcutaneous infusion pump; Super-androgen receptor antagonists: P450 17A1 inhibitor – Abiraterone acetate, CRH receptor antagonist – NBI-77860, NBI-74788, SPR-001 = Tildacerfont and ACAT1 (SOAT1) inhibitor – ATR-101 (Nevanimibe).
- Abiraterone for 21OHD – Abiraterone acetate is a potent P450 17A1 inhibitor that is FDA-approved for the treatment of prostate cancer with prednisone to prevent hypertension and hypokalemia. The concept is to add abiraterone acetate to replacement hydrocortisone to control androgen excess and mitigate the consequences of chronic supraphysiologic glucocorticoids.

Abiraterone acetate at 250 mg/day with hydrocortisone 20 mg/day for 1 week normalizes androgens in the majority of adult women with classic 21OHD, without causing hypertension or hypokalemia.

PREVENTION OF TYPE 2 DIABETES: GLOBAL PERSPECTIVE

Dr Ashok Kumar Das, Puducherry

- Triad of modalities in preventing type 2 diabetes – Diet, exercise and medication.
- Lifestyle intervention can prevent type 2 diabetes onset. Several randomized trials have shown that interventions – lifestyle, medications – can decrease the rate of onset of diabetes. These include Da Qing Study, Finnish Diabetes Prevention Study and Diabetes Prevention Program for lifestyle interventions; and Diabetes Prevention Program (metformin), The Stop-NIDDM and ACT NOW (pioglitazone) for medications.
- ACT NOW - Pioglitazone reduced the risk of type 2 diabetes mellitus by 72% vs. placebo. Pioglitazone reduced fasting glucose, 2-hour glucose and HbA1c.

- ADA 2019 nutritional recommendations – The eating patterns that may be helpful for those with prediabetes include a Mediterranean eating plan and a low-calorie, low-fat eating plan. Higher intakes of nuts, berries, yogurt, coffee and tea are associated with reduced diabetes risk.
- ADA 2019 pharmacological recommendations – Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years and women with prior gestational diabetes mellitus. Metformin has the strongest evidence base and demonstrated long-term safety as pharmacologic therapy for diabetes prevention.

We must identify patients at high risk (prediabetes). Modest lifestyle changes are most effective. Increase opportunities for community programs to support prevention. Delaying or preventing type 2 diabetes is cost-effective and will help turn the tide on the diabetes epidemic.

APPROACH TO ADAM

Dr KVS Hari Kumar, Panchkula, Haryana

- Androgen deficiency in aging male (ADAM) is functional hypogonadism and is a diagnosis of exclusion.
- Sexual symptoms (erectile dysfunction and reduced sexual thoughts) are significant symptoms for the diagnosis.
- Diagnosis is based on the demonstration of low levels of total testosterone done at least twice along with symptoms.
- Other hormonal panel aids in the exclusion of other causes.
- Free testosterone has limited role in the diagnosis.
- Testosterone therapy is not approved by US FDA for ADAM and is considered as off-label use only.
- Prostate and breast carcinoma are absolute contraindications for testosterone therapy and beware of the risks involved with therapy.
- Anabolic steroids and other compounds have limited benefit.

Testosterone offers moderate benefit on sexual symptoms and modest benefit on body composition, bone density and cognition. Individualized testosterone therapy is recommended by guidelines from the Endocrine and Geriatric societies.

GRAVES' DISEASE: PREDICTORS OF REMISSION

Dr KM Prasanna Kumar, Bengaluru, Karnataka

- Hyperthyroidism relapses in the majority of patients with Graves' disease treated with antithyroid drug (ATD).
- Among different clinical and laboratory features, age at onset of hyperthyroidism, goiter size and TSH-receptor antibody (TRAb) level are particularly helpful in identifying those patients who are more prone to undergo a remission of hyperthyroidism, after medical treatment.
- Remission is independent of the type of ATD (methimazole, propylthiouracil and carbimazole).
- Graves' patients with the G allele in exon 1 of the CTLA-4 gene, were required to continue ATD treatment for longer periods to achieve remission.
- Children with hyperthyroidism often require prolonged courses of antithyroid medication to achieve remission, and long-term compliance is problematic.

Age at onset of hyperthyroidism, goiter size and TRAb level help identify patients more prone to undergo a remission of hyperthyroidism.

The most relevant predictor of Graves' disease outcome seems to be serum level: TRAb at the time of Graves' disease diagnosis <2.5 times the upper reference limit, TRAb normalization during ATD and TRAb normalization timing each may predict positive outcomes.

OBESITY AND FERTILITY

Dr Sarita Bajaj, Prayagraj, Uttar Pradesh

- Obesity in men and women is associated with impaired reproductive function.
- Preconceptional counseling for obese couples should address the reproductive and maternal-fetal consequences of obesity.
- Lifestyle modification is the first-line treatment for obesity, followed by adjunctive medical therapy.
- Elimination of tobacco, alcohol and stress management may be of more immediate benefit in achieving conception. Bariatric surgery is an important adjuvant to lifestyle modification and medical therapy for weight loss, but pregnancy in women should be deferred for 1 year post-op.
- The excess reproductive morbidity associated with obesity may increase with longer duration, making the current trends among children and young

adults particularly critical in terms of their future reproductive potential.

- Conveying the impact of these lifestyle changes on future progeny can serve as a powerful tool for obese people to modify their behavior.

Reproductive urologists and endocrinologists must learn about the importance of paternal preconception health.

STEM CELL THERAPY IN DIABETES

Dr Ganapathi B, Bengaluru, Karnataka

- Stem cell therapies for type 1 diabetes are novel.
- The use of stem cells in the generation of a renewable source of β-cells remains a promising reality.
- A meta-analysis of the clinical efficacy of stem cell therapy for diabetes mellitus revealed the following: (1) remission of diabetes mellitus is possible following stem cell therapy; (2) stem cell transplantation can be a safe and effective approach for therapy of diabetes mellitus; (3) available data indicate that the most promising therapeutic outcome was shown in mobilized marrow $CD34^+$ hematopoietic stem cells (HSCs); (4) patients with previously diagnosed diabetic ketoacidosis are not good candidates for the applied approaches stem cell therapy; (5) stem cell therapy at early stages after diabetes diagnosis is more effective than intervention at later stages and (6) well-designed large scale randomized studies considering the stem cell type, cell number and infusion method in diabetes patients are urgently needed (El-Badawy A, El-Badri N. *PLoS One*. 2016;11(4):e0151938).
- Autologous umbilical cord blood transfusion in children with type 1 diabetes is safe but has yet to demonstrate efficacy in preserving C-peptide (Haller MJ, et al. *Diabetes Care*. 2009;32(11):2041-6).
- A major issue that needs to be addressed is the *in vitro* maturation of insulin-positive cells.

Even with an abundant supply of stem cell-derived β-cells with robust glucose-responsiveness, many issues still need to be addressed and resolved before this approach becomes a therapeutic option.

THYROID STORM

Dr RV Jayakumar, Cochin, Kerala

Thyroid storm is an important endocrine emergency. Suspect the condition in any severely ill patient with tachycardia, high fever and a thyroid swelling. Early treatment with antithyroid drugs, iodine, steroids, β-blockers and supportive measures reduces mortality. Treatment of the precipitating factors is also important. Once treated for the acute problem, don't forget the long-term management of thyrotoxicosis.

***Remember 5 B's in management - B**lock Synthesis - Antithyroid drugs; **B**lock Releasers - Iodine; **B**lock T4 to T3 conversion - Propylthiouracil (PTU), Steroids; **B**eta-blockers - for symptomatic relief; **B**lock enterohepatic circulation - Cholestyramine.*

ECTOPIC ACTH-PRODUCING CUSHING'S SYNDROME

Prof Nihal Thomas, Vellore, Tamil Nadu

- This is an important differential diagnosis for adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. It has a more rapid and fulminant onset with significantly higher levels of ACTH, serum hypercortisolemia and urine free cortisol levels when compared with pituitary-dependent Cushing's syndrome.
- Intrathoracic origin for ectopic ACTH-producing tumors is the most common; particularly thymic, bronchial carcinoid and bronchogenic carcinoma.
- Opportunistic infections which are secondary to immune suppression are more common and can be lethal if not treated aggressively.
- Thymomas are frequently malignant and clinical remission postoperatively is uncommon.

In patients with severe clinical symptoms of Cushing's, control of hypercortisolemia with medical management, particularly ketoconazole, and in refractory cases, early adrenalectomy may precede the excision of the primary tumor.

TYPE 2 DIABETES MELLITUS IN INDIANS – NOVEL INSIGHTS

Prof (Dr) SV Madhu, New Delhi

- The burden of type 2 diabetes mellitus continues to rise.
- The way our body handles meal-related surges in lipids and the associated postprandial triglyceride dysmetabolism appears to be a major determinant of our risk of developing type 2 diabetes mellitus.
- We have obtained unequivocal evidence that postprandial hypertriglyceridemia leads to the development of insulin resistance, glucose intolerance and type 2 diabetes mellitus in a diet-induced rat model of type 2 diabetes mellitus.
- Polymorphisms of RAGE gene have significant effects on advanced glycation end products (AGEs)

level and PON1 activity in diabetic subjects as compared to healthy individuals.

- Transcriptional expression of RAGE mRNA in peripheral blood mononuclear cells (PBMCs) has been found to be significantly higher in diabetic patients than in controls.
- Role of arginine vasopressin pathways in chronic stress coping is being increasingly recognized.
- A chronically hyperactive and dysregulated HPA axis is associated with enhanced diabetes risk.
- Other novel risk factors for type 2 diabetes mellitus include circadian disruption and environmental pollutants. Shift work is associated with metabolic and genetic dysregulation among Indians.
- Postprandial triglyceride dysmetabolism appears central to the pathogenesis of type 2 diabetes mellitus.
- Genetic/molecular studies can also help in understanding the underlying pathogenetic mechanisms of type 2 diabetes risk.
- Longitudinal studies throw up challenges to traditional concepts and widen the scope of our understanding of the disease.
- We need to develop culturally sensitive diabetes management recommendations that allow women to remain integrated in protective social and family roles while still successfully managing blood sugar.

There is a strong inverse link of stress coping capabilities with diabetes risk. Hence, there is a need to focus on strategies to improve stress coping.

NONGLYCEMIC EFFECTS OF SGLT-2 INHIBITORS

Dr Shashank Joshi, Mumbai, Maharashtra

- Nonglycemic benefits with sodium-glucose cotransporter-2 (SGLT-2) inhibitors – Metabolic benefits, weight/fat loss benefits, cardiovascular (CV) benefits and renal benefits.
- Cardiovascular disease (CVD) mortality in type 2 diabetes mellitus has remained a significant challenge over the years, and targeting vasculo-metabolic axis is key to sustained improvement in health outcomes.
- Personalized medicine approach and guidelines suggest the preferential use of SGLT-2 inhibitors, for compelling reasons of atherosclerotic CVD (ASCVD), heart failure (HF) or chronic kidney disease (CKD), weight loss or lower risk of hypoglycemia. Agents with proven CVD benefit are recommended for patients with ASCVD.
- SGLT-2 inhibitors have demonstrated consistent CV benefits, including reductions in CV death, HF hospitalizations and nephropathy in type 2 diabetes mellitus with CVD.
- Start early with SGLT-2 inhibitors for cardiorenal protection.
- CREDENCE is the first dedicated kidney outcome trial which showed 30% reduction in primary outcomes like end-stage kidney disease, doubling of serum creatinine or renal or CV death with SGLT-2 inhibitor therapy.

Optimize clinical considerations of risk-benefit for each antidiabetic agent, in principle of individualized approach for every patient.

FERTILITY PRESERVATION IN PATIENTS UNDERGOING CANCER TREATMENT

Prof Jubbin Jagan Jacob, Ludhiana, Punjab

- Better survival among adolescents and young adults with cancer means that fertility issues become important among survivors.
- Current recommendations from American Society of Clinical Oncology suggest that counseling of all adults in reproductive age group and parents of children undergoing cancer therapy for reproductive and fertility issues be undertaken. For post-pubertal males, the best option for fertility preservation remains cryopreservation of semen for use subsequently. Gonadotropin-releasing hormone (GnRH) analogues are not recommended as they do not have much success.
- GnRH analogues work by shutting down the hypothalamic-pituitary-gonadal axis and this, in turn, reduces gonadotoxicity by: a) Reduction in recruitment of active gametes. b) Reduction in blood supply to the gonad reducing the exposure of the gonad to toxic drugs. For prepubertal people, the only option is gonadal shielding when being administered radiation. Other avenues for fertility preservation are currently experimental only.

For post-pubertal females, embryo preservation gives the highest chance of success followed by oocyte cryopreservation. However, when both these avenues are not possible then the use of GnRH analogues is an option.

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News and Views

IV Esketamine, Ketamine Equally Effective for Resistant Depression

Intravenous (IV) esketamine has been found to be as safe and effective as IV ketamine for patients with treatment-resistant depression in a new research that was scheduled to be presented at the Anxiety and Depression Association of America (ADAA) Conference 2020. The randomized, double-blind noninferiority trial compared IV racemic ketamine and esketamine in 63 participants (61.9% women; mean age 47 years) with treatment-resistant major depressive disorder. The trial revealed that esketamine was noninferior to ketamine in remission of depressive symptoms 24 hours following a single IV dose and the two drugs had similar side effect profiles… (*Medscape*)

Pediatric-onset IBD may Double Cancer Risk in Later Life

Pediatric-onset of inflammatory bowel disease (IBD) could lead to a twofold increase in the risk of developing cancer in adulthood, suggests a Canadian study.

The population-based case-control study revealed that 1.7% of patients with childhood-onset IBD developed cancer, in comparison with 0.8% of controls (hazard ratio [HR] 2.00, 95% confidence interval [CI] 1.16-3.43). This amounted to overall cancer rates of 114 and 57 per 1,00,000 person-years, respectively, reported the study published online in *Gastroenterology*.

Children in the DRC at Risk from Measles, Cholera Epidemics

The Democratic Republic of the Congo (DRC) is in need of urgent support as it struggles with measles and cholera epidemics that kill thousands of children, besides the increasing threat from the COVID-19 pandemic, says UNICEF.

In a recent report, the agency said that ongoing efforts to contain the Ebola outbreak in the eastern part of the country have diverted attention and resources from already weakened healthcare facilities that are dealing with several deadly endemic diseases… (*UNICEF*)

Coronavirus can Spread One-to-Three days Before Symptoms Appear, Says CDC Study

People infected with the novel coronavirus can potentially transmit the infection one-to-three days prior to symptom onset, suggests a study published by the US Centers for Disease Control and Prevention (CDC).

The study assessed 243 cases of coronavirus disease (COVID-19) reported in Singapore from January 23 to March 16. Seven clusters were identified where presymptomatic transmission was likely, and in four such groups, where the date of exposure could be determined, presymptomatic transmission was noted one-to-three days before symptoms appeared in the source patient. The findings suggested that it might not be enough for people with symptoms to limit contact to control the pandemic, researchers stated in the CDC's *Morbidity and Mortality Weekly Report*, published online… (*Reuters*)

Pre-eclampsia Tied to Neurologic Disease in Full-term Babies

Full-term infants whose mothers had pre-eclampsia during pregnancy had increased odds of developing a range of neurologic diseases subsequently, suggested a population-based cohort study in Norway.

These included attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), epilepsy and intellectual disability. The study also showed an apparent link between pre-eclampsia and cerebral palsy. The findings were published online in *JAMA Psychiatry*.

New WHO Guide to Help Countries Increase Access to Essential Medicines

The World Health Organization (WHO) has issued a new user guide for countries – "Selection of medicines at country level" – that is based on the WHO Model List of Essential Medicines.

It outlines the key actions that the countries must undertake to develop and update their own national essential medicines lists based on the treatment requirements of their populations and their capacity to reimburse payments for medicines. The document is also intended at supporting countries in progressing towards universal health coverage… (*WHO*)

Loss of Taste, Smell Key COVID-19 Symptoms, Says British Scientists' Study

Losing sense of smell and taste may be the best way to tell if you have COVID-19 infection, suggests a study of

data collected through a symptom tracker app developed by British scientists to help monitor the pandemic.

Nearly 60% of patients who were later confirmed as positive for COVID-19 had reported losing their sense of smell and taste, revealed an analysis of data by the researchers… (*Reuters*)

Mindfulness Interventions Tied to Cognitive Benefit

Mindfulness-based interventions can have a beneficial effect on cognition, although only in certain cognitive domains, suggests new research that was scheduled to be presented at the ADAA Conference 2020.

A meta-analysis of 78 randomized controlled trials with 5,918 participants suggested that mindfulness-based interventions improved attention, memory and processing speed. Mindfulness-based interventions had significant effects in 9 of the 17 cognitive domains evaluated… (*Medscape*)

Add-on Colchicine Cost-effective After MI

Low-dose colchicine decreased the risk of ischemic cardiovascular (CV) events after myocardial infarction (MI), and was cost-effective, suggested the Canadian COLCOT trial.

The primary efficacy outcome, i.e., CV death, MI, stroke, resuscitated cardiac arrest or urgent hospitalization for unstable angina leading to revascularization, occurred in 5.5% of the colchicine group compared to 7.1% of the placebo group, reported Michelle Samuel, PhD, of the Montreal Heart Institute, at the virtual American College of Cardiology (ACC) meeting… (*Medpage Today*)

Coronavirus Life on Surfaces

It is always better to wait. WEBMD posted this data recently.

Metal	Doorknobs, jewelry, silverware	**5 days**
Wood	Furniture, decking	**4 days**
Plastic	Packaging like milk containers and detergent bottles, subway and bus seats, backpacks, elevator buttons	**2-3 days**
Stainless steel	Refrigerators, pots and pans, sinks, some water bottles	**2-3 days**
Cardboard	Shipping boxes	**24 hours**
Copper	Pennies, tea kettles, cookware	**4 hours**
Aluminum	Soda cans, tinfoil, water bottles	**2-8 hours**
Glass	Drinking glasses, measuring cups, mirrors, windows	**Up to 5 days**
Ceramics	Dishes, pottery, mugs	**5 days**
Paper		The length of time varies. Some strains of coronavirus live for only a few minutes on paper, while others live for up to 5 days.
Food		Coronavirus doesn't seem to spread through exposure to food. Still, it's a good idea to wash fruits and vegetables under running water before you eat them. Scrub them with a brush or your hands to remove any germs that might be on their surface. Wash your hands after you visit the supermarket. If you have a weakened immune system, you might want to buy frozen or canned produce.
Water		Coronavirus hasn't been found in drinking water. If it does get into the water supply, your local water treatment plant filters and disinfects the water, which should kill any germs.
		Coronaviruses can live on a variety of other surfaces, like fabrics and countertops.

To limit your chances of contracting or spreading coronavirus, clean and disinfect all surfaces and objects in your home and office on a daily basis. This includes:

- Countertops
- Tables
- Doorknobs
- Bathroom fixtures
- Phones
- Keyboards
- Remote controls
- Toilets.

You may use a household cleaning spray or wipe. If the surfaces are visibly dirty, clean them first with soap and water and then disinfect them.

Keep surfaces clean, even if everyone in your house is healthy. People who are infected may not show any symptoms, but can still shed the virus onto surfaces.

After you visit the drugstore or supermarket, or bring takeout food or packages, wash your hands for at least 20 seconds with soap and warm water. Do the same after you pick up a delivered newspaper.

Inclisiran Treatment Leads to Considerable Reduction in LDL

Treatment with an investigational proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor reduced low-density lipoprotein cholesterol (LDL-C) by more than half in patients with atherosclerotic cardiovascular disease (ASCVD), suggested a pooled analysis of three trials.

An analysis of the ORION 9, ORION 10 and ORION 11 studies revealed that the primary outcome, i.e., mean percent change in LDL-C at 510 days, was -56 in the inclisiran group compared with 1 in the placebo group, reported R Scott Wright, MD, of the Mayo School of Medicine in Rochester, Minnesota in a late-breaking presentation at the virtual American College of Cardiology (ACC) meeting… (*Medpage Today*)

More Evidence Suggests Acupuncture Beneficial for Migraine

A randomized single-blind study has revealed that participants receiving acupuncture experienced about two fewer headache days per month and fewer migraine attacks in comparison with those who received sham or usual care (UC).

The therapeutic effect was noted earlier and was larger in patients receiving manual acupuncture. These patients also had better quality of life and sleep quality scores. The report was published online March 25 in the *BMJ*.

FDA Approves MS Drug Ozanimod

Ozanimod, an oral sphingosine-1-phosphate (S1P) receptor modulator, has been approved by the Food and Drug Administration (FDA) to treat relapsing multiple sclerosis (MS), including clinically isolated syndrome.

The approval has come 2 years after the FDA rejected the drug's original application, stating that the drug maker did not provide enough pharmacology information.

Since the country is dealing with the unprecedented COVID-19 pandemic, commercialization of the drug has been postponed. (*Medpage Today*)

Success for Oral CKD-related Pruritus Agent in Phase II Trial

The investigational oral treatment difelikefalin was found to reduce pruritus in patients with chronic kidney disease (CKD) in a phase II trial.

In 269 patients with moderate-to-severe CKD, 1 mg of difelikefalin significantly reduced itching intensity in comparison with placebo as measured by the daily 24-hour Worst Itching Intensity Numeric Rating scale (-4.4 vs. -3.3 placebo), reported researchers in a late-breaking abstract presented at the National Kidney Foundation's virtual Spring Clinical Meeting 2020… (*Medpage Today*)

Autism Prevalence Shows Rise in Communities Monitored by CDC

One in 54 8-year-old children have been identified with autism, reveals an analysis of 2016 data published in CDC's *Morbidity and Mortality Weekly Report (MMWR)* Surveillance Summary.

This is higher than the previous estimate an 1 in 59 prevalence among 8-year-old from 2014 data. The data involve 11 US communities in CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network. The new data also reveal that an increasing number of children are being assessed and identified with autism at younger ages… (*CDC*)

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Understanding Who We are...

KK AGGARWAL

The classical description of 'who we are' comes from Adi Shankaracharya's Bhaja Govindam, where he says that even the wife refuses to touch the same physical body after death, and if she touches it, a ritual bath has to be taken. This means physical body is not what we are.

If we weigh physical body before and after death there will be no difference. The life force, also called consciousness or atman, has no weight, shape or dimensions.

In Bhagavad Gita, in Chapter 2, Krishna describes its characteristics as "fire cannot burn it, air cannot dry it, weapons cannot cut it and water cannot wet it. It is omnipotent, omnipresent and omniscient."

Though modern medicine may not talk about soul but it does differentiate life and death based on certain parameters.

Vedic description describes five different movement forces in the body: Apana vayu expulses urine, stool, baby and menses; Samana vayu controls the intestinal movements; Vyana vayu controls the circulatory system; Udana vayu controls the neurological impulses and the connection between soul and spirit and Prana vayu controls the brain stem reflexes.

Soul or consciousness is linked to udana vayu and prana vayu. The best description of these five forces apart from Ayurveda text comes from Prasannopanishad.

A patient with brainstem death can be kept on ventilator for months together, as the body has normal vyana vayu, samana vayu and apana vayu. The patient will therefore, maintain blood pressure, gastrointestinal (GI) functions, urinary functions and reproductive functions. These three vayus are controlled by the atmospheric oxygen and not by the life force.

Can anyone remember the weight, height, abdominal circumference or size of collar, waist or shoes of Lord Krishna? He is only known from his actions and the soul profile.

Group Editor-in-Chief, IJCP Group

All of us have physical, mental, intellectual, ego and soul characteristics. Soul characteristics are same in all and are positive. The examples are love, compassion, care, humility, etc. These soul characteristics are influenced by the subtle mind, intellect and ego characteristics.

While introducing ourselves, most of the times we talk about our intellectual or ego profile and not the soul profile. When we describe our status, house, car or money, we are describing our ego profile and not the soul profile. Our aim in life should be to understand our soul profile, as without the soul, nobody will come near us. The very same people will dispose of our body at the earliest opportunity they get.

Most of us correlate life span with the life span of the physical body, which has to perish sooner or later. When we ask people how long they want to live, their usual answers are 60 years, 70 years, 80 years or 90 years. Nobody thinks beyond physical death. People like Mahatma Gandhi, Indira Gandhi and Mother Teresa are not dead. Though their physical body does not exist, their good karmas, work, memories and the soul profiles are still alive.

The purpose of life should be to create an atmosphere or an aura in such a way that the society remembers us after the death of our physical body. This is only possible when we shift our thinking from the ego profile to the soul profile.

Soul is nothing but an energized field of information and can be equated to the live information fed in any computer or mobile phone. Both computer and mobile phones with and without information weigh the same. Similarly, weight of radio does not change whether the radio is on or off. The live data information in the TV, radio or mobile phone can be termed as their soul. A computer without this soul is useless, so are the mobile and radio sets.

The information is always static and still without any movements. This information in a computer requires a software to run. The static soul in our body also requires a software called life force.

Soul, thus, can be described as a combination of the life force and the static information. In Hindu mythology, this is called Shiva and Shakti. Some people describe

them as prana and chitta. In Vedic philosophy, by controlling prana, one can control chitta and vice versa.

For a computer to operate, two softwares are required: operational software and application software. Operational software makes the computer do basic work and application software helps one to manipulate the data the way one wants.

All of us are born with the operational software or the life force. We develop and create our own application software over a period of time by using the triad of action, memory and desires.

To understand oneself, therefore, one needs to control our own application software and do not let it go beyond its desired scope of work.

■■■■

Bacteria in Parts of the Body may be Associated with Type 2 Diabetes

A clear difference has been found in the bacterial signature between individuals with diabetes and those without.

The greatest amount of bacteria was reported in the liver and fatty material connecting the stomach and the colon. It is suspected that the bacteria found in the tissue of people with diabetes came from their intestines… (*Medical News Today*)

Brain Cell that Triggers Tremor Discovered while Working with Experimental Models

The researchers have discovered that Purkinje cell, a type of brain cell, triggers tremor when its pattern of signaling to other neurons changes from a regular pattern to signaling in bursts.

The findings of this study published in the journal *eLife* showed that the tremor stopped when the experimental models were treated with deep-brain stimulation directed at a group of cerebellar neurons that communicate with Purkinje cells.

Lack of Walking, a Major Contributor to Premature Death in Osteoarthritis Patients

Researchers have revealed that people with osteoarthritis are at 11% greater risk of premature death compared to their healthy counterparts. A major contributing factor to this is lack of regular walking.

Other underlying factors that were identified were unrefreshed sleep and depression and anxiety.

However, the difference was too small to be clinically relevant. Thus, it is suggested that clinicians should prioritize keeping people with osteoarthritis active to lower their risk of death… (*Medical News Today*)

Multi-tissue Model Developed to Study the Relationships Between Different Organs and the Immune System

A multi-tissue model has been created by biological engineers to study the relationships between different organs and the immune system on a microfluidic chip seeded with human cells.

Using this "organs-on-a-chip", also known as "physiome-on-a-chip" model, the role of immune cells in ulcerative colitis and other inflammatory diseases could be explored, suggests a study published in the journal *Cell Systems*.

High-pitched Sounds can be Reduced, Propose Physicists

Materials made up of tapered chains of spherical beads could help in dampening sounds that lie at the upper range of human hearing or just beyond it.

The best set-up found by the theoretical physicists consisted of tapered chains of beads made from a metal called tungsten carbide, alternating with tapered chains of beads made from a plastic called Delrin. The material is yet to be tested in the laboratory… (*Science Daily*)

The Talking Bird

A fellow lived alone and went to a pet store to buy a parrot. He thought the bird might keep him company in his lonely hours. However, the very next day, he went back to complain that the bird didn't talk.

The store owner asked if he had a mirror in its cage, and the man replied that he didn't. The store owner said that parrots love mirrors. When he will see his reflection in the mirror, he'll start talking. So, he sold him a birdcage mirror.

The bird owner came back the next day to complain that the parrot still hadn't said a word. "That's peculiar", said the pet expert. He suggested that the bird owner should have a swing as birds really love little swings, and a happy parrot is a talkative parrot. So, the man bought a swing and installed it in the cage.

However, he was back the next day with the same complaint. The salesman asked whether he has a ladder in the cage. He suggested that once he has a ladder, he'll probably start talking. So, the man bought a ladder.

The man went back at the pet store the next day. The owner knew something was wrong and immediately asked, "Didn't your parrot like the ladder?" The bird owner said, "The parrot died".

"I'm so sorry", the store owner said. "Did he say anything?"

"Well, yes. He finally talked just before he died. In a weak little voice, he asked me, "Don't they sell any bird seed at that pet store?"

Some of us mistakenly believe that happiness lies in lining our cages with toys, gadgets, and other expensive stuff. Excessive consumption has become the hallmark of our life. Whoever has the most toys wins seems to be the rule. But is it actually so?

The spiritual hunger in the human heart that can't be satisfied by seeing one's own image reflected back in vanity mirrors, playing with our grown-up toys or climbing the corporate ladder. Our hearts yearn for real nourishment. The love of family and friends, relationships over the pursuit of more things, personal integrity, a secure connection to God are the things that feed the soul.

■■■■

C-reactive Protein Shows Nonsignificant Rise

COVID-19 increases C-reactive protein (CRP). This seems to follow with disease severity and prognosis. In patients with severe respiratory failure with a normal CRP level, an alternative diagnosis should be sought.

[*Source: International Pulmonologist's Consensus on COVID-19: Dr Tinku Joseph (India), Dr Mohammed Ashkan Moslehi (Iran)*]

Social Distancing cannot be Intermittent

A new study by the Harvard School of Public Health researchers has suggested that staggered intervals of social distancing could save more lives than the one-time social distancing guidelines as currently issued by the United States government. Federal authorities have extended the advisory, which was issued March 16, until April 30. The team proposed practicing intermittent social distancing, wherein distancing is enforced when cases rise above a set threshold and then measures can be alleviated when cases drop below a set threshold.

Digital Mass Surveillance does not Help

Most of us have a smart watch of some kind. It has already been shown that the heart rate from that data can help identify a flu outbreak before it actually happens. There is a report on just using body temperature with a smart thermometer. With digital tracking at scale, it could be possible to detect the outbreak before it happens, because if we get it at the earliest possible time, precise isolation can be done and we can prevent exponential growth in the community.

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Indian Journal of Clinical Practice, Vol. 30, No.11, April 2020

Lighter Side of Medicine

HUMOR

DREAM OF A NECKLACE

After she woke up, a woman told her husband, "I just dreamed that you gave me a pearl necklace for our anniversary. What do you think it means?"

"You'll know tonight", he said.

That evening, the man came home with a small package and gave it to his wife.

Delighted, she opened it to find a book entitled "The Meaning of Dreams."

THINK ABOUT ME

Think big, Think smart,

Think positive, Think beautiful,

Think great, I know this is too much for you, so here is a shortcut.

Just think about ME…

FOR CRYING OUT LOUD

With all the new technology regarding fertility, an 88-year-old woman was able to give birth to a baby recently. When she was discharged from the hospital and went home, various relatives came to visit. "May we see the new baby?" one of them asked. "Not yet," said the mother. "I'll make coffee and we can visit for a while first."

Another half-hour passed before another relative asked, "May we see the new baby now?"

"No, not yet," said the mother. A while later and again the guests asked, "May we see the baby now?"

"No, not yet," replied the mother.

Growing impatient, they asked, "Well, when can we see the baby?"

"When it cries!" she told them.

"When it cries?" they gasped. "Why do we have to wait until it cries?"

"Because, I forgot where I put it."

NEW DISEASE

A recent college graduate took a new job in a hilly city and began commuting each day to work through a tiring array of tunnels, bridges and traffic jams. Thinking it would make the trip more bearable, he invited several coworkers to share the ride. However, the commute actually got more stressful, especially the trips through the tunnels. He consulted the company doctor.

"Doc", the frustrated commuter complained, "I'm fine on the bridges, in the traffic, in the day and at night, and even when Joe forgets to bathe all week. But now, when I get in the tunnels with those four other guys crowded into the car, I get anxious and dizzy, and I feel like I'm going to explode."

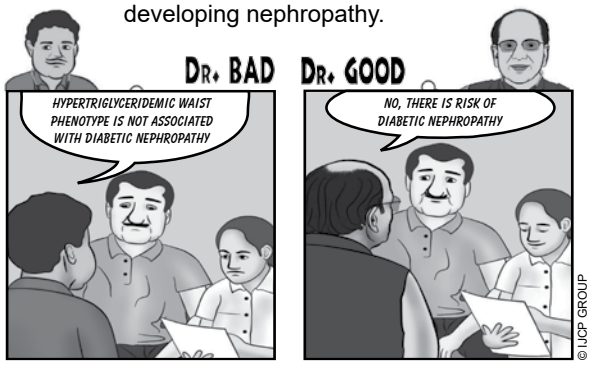
Without further analysis, the doctor announced he had diagnosed the ailment. "What is it, Doc? Am I going insane?"

"No, no, no, my boy. You have something that is becoming more and more common." "Tell me! What is it?"

"You have what is known as Carpool tunnel syndrome."

Dr. Good and Dr. Bad

SITUATION: A man with type 2 diabetes who had hypertriglyceridemic waist phenotype marked by serum triglyceride concentrations as 195 mg/dL and waist circumference as 94 cm was informed to be at risk of developing nephropathy.



LESSON: A cross-sectional study has shown a significant link between hypertriglyceridemic waist phenotype and early diabetic nephropathy in individuals with type 2 diabetes.

Cardiorenal Med. 2017;7(4):295-300.

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

Books

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

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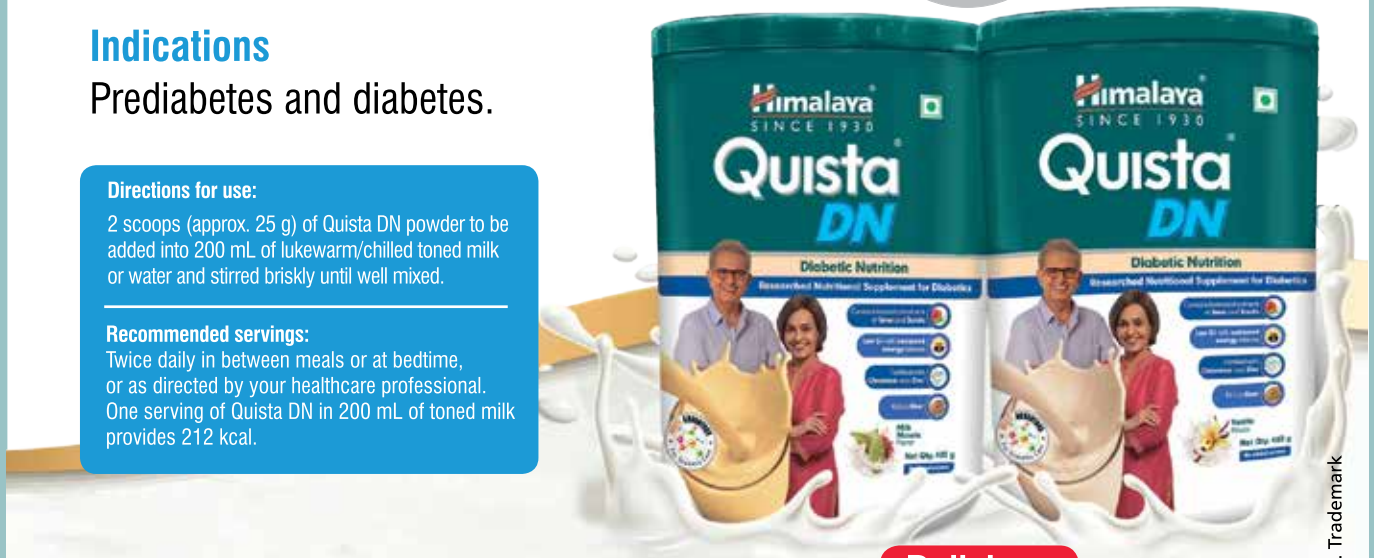

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