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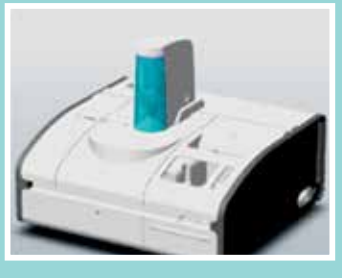

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CASE REPORT

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CMAAO IMA Consensus Statement on Protocol Recommended by CMAAO-IMA to Reduce Mortality among Healthcare Workers in Asian Countries with Special Focus on Resource-limited Countries

COVID-19: DEFINITION

Acute manageable immunogenic thrombogenic inflammatory notifiable viral disease.

PREVENTION

- All healthcare professionals (HCPs) (caregivers) while on duty (clinical and non-clinical areas) should wear N95/FF2P/surgical 3-layered mask (correct and consistent use). Transmission risk is <0.5% with N95 mask (*Y Qian, et al. Performance of N95 respirators: filtration efficiency for airborne microbial and inert particles. Am Ind Hyg Assoc J. 1998;59(2):128-32*).
- Consider wearing a surgical mask over N95 in OPDs (change the surgical mask after every patient examination).
- Hand washing to be done as per World Health Organization (WHO) protocol (*Hand hygiene: why, how & when? Revised August 2009. https://www.who.int/gpsc/5may/Hand_Hygiene_Why_How_and_When_Brochure.pdf*).
- In India, healthcare workers (HCWs) (caregivers) in practice may consider the Indian Council of Medical Research (ICMR) recommendation and take hydroxychloroquine (HCQ) 400 mg/week, if not contraindicated (*Revised advisory on the use of hydroxychloroquine (HCQ) as prophylaxis for SARS-CoV-2 infection, ICMR, 22/05/2020*). This may change from country/state to country/state or as per WHO.
- If HCQ is contraindicated or by choice, consider ivermectin 12 mg once a week (UP protocol 1, 7, 30 days and then once a month) (*Vora A, et al. White paper on Ivermectin as a potential therapy for COVID-19. Indian J Tuberc. 2020;67(3):448-51*). This may change from country/state to country/state or as per WHO.
- Physical distancing at least 3 ft × 3 ft (6 ft × 6 ft preferable); if not possible, add extra protection (double masking, gloving, personal protective equipment (PPE) kit, oral disinfectant gargles with povidone-iodine or benzydamine) (*Chu DK, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020;395(10242):1973-87. Anderson DE, et al. Povidone-iodine demonstrates rapid in vitro virucidal activity against SARS-CoV-2, the virus causing COVID-19 disease. Infect Dis Ther. 2020:1-7. Turnbull RS. Benzydamine hydrochloride (Tantum) in the management of oral inflammatory conditions. J Can Dent Assoc. 1995;61(2):127-34*).
- PPE kit (appropriate, without breach, proper doffing and donning): In poorly ventilated clinics/OPDs,

consider wearing shirt/trousers made of 30 GSM laminated non-woven material with a white coat also made of the same material (*Kilinc FS. A review of isolation gowns in healthcare: fabric and gown properties. J Eng Fiber Fabr. 2015;10(3):180-90*). GSM is our recommendation.

- Proper disposal of PPE kits, including masks, as per national or state pollution control guidelines.
- Proper environmental cleaning and disinfection, including engineering controls of common areas as per national guidelines.
- Regular updated orientation and training of HCWs on prevention methods.
- Consider zero power eye glasses for protection (*Maragakis LL. Eye protection and the risk of coronavirus disease 2019: does wearing eye protection mitigate risk in public, non-health care settings? JAMA Ophthalmol. 2020 Sep 16*). Glasses provide partial barrier.
- Consider shoe covers in OPD areas (patients, relations and HCWs) (*National Guidelines for Infection Prevention and Control in Healthcare Facilities, NCDC, DGHS, MOHW, January 2020*).
- In OPD areas, consider screening for loss of taste and smell/fever/SpO_2/hand grip before entry.
- Take patient history on phone; only quick examination to be done in face-to-face meeting and follow-up with telephonic counseling. Try to finish the face-to-face consultation in less than 15 minutes.
- Every patient and their relations visiting the clinic should be considered positive unless tested negative.
- Patients and relatives (caregivers) should wear medical (surgical 3-layered) mask and not fabric mask (*WHO Advice on the use of masks in the context of COVID-19 Interim guidance, 5 June 2020*).
- Add extra protection in the form of oral povidone-iodine (>0.5%) gargles and nasal spray, particularly for ENT, oral, dental and eye examinations (*Anderson DE, et al. Povidone-iodine demonstrates rapid in vitro virucidal activity against SARS-CoV-2, the virus causing COVID-19 disease. Infect Dis Ther. 2020:1-7. Pattanshetty S, et al. Povidone-iodine gargle as a prophylactic intervention to interrupt the transmission of SARS-CoV-2. Oral Dis. 2020;10*).
- Add high speed suction and extraoral suction for dental procedures/oral cavity examination.
- Consider plasma and air purifiers for clinics if proper ventilation or AC ventilation is not possible (Also called portable air cleaners) (*ISHRAE COVID-19 Guidance Document for Air Conditioning and Ventilation, April 13, 2020. https://ishrae.in/mailer/ISHRAE_COVID-19_Guidelines.pdf; EPA Air cleaners, HVAC filters, and coronavirus (COVID-19). https://www.epa.gov/coronavirus/air-cleaners-hvac-filters-and-coronavirus-covid-19*).
- Make sure that the clinic has a well-ventilated common toilet with working exhaust (with filter if possible) fan (*ISHRAE COVID-19 Guidance Document for Air Conditioning and Ventilation, April 13, 2020. https://ishrae.in/mailer/ISHRAE_COVID-19_Guidelines.pdf*).
- All HCWs should be up-to-date with their adult vaccination as recommended (*Summary of WHO Position Papers – Immunization of Health Care Workers, Updated September 2020*).
- No eatables should be allowed in the clinic.
- Do baseline C-reactive protein (CRP), complete blood count (CBC), erythrocyte sedimentation rate (ESR), A1c (if diabetic), blood group (if not known), thyroid-stimulating hormone or TSH (if known hypo- or hyperthyroid), 6-minute walk distance and saturation.
- Treat deficiencies of vitamins and minerals, if any: Vitamin D (2,000 IU daily); zinc (>50 mg daily), vitamin C (500 mg daily), B12, if vegetarian or known deficiency.
- Get minimum of 7-8 hours sleep per night.

PRECAUTIONS THAT HCWs SHOULD TAKE AT HOME TO PROTECT THEIR FAMILY FROM EXPOSURE TO COVID-19

- Wash all clothes in hot water using a disinfectant immediately after returning home or separate them.
- Full head bath should be taken and change into clean clothes.
- At the entry, remove shoes.

(*Berg S. How doctors can keep their families safe after providing COVID-19 care. April 8, 2020. https://www.ama-assn.org/practice-management/physician-health/how-doctors-can-keep-their-families-safe-after-providing-covid; Nelson K. Protect your family from coronavirus. April 17, 2020. https://healthfocussa.net/infections/protect-your-family-from-coronavirus/*).

DUTY HOURS

- 7/7/7 days is the standard recommendation.

- In clinics, working hours can be up to 4 hours daily ± 1-2 hours (preferably day light hours); evening clinic can be conducted *via* teleconsultation.

DIAGNOSIS

- Antibody test can be done once a month to check for exposure.
- Pooled RT-PCR (reverse transcription polymerase chain reaction) of staff can be done every week (5 samples can be tested at a time) (*ICMR Advisory on feasibility of using pooled samples for molecular testing of Covid-19. https://www.mohfw.gov.in/pdf/letterregguidanceonpoolingsamplesfortesting001.pdf*).
- RT-PCR is preferred over rapid antigen test at present (till other sensitive tests are available); ask for Ct (cycle threshold) values as doctors generally have a high viral load due to repeated exposures **(***Interim guidance for rapid antigen testing for SARS-CoV-2, updated Sept. 4, 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html; Chang MC, et al. Interpreting the COVID-19 test results: a guide for physiatrists. Am J Phys Med Rehabil. 2020;99(7):583-5*).
- Rule out existing disease as prevalent in respective countries.

TREATMENT

- Once diagnosed or suspected, on Day 1, do baseline (minimum) tests: quantitative CRP, CBC, blood sugar, ESR, 6-minute walk test (6MWT) (May add ferritin, D-dimer, interleukin [IL]-6, tumor necrosis factor [TNF]-α, lactate dehydrogenase [LDH], red cell distribution width [RDW], fibrinogen levels to decide about clinical severity).
- On Day 1, consider starting azithromycin/doxycycline, ivermectin, vitamins, melatonin, favipiravir, famotidine.
- In HCWs or high risk individuals with baseline CRP >1 mg/L, start blood thinner (dabigatran 110 mg BD or rivaroxaban 10 mg OD or abciximab 2.5 mg BID or enoxaparin SC, if hospitalized). Aspirin may not be helpful in high viral load.
- If high risk with comorbid condition, start low-dose steroids on Day 3 (if there is evidence of pneumonia as evident by fever >101°, CRP >10 mg/L, cough starting on Day 3 or fall in SpO_2 saturation by 4% or CT proven).
- Do 6MWT and CRP daily on Days 1-5.
- Treat fever with mefenamic acid if not contraindicated (*Pareek RP. Use of mefenamic acid as a supportive treatment of COVID-19: a repurposing drug. IJSR. 2020;9(6):69*). Indomethacin/naproxen are other options.
- Consider HRCT chest in HCWs on Day 3 of the illness (*Ai T, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020;200642*).
- Loss of smell and/or taste are indicative of mild illness (*Sudden loss of taste and smell should be part of COVID-19 screen - Medscape - Apr 21, 2020; Boscolo-Rizzo P, et al. Evolution of altered sense of smell or taste in patients with mildly symptomatic COVID-19. JAMA Otolaryngol Head Neck Surg. 2020;146(8):729-32*).
- Small intestinal diarrhea without pneumonia suggests mild disease (*Chaoqun Han, et al. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol. 2020;115(6):916-23*).
- Infection in less than 12 years is mild; in over 12 years, treat as adults.
- Look out for probable re-hospitalization between 14 and 28 days.
- Continue anticoagulant for at least 28 days.
- HCWs with confirmed infection may be allowed 28 days off from work (Coronavirus disease [COVID] and post-COVID sickness).
- Watch for symptoms from 14-28 days; start treatment with anti-inflammatory drug, if CRP >10 mg/L.
- Quit smoking. Quit alcohol or reduce to permissible limits.
- If symptomatic tachycardia, look for low TSH (with low T3), fall of hemoglobin (decline of 1 g), autonomic dysfunction, high CRP, inappropriate sinus tachycardia or underlying heart disease.
- If inappropriate sinus tachycardia, consider ivabradine (*Achike O, et al. Ivabradine and inappropriate sinus tachycardia: a funny target for an inappropriate disease. JACC. 2018;71(11):2606*).
- Do not miss myocardial infarction or cerebrovascular accident (CVA) as the first presentation. (*Siddamreddy S, et al. Corona virus disease 2019 (COVID-19) presenting as acute ST elevation myocardial infarction. Cureus. 2020;12(4):e7782. Avula A, et al. COVID-19 presenting as stroke. Brain Behav Immun. 2020;87:115-9*).

- Do not miss COVID cystitis (pus cells with culture negative and no bacteria).
- High CRP can cause sudden reduction of low-density lipoprotein (LDL); be on the alert.
- Consider high-dose statin for low-grade inflammation (CRP 1-3 mg% and high LDL >80 mg%).
- On Day 0, if CRP is 1-3 mg/L and LDL is high, there is high risk of atherosclerosis.
- Most antenatal cases (50%) will be asymptomatic (*Allotey J, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320*).
- Consider preoperative RT-PCR in elective surgeries (*Somashekhar SP, et al. ASI's Consensus Guidelines: ABCs of What to Do and What Not During the COVID-19 Pandemic. Indian J Surg. 2020:1-11*) along with pooled RT-PCR of family.
- Isolation, quarantine and monitoring: You should isolate, quarantine and all family members and close contacts should monitor themselves.

KEY POINTS

- The virus is nonreplicating after Day 9 (*Cevik M, et al. SARS-CoV-2, SARS-CoV-1 and MERS-CoV viral load dynamics, duration of viral shedding and infectiousness: a living systematic review and meta-analysis, MedRxiv. Posted July 29, 2020*).
- RT-PCR may be positive up to 90 days, but Ct value should increase (*Uptodate*).
- If RT-PCR is positive for >3 months or becomes positive after 2 consecutive negatives, consider possible reinfection (*Gupta V, et al. Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. Clin Infect Dis. 2020 Sep 23;ciaa1451*).
- Fever >101^{0}F, CRP >10 mg/L, rapid rise of CRP, cough on Day 3 or fall of SpO_2 on 6MWT by 4% are suggestive of pneumonia.

RED FLAGS

- Fever >101°F with drugs or >103^{0}F without antipyretics.
- Persistent cough starting after Day 3.
- Sudden onset of shortness of breath (or exertional SOB).
- Rapid rise in CRP (>10 mg/L).
- More than 50% lung involvement on CT (13/25 score).

HOME CARE

- If you need up to 2 liters of oxygen.
- For first 1-7 days: add montelukast + famotidine/ranitidine: give levocetirizine if allergic component is high.
- Consider colchicine 500 mcg twice daily during and post-COVID persistent inflammation.
- Consider HCQs in post-COVID inflammation as it is steroid-sparing.
- BCG and MMR based on personal preferences and evidences.

10 SUTRAS TO REMEMBER

1. Universal masking (correct, consistent and 3-layered) is THE prevention (*J Gen Intern Med. 2020;1-4*).
2. RT-PCR Ct is gold standard THE test for diagnosis (*J Clin Microbiol. 2020;58(6):e00512-20*).
3. Zinc is THE mineral (*Front Immunol. 2020;11:1712*); D is THE vitamin (*PLoS One. 2020;15(9):e0239799*).
4. Day 5 is THE day in COVID phase (*Lancet. 2020;395(10229):1054-62*).
5. Day 90 is THE day after which the word COVID ends (*CDC Duration of isolation and precautions for adults with COVID-19. Updated Sept. 10, 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html*).
6. Home isolation is THE modality of treatment (*Int J Surg. 2020;77:206-16*).
7. Twelve years is THE age when the mortality starts (*Annex: Advice on the use of masks for children in the community in the context of Covid-19, Aug 21, 2020, WHO UNICEF*).
8. CRP is THE lab test for seriousness (*BMJ. 2020;370:m3339*).
9. Loss of smell and taste are THE symptoms equal to RT-PCR test (*ORL J Otorhinolaryngol Relat Spec. 2020;82(4):175-80*).
10. Fifteen minutes is THE contact time to get the infection (*CDC Contact Tracing for COVID-19*).

(Inputs: Round Table HCFI, CMAAO Weekly Meeting, IMA)

With input from Dr Monica Vasudev

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Types and Classification of Nerve Injury: A Review

R JAYASRI KRUPAA*, KMK MASTHAN†, ARAVINTHA BABU N‡, SONA B#

ABSTRACT

Nerve injuries are the most common conditions with varying symptoms, depending on the severity, intensity and nerves involved. Though much information is available on the mechanisms of injury and regeneration, reliable treatments that ensure full functional recovery are limited. The type of nerve injury alters the treatment and prognosis. This review article aims to summarize the various types of nerve injuries and their classification.

Keywords: Axonotmesis, neurotmesis, neurapraxia, Wallerian degeneration

Nerve injuries are the most common conditions with varying symptoms depending on the severity, intensity and nerves involved. Recovery after any nerve injury is variable. Though much information exists on the mechanisms of injury and regeneration, reliable treatments that ensure full functional recovery are limited. The type of nerve injury alters the treatment and prognosis. This review article aims to summarize the various types of nerve injuries and classification of nerve injuries, which is useful in understanding their pathological basis, and to evaluate the prognosis for recovery.

Understanding the basic nerve anatomy is important for the classification and also essential to evaluate the clinical prognostic value. In the central nervous system (CNS) and peripheral nervous system (PNS), there are three connective tissue layers:

- *Endoneurium:* Individual nerve fibers (single axons) are covered with varying amounts of myelin and then covered by endoneurium.
- *Perineurium:* These individually wrapped nerve fibers (endoneurium) are then grouped into bundles of fibers called fascicles, which are covered by perineurium.
- *Epineurium:* Finally, groups of fascicles are bundled together to form the peripheral nerve (such as the median nerve), which is covered by epineurium.

CLASSIFICATION

Classification by Type of Nerve Injury

There are three types of nerve injuries:

Nerve section

Nerve section can be partial or complete, sharp or blunt. They are often caused by sharp wounds by glass, firearms or knives.

Nerve strecthing

Stretching can occur in association with displaced fractures. During traction, the perineurium is elongated, the axons and epineurium stretch and tear.

Nerve compression

Compression can either be extrinsic or intrinsic. Extrinsic is more common in median nerve injury in the carpal tunnel and ulnar nerve at the elbow. Intrinsic compression is usually caused by the nerve tumor.

There are two mechanisms of peripheral nerve injury resulting from compression:

- *Indirect mechanism:* Acute or repeated prolonged compression may cause vascular stasis with increased vascular permeability and formation of endoneurial edema.
- *Direct mechanism:* A direct mechanical damage to the myelin sheath or the axon itself, thus restricting nerve conduction.

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Anatomical Nerve Injury

There are two main types of nerve injuries based on the part involved and classified based on correlation with the electromyography (EMG) finding:

- Seddon's classification
- Sunderland's classification.

Seddon's classification

Seddon provided a basis for assessment, prognosis and management of nerve injury. He classified nerve injuries into three categories - neurapraxia, axonotmesis and neurotmesis.

Neurapraxia

It is the least severe nerve injury, caused by transient compression or stretch. Conduction block results in loss of nerve function. Paralysis of muscles innervated by the nerve is complete. This type of injury will recover completely provided the cause, for example, ongoing compression, is removed. Recovery will take hours to months (average 6-8 weeks).

Axonotmesis

This is an anatomical interruption of the axon with no or only partial interruption of the connective tissue (endoneurium, perineurium and epineurium). This type of nerve injury requires regeneration of about 1.5-3 mm/day of the axon to the target muscle which is inhibited by scar formation. Wallerian degeneration occurs due to loss of axoplasmic flow. Patients with axonotmesis will require surgical treatment depending on the number of axons disrupted and the extent of scar formation at the site of nerve injury. Axons grow in adults at about 1 inch per month, and the recovery may take weeks to months. In infants, the axon may regenerate more rapidly, and the distance to be covered is much less. When a muscle loses its innervation, the nerve receptors will disappear over a period of 1-2 years. This may require neurosurgical intervention because a repair regenerated too late will not have receptors in the muscles for the regeneration of nerves.

Neurotmesis

Here, the nerve is completely disrupted or badly disorganized. This is the most severe form of nerve injury. Along with axons, all the connective tissue layers of the nerve are disrupted. There is axon degeneration distal to the injury. Neurotmesis may be caused by laceration or high energy traction injuries. Ischemia or injection of noxious drugs can also cause nerve injury. Recovery can only occur after appropriate surgical repair of the nerve and relies on axonal regeneration. Mixing and disruption of fibers at the site of the repair result in failure of correct distal connections. So, the recovery is either imperfect or incomplete.

Limitations of Seddon's classification

All grades of intraneural damage are not distinguished with Seddon's classification. Lesions classified as axonotmesis have been observed to have variable recovery. This could occur because variable degrees of damage to the connective tissue layers of the nerve, including the endoneurium and perineurium and disruption of axons are possible without loss of continuity of the nerve trunk.

Sunderland's classification

Sunderland, in 1951, described 5 degrees of nerve injury based on the disruption of the nerve and their continuity with the connective tissue. Mackinnon and Dellon added a 6th degree injury to Sunderland's classification where there was variable degrees of nerve injury.

- 1st degree - conduction block (neurapraxia).
- 2nd degree - axonal injury (axonotmesis).
- 3rd degree - axonal injury with endoneurium injury.
- 4th degree - axonal injury with endoneurium injury and perineurium injury.
- 5th degree - axonal injury with endoneurium injury, perineurium injury and neurapraxia.
- 6th degree - combination of previous injuries.

Table 1 summarizes the correlation between Sunderland and Seddon classifications and intact connective tissue.

DISCUSSION

If there is a trauma and signs of a nerve injury then surgery will be necessary to look at the nerve and if there, whether it has been partly or completely disrupted. If there is no wound, then it is likely that a "wait and watch" policy will be adopted. Under these circumstances, further investigations may be carried out to try and assess the damage to the nerve. There are various investigation methods to diagnose the degree of nerve injury; this is done using neurophysiology testing where the nerves are stimulated with an electric current and the speed at which the nerve conducts is measured (electromyography). Neurophysiology tests can distinguish between injuries where axons have not degenerated (neurapraxia) and those where axons have degenerated distally (axonotmesis and

Table 1. Correlation Between Sunderland and Seddon Classifications and Intact Connective Tissue

Sunderland's	Seddon's	Axon	Endoneurium	Perineurium	Epineurium	Fibrillation potential on EMG	Clinical sign	Recovery
1st degree	Neurapraxia	+	+	+	+	Absent	Paresthesia, partial or total palsy	Full (1 day to 3 months)
2nd degree	Axonotmesis	–	+	+	+	Present	Paresthesia, partial or total palsy	Generally full (1-6 months)
3rd degree	Axonotmesis	–	–	+	+	Present	Paresthesia, dysesthesia, partial or total palsy	Partial (12-24 months)
4th degree	Axonotmesis	–	–	–	+	Present	Hypoesthesia, dysesthesia, total palsy	None without repair
5th degree	Neurotmesis	–	–	–	–	Present	Anesthesia, total palsy	None without repair
6th degree	Combination of prevoius injury	–	–	–	–	Present	Paresthesia, partial or total palsy	None without repair

'+' = Intact nerve; '–' = Injured nerve (not intact).

neurotmesis). If axonotmesis has affected all the fibers in a nerve, then the findings will be indistinguishable neurotmesis. However, in mixed lesion, with some fibers intact, detection of these will imply that there is no disruption of the nerve trunk. In addition, very fine needles may be inserted into an affected muscle and recordings made of the activity in that muscle. Normal nerves can be visualized on magnetic resonance imaging (MRI), although their signal characteristics are not distinct from other tissues. A technique called magnetic resonance neurography, which enhances neural tissue on images, was reported by Filler. Modern ultrasound scanners have improved to the extent that resolution is now greater than MRI. Ultrasound is being used increasingly to examine nerves damaged by closed trauma. These will help to grade the level of injury and can help in treatment planning and giving information on the potential outcome of the injury.

CONCLUSION

The result of a nerve injury depends on many variables, as detailed in this article. The important thing to remember is that nerves take many months to years to repair and recover. The final result may not be known for 2 years or more. The purpose of this article is to outline the main types, classification and correlating the nerve injuries to evaluate their clinical value and to improve the prognosis of nerve recovery.

SUGGESTED READING

1. Kouyoumdjian JA. Peripheral nerve injuries: a retrospective survey of 456 cases. Muscle Nerve. 2006;34(6):785-8.
2. Alant JD, Kemp SW, Khu KJ, Kumar R, Webb AA, Midha R. Traumatic neuroma in continuity injury model in rodents. J Neurotrauma. 2012;29(8):1691-703.
3. Sunderland S. The nerve lesion in the carpal tunnel syndrome. J Neurol Neurosurg Psychiatry. 1976;39(7):615-26.
4. Seddon HJ. A classification of nerve injuries. Br Med J. 1942;2(4260):237-9.
5. Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain. 1951;74(4):491-516.
6. Mackinnon SE, Dellon AL (Eds.). Classification fo nerve injuries as the basis of treatment (Chap. 2). Surgery of the Peripheral Nerve. New York: Thieme Medical Publisher; 1988. pp. 35-63.
7. Losher W, Bischoff C. Basics in clinical neurophysiology: Nerve conduction studies and needle electromyography in nerve entrapment syndromes. In: Handchirurgie Weltweit e V (Ed.). Living Textbook of Hand Surgery. Version 2016-04-28. Cologne; 2014. Available at: http://www.gms-books.de/book/living-textbook-hand-surgery/chapter/basics-clinical-neurophysiology-nerve-conduction-studies-0.
8. Filler AG, Kliot M, Howe FA, Hayes CE, Saunders DE, Goodkin R, et al. Application of magnetic resonance neurography in the evaluation of patients with peripheral nerve pathology. J Neurosurg. 1996;85(2):299-309.
9. Bodner G, Buchberger W, Schocke M, Bale R, Huber B, Harpf C, et al. Radial nerve palsy associated with humeral shaft fracture: Evaluation with US – Initial experience. Radiology. 2001;219(3):811-6.

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Ivermectin – A Potent Weapon in the Anti-COVID-19 Armamentarium

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has become an earth-shattering menace afflicting the entire globe. With no effective antiviral drugs in sight, the repurposing of many currently available drugs has been considered the mainstay of treatment. One such drug is ivermectin (IVM), a Food and Drug Administration (FDA)-approved antiparasitic agent that has been shown to exhibit antiviral activity against a broad range of viruses. Ivermectin proposes many potential effects to treat a range of diseases, with its antimicrobial, antiviral and anticancer properties as a wonder drug. Several studies have reported antiviral effects of IVM on RNA viruses such as Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, porcine reproductive and respiratory syndrome, human immunodeficiency virus type 1 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Recent studies have suggested that IVM inhibits the replication of (SARS-CoV-2) *in vitro*, thus suggesting its potential for use against COVID-19. In this review, we describe the mechanism of action, rationale, dosing protocols of IVM in the management and prophylaxis of COVID-19 infection.

Keywords: SARS-CoV-2, antiviral drugs, ivermectin, treatment

Almost 9 months have passed in the search for the "Magic bullet" to kill the novel coronavirus since the first case was detected in Wuhan in late December 2019. The world has come to a standstill, with more than 35 million coronavirus positive cases and 1 million deaths (as on October 4, 2020). People are quickly losing patience and faith in our ability to find a cure. An effective vaccine is at least 6-9 months away. There is a ray of hope in the antiparasitic drug named Ivermectin (IVM).

This 4-decade-old drug is FDA-approved for many other parasitic infections. It has been extensively used in India, given as an oral tablet, once or twice a year, on Anti-Filaria Day, where it has been effective to control filariasis. Can this be replicated for coronavirus disease 2019 (COVID-19) too? For this "wonder drug", Satoshi Omura, a Japanese scientist who discovered it in 1970's and William Campbell who commercialized it in 1981, were awarded the Nobel Prize for Medicine in 2015.[1] In a recent paper by Caly et al, IVM inhibited the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *in vitro* and ~5000-fold reduction in viral RNA was observed at 48 hours.[2] A number of trials, studies and case reports have appeared in literature, covering the entire severity spectrum of COVID-19. During the viremic phase, it has the potential to convert reverse transcription polymerase chain reaction (RT-PCR) positive to negative quickly. In the symptomatic and pulmonary phase, it disrupts the viral propagation and improves survival. In the stage of complications, it has the potential to significantly decrease mortality by preventing clot formation and reversing happy hypoxia with higher IVM doses. Such encouraging results obtained with the use of IVM alone or in combination with other medications have appeared in literature. All in all, IVM decreases severity, duration and community spread of infection.

IVERMECTIN – A MULTIFACETED "WONDER" DRUG

Ivermectin – a drug derived from avermectin, has an extraordinary history. It is a semisynthetic analog of the

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natural product avermectin B1a, a lipophilic macrolide isolated from *Streptomyces avermitilis*. It was initially developed as insecticide for crop management and later used as an antihelminthic. William C Campbell and Satoshi Ōmura were awarded the Nobel Prize in Physiology or Medicine in 2015, for discovering avermectin, the derivatives of which have drastically lowered the incidence of river blindness and lymphatic filariasis. The plethora of evidence from publications on IVM has surprised us with new indications appearing ever so often, from antihelminthic to antibacterial to anticancer and now antiviral effects. It has been found to be effective against certain flavivirus (dengue fever, Japanese encephalitis and tick-borne encephalitis virus) and chikungunya. In a recent *in vitro* study by Caly and his team at Monash University's Biomedicine Discovery Institute (BDI) and the Peter Doherty Institute of Infection and Immunity, it was found that the exposure of Vero/hSLAM (human signalling lymphocyte-activation molecule) cells infected with the SARS-CoV-2 or COVID-19 virus, to 5 μM IVM, kills SARS-CoV-2 virus in the lab, with 93% reduction in viral RNA in 24 hours and 99.8% in 48 hours, i.e., a 5,000-fold reduction in viral RNA load (killing almost all the viruses). This indicated that IVM could form the basis of a COVID-19 treatment protocol, given that it has proven successful in *in vitro* tests against the viruses.[2] Ivermectin is an old molecule with proven safety. It is FDA-approved for treatment of parasitic infections. Ivermectin is widely available due to its inclusion on the World Health Organization (WHO) model list of essential medicines. It has been used in India in the mass drug administration program under the Ministry of Health and Family Welfare (MoHFW), for eradication of lymphatic filariasis.[3] Human studies will be required to test its efficacy against the coronavirus, which has a potential for repurposing.

IVERMECTIN – MECHANISM OF ACTION

The current COVID-19 pandemic is caused by SARS-CoV-2, a single-stranded positive sense RNA virus that is closely related to SARS-CoV of 2002. There are multiple avenues by which the drug is effective in SARS-CoV-2 infection:

Inhibition of Viral Replication

Ivermectin selectively inhibits host importin $\alpha/\beta1$ transporter protein which decreases translocation (shutting) of SARS-CoV nucleocapsid protein (NCP) from the cytoplasm to the nucleus. Altered NCP distribution disrupts viral propagation and survival. This is a vital step in viral pathogenesis and defense against host immune response.[2]

Blockade of the Entry of the Virus into the Host Cell

Ivermectin also attaches to a spike receptor binding domain attached to angiotensin-converting enzyme 2 (ACE2) receptor, preventing the entry of the virus into the host cell.[4]

Action as an Ionophore Molecule

Ivermectin binds to metal cations like zinc and forms lipid-soluble complexes that facilitate their transport across cellular membranes, and deregulate osmosis and direct cytotoxic effects killing the cell. This is achieved at concentrations that are easily reachable clinically.[5,6]

Prevention of Microvascular Thrombosis

Ivermectin normalizes the microvascular abnormalities by alleviation of CD147-mediated "catch and clump mechanism", which is responsible for silent hypoxia. The CD147 receptors on red blood cells (RBCs) are a key to adhesion for the SARS-CoV-2 virus, which gets blocked by IVM. This prevents microvascular thrombosis and alleviates intravascular clumping and agglutination. However, this process is dependent on the IVM concentration.[7]

Sequestration in the Pulmonary Tissue

Ivermectin has been found to selectively concentrate in the pulmonary tissue, around 3 times the plasma concentration and is sequestered in the pulmonary tissue with a long residence time.[8]

SYNERGISTIC EFFECT WITH OTHER ANTI-COVID DRUGS

Ivermectin can be used with other drugs with synergistic effect.

- Ivermectin-Doxycycline-Zinc triple drug therapy: The miraculous antiviral effect of IVM-zinc-doxycycline combination in COVID-19 patients is possibly due to the following actions:[9]
  - Inhibition of spike-ACE2 and thereby blocking the virus entry
  - Chelation of the zinc and immunomodulatory property
  - Inhibition of viral RNA replication within the host cell.

- Ivermectin and hydroxychloroquine (HCQ) combination therapy: It has also been hypothesized that combination therapy using HCQ and IVM may exert a synergistic inhibitory effect where both block ACE2 receptors,[10] whereas IVM further enhances the antiviral activity by inhibiting viral replication.[11]

DOSING AND PHARMACOKINETICS

Ivermectin has a wide therapeutic index and is widely used in humans for treatment of parasitic diseases at single or repeated doses. It has a proven safety profile when taken orally as a tablet. Recommended safe dose is 150-200 μg/kg body weight per day and a weight-based dosing chart is depicted in Table 1. The IVM dose and duration can be tailored to the severity of disease based on various clinical studies.

Despite the enterohepatic circulation, its effect is short-lived (6-11 days). Previous studies have shown doses up to 2,000 μg/kg (i.e., 10 times the US FDA approved dose) are well-tolerated and safe.[12] Ivermectin is extensively metabolized *in vitro* by liver microsomal cytochrome P450 3A4 to hydroxylated and demethylated metabolites. The mean half-life of IVM, when administered orally, ranges from about 15 to 20 hours. It is eliminated mainly in the feces, with minimal urinary excretion (≤1% of the administered dose). From past 25 years of experience, no resistance to this novel drug has been reported in humans for tropical diseases.[13] Bioavailability of IVM increases about 2.5 times when administered with a high fat meal.[14] Ivermectin should be taken at least 2 hours after the meal. Further, citrus juice, milk and alcohol should be avoided.[15]

ADVERSE REACTIONS

Ivermectin is generally well-tolerated. Adverse effects, which are mild and transient in nature, include diarrhea, muscle or joint pain, dizziness, fever, headache, fast heartbeat, skin rash and itching. A very serious allergic reaction to this drug is rare. Ivermectin should not be given to patients with chronic liver disease with cytochrome P450 disorder and seizure disorder.[16]

Table 1. A Weight-based Dosing Regimen for Ivermectin Use in COVID-19 Infection

Body weight	Dose
Below 2 years & <15 kg	Not allowed
15-30 kg	6 mg/day
31-60 kg	12 mg/day
61-90 kg	18 mg/day
>90 kg	24 mg/day

SPECIAL POPULATIONS[17]

Pregnancy

Ivermectin has not shown any teratogenic effect during pregnancy. There is; however, scarcity of adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Nursing Mothers

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who wish to breastfeed should be undertaken only when the risk of delayed treatment to the mother outweighs the possible risk to the neonates.

Pediatric Use

Safety and effectiveness in pediatric patients weighing less than 15 kg are not known.

Geriatric Use

Clinical studies of the drug did not include sufficient numbers of subjects aged 80 and above to determine if they respond differently from younger subjects. Other reported clinical experience has not shown differences in responses between the elderly and younger patients.

Miscellaneous

Need caution in prescribing IVM to patients with seizures and liver disease.

INDICATIONS IN COVID-19

It is indicated in a broad range of COVID patients, ranging from those who are asymptomatic, mildly symptomatic, to those with moderate-to-severe COVID-19 disease. Latest trial results show that it works very well in protecting close contacts and family members of COVID-positive patients. While waiting for an effective vaccine, it can be used as a prophylactic in healthcare workers and COVID warriors. It is to be mentioned here that more than 500 doctors have lost their lives in the war against COVID-19. It is a big loss for us, including medical fraternity, community and country at large. Understanding COVID-19 infection and its impact on health workers is crucial not only for

characterizing the transmission pattern of the virus but also as a means of prevention of the infection amongst the providers of healthcare who have a key role in saving the world from this pandemic.[18] Mass treatment with IVM is an underutilized public health strategy today.

PROPHYLAXIS

The suggested prophylaxis regimens with the drug are summarized below (Fig. 1):

- For contacts of COVID-19 positive patients: 200 μg/kg body weight per day doses on Day 1 and 7.
- COVID warriors, including healthcare workers: 200 μg/kg body weight per day doses on Day 1, 7, & 30 and monthly thereafter for 6 months.

IVERMECTIN FOR COVID-19 IN INDIA

A total of 10 trials are underway as listed in in the Clinical Trials Registry - India (CTRI), but recruitment of patients is very slow. Their results are awaited. Recently, a white paper has been published on IVM by Indian experts and this is a proud moment for us that the paper is reflected on WHO website.[19,20]

Uttar Pradesh Model[21]

The health department of the government of Uttar Pradesh issued an order to replace HCQ with IVM and doxycycline to treat:

- COVID-19 patients
- Close contacts
- As a prophylaxis for healthcare workers.

This drug should not be given to pregnant women and children below 2 years of age.

New Delhi's Lok Nayak Hospital has added IVM and remdesivir to the management protocol for COVID-19 patients.[22] The Tata Main Hospital, Jamshedpur has also included IVM and doxycycline combination in their armamentarium to fight against COVID-19.[23] The Assam state government has also included IVM in their protocol to treat mild-to-moderate COVID cases.[24]

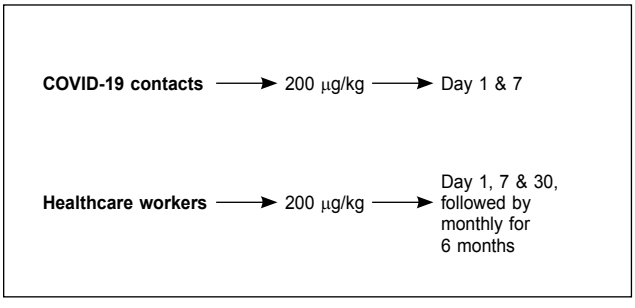

Figure 1. Prophylaxis regimens for ivermectin according to clinical scenarios in COVID-19 infection.

Cost and Availability of Ivermectin in India

Ivermectin therapy costs less than Rs. 1000 (15 USD) for the complete course (at a dose of 12 mg BID for 3-7 days). Ivermectin is easily available at retail stores throughout India at the price of INR 20-35 approximately per 12 mg tablet. In short, IVM can justify the abbreviation "I-SEE" i.e., Ivermectin is Safe, Effective and Economical. This is an easily available and affordable therapeutic option.[8]

INTERNATIONAL STATUS

Latin American Scenario

In mid-April 2020, just after the publication of the Monash study, physicians in the Dominican Republic were compelled to use IVM in mild-to-moderate COVID-19 cases due to unavailability of HCQ. They treated 150 cases successfully without any mortality. Encouraged by the astounding results, doctors in Peru voluntarily administered IVM to a large population. Peru became the epicenter of the movement for off-label use of IVM. Backed by sufficient evidence, the government accepted it as a therapeutic option.[25] In Beni, a district of Bolivia, the government handed out 3,50,000 doses of this drug for mildly symptomatic patients.[26] Brazil, Colombia and Argentina followed the trend.

Bangladesh

Several studies and a trial have been completed and published in Bangladesh. They used IVM and doxycycline to reduce COVID-19 symptoms in patients in just 3 days. They also tested RT-PCR negative in the next 4 days. Trial showed nearly 100% success without any mortality. Treating COVID-19 cases early saves patients from severe, critical disease and decreases mortality by 20%.[27,28]

Australia

To combat the Australian COVID-19 crisis, triple drug combination of IVM, doxycycline and zinc is being promoted. These three medicines are already approved and are listed in Australian Therapeutic Goods Administration.

United States of America

Two observational studies have been completed with favorable results of IVM in the treatment of COVID-19

patients. A dynamic research organization in Ventura, California, named Progenabiome, LLC is set to start a Phase 2 clinical trial titled "A Phase II Double-blind Randomized Placebo-controlled Trial of Combination Therapy to Treat COVID-19 Infection." The intervention arm includes IVM as well as the antibiotic doxycycline, zinc, vitamin D3 and vitamin C.[29]

Global Clinical Trials and Observational Studies on Ivermectin

There are around 50 clinical trials currently going on globally. Of these, 3 trials have been completed, and their results are being evaluated.

Efficacy of ivermectin as add-on therapy in COVID-19 patients

This pilot clinical trial was conducted among hospitalized adult patients with mild-to-moderate COVID-19 diagnosed in line with the WHO interim guidance. Sixteen patients were administered a single dose of IVM 200 μg/kg on admission as add-on therapy to HCQ and azithromycin (AZT) and were compared with 71 controls who were given HCQ and AZT, matched in age, gender, clinical features and comorbidities.

Primary outcome target: Percentage of cured patients, defined as symptoms free to be discharged from the hospital and 2 consecutive negative PCR tests from nasopharyngeal swabs at least 24 hours apart.

Secondary outcomes target: Time to cure in both groups, assessed by measuring time from admission of the patient to the hospital till discharge.

Among 87 patients, the mean age ± SD (range) of patients in the IVM group was similar to controls (44.87 ± 10.64 [28-60] vs. 45.23 ± 18.47 [8-80] years, p = 0.78). Majority of patients in both the groups were male but it was statistically not significant. All the patients in the IVM group were cured compared with the controls (16 [100%] vs. 69 [97.2%]). The mean time of hospital stay was significantly lower in IVM group compared with the controls (7.62 ± 2.75 vs. 13.22 ± 5.90 days, p = 0.00005, effect size = 0.82). No adverse events were observed.

The study concluded that add-on IVM to HCQ and AZT was associated with better effectiveness, shorter hospital stay, and was relatively safe compared with controls. However, a larger prospective study with longer follow-up may be needed to confirm the findings.

Prophylactic ivermectin in COVID-19 contacts

A randomized controlled trial on prophylactic use of IVM enrolled 304 participants. Albeit 59 out of 101 in the control group that didn't receive IVM prophylaxis developed COVID-19 (58%). Out of 203 in the IVM group, only 15 (7.4%) developed COVID-19. The trial was conducted on family members and close contacts of confirmed COVID-19 cases.

A comparative study on ivermectin and hydroxychloroquine on COVID-19 patients in Bangladesh[30]

The study enrolled 116 patients who were divided randomly into two groups. Ivermectin 200 μgm/kg single dose + doxycycline 100 mg BID for 10 days was given to patients in Group A, and HCQ 400 mg 1st day, followed by 200 mg BID for 9 days + AZT 500 mg daily for 5 days was administered to patients in Group B. All patients in Group A exhibited a negative PCR for SARS-CoV-2, at a mean of 8.93 days, and all attained symptomatic recovery, at a mean of 5.93 days, with 55.10% symptom-free by the 5th day. In Group B, 96.36% patients exhibited a negative PCR at a mean of 6.99 days and were symptom-free at 9.33 days. Ivermectin-Doxycycline combination showed a trend towards superiority to the HCQ-AZT combination therapy in patients with mild-to-moderate COVID-19, though the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant.

Completed Observational Studies

USA: ICON (Ivermectin in COvid Nineteen Ivermectin in COVID-19) study by Rajter et al showed significantly lower mortality rates in those who received IVM compared with usual care (15% vs. 25.2%; p = 0.03). It was a retrospective cohort study (n = 280) in hospitalized patients with confirmed SARS-CoV-2 infection. The mortality rate was also lower among the 75 patients with severe pulmonary disease treated with IVM (38.8% vs. 80.7%; p = 0.001), although the rate of successful extubation did not differ significantly.[31]

Dominican Republic Study: Ivermectin was administered in 1,300 early stage COVID-19 patients. Treatment began with a standard dose of 100-200 μg/kg and escalated to 400 μg/kg. Some of the patients also received AZT. Nearly 99% of them were cured. Average duration of full infection went down from 21 days to 10 days. Ivermectin starts inhibiting the virus within a couple days in humans. Only side effects reported were mild heartburn and diarrhea.[32]

Bangladesh: A comparative study included 400 COVID-19 positive patients who were divided into two groups - Group A received IVM with doxycycline while Group B received HCQ with AZT. Viral clearance was noted in 66% on Day 5 and 83.5% on Day 6 in Group A. Among them, 16.5% remained PCR positive after 6th day of IVM ingestion in Group A. There was viral clearance in 77% on 11th day and in 81.5% on 12th day of HCQ treatment in Group B. Among them, 18.5% remained PCR positive after 12 days in Group B. The p value was 0.000427 which is significant considering 5th day viral clearance after IVM ingestion and 11th day after HCQ ingestion. Considering 6th day and 12th day, the p-value was 0.59, which was not significant. Ivermectin and doxycycline appear safe and effective combination drug therapy in COVID-19–infected patients; however, further extensive study is needed to find out the scope of application on other groups of patients.[33]

In another study from Bangladesh, a case series of 100 COVID-19 positive patients treated with combination of IVM and doxycycline, combination of IVM and doxycycline was found to be very effective in viral clearance in mild and moderately sick COVID-19 patients.

Ongoing and Promising Trials

University of Tanta, and Mansoura University, Egypt have started two Phase II/III randomized, parallel assigned, five arm study and three arm study, respectively with COVID-19 patients. The primary endpoint is involving the total number of patients with virological cure over a duration of 6-month period.[34]

University of Kentucky (UK) will investigate the effectiveness of azithromycin, IVM and camostat mesylate—drugs that could inhibit replication of SARS-CoV-2. The drugs will be tested either as stand-alone therapies or in combination with the antimalarial drug HCQ. The trial has a "pick-the-winner" design, which will allow researchers to understand what potential therapies appear to be effective, guiding patients to treatments that work and researchers to promising drugs that need added investigation.[35]

Clinica Universidad de Navarra, Spain has initiated the study titled as SARS-CoV-2/COVID-19 Ivermectin Navarra-ISGlobal Trial (SAINT). This is a double-blind, randomized controlled trial with two parallel groups and determines the efficacy of IVM in reducing nasal viral carriage at 7 days after treatment in SARS-CoV-2–infected patients who are at low-risk of progression to severe disease. The trial is currently planned at a single center in Navarra. Primary endpoint is to determine the proportion of patients with a positive SARS-CoV-2 PCR from a nasopharyngeal swab at day 7 post-treatment.[36]

Combined Military Hospital Lahore, Pakistan has designed a randomized, controlled trial to investigate the efficacy of IVM in COVID-19 patients. Patients will be allocated into two groups – one will be given IVM with standard chloroquine regimen, and the other group will be given chloroquine only. The outcomes will be recorded by documenting PCR reports at 48, 96 and 144 hours. The study was initiated on April 15, 2020 and runs till July 2020. It enrolls 100 patients and precludes those with severe conditions or comorbidities such as malignant disease, diabetes, etc.[37]

Laboratorio Elea Phoenix S.A., Argentina: Argentina's Laboratorio Elea Phoenix S.A. (Elea Laboratories) has launched a proof-of-concept clinical trial that involves 45 patients to look into the efficacy of IVM as a treatment for patients infected with SARS-CoV-2. The pharmaceutical company based its decision on the important Monash University lab study and the fact that IVM has been widely in use for decades.[38]

HCQ and IVM: The study seeks to investigate the safety and efficacy of a treatment involving HCQ and IVM for serious COVID-19 infections in non-critical hospitalized patients. Prior to any patient randomization, the investigational team will assess cardiovascular complications determined by the corrected QT interval, related to HCQ intake. For example, if a patient is at high-risk, they will be placed in the IVM group only or allocated to placebo in an independent randomization.[39]

Table 2 summarizes the ongoing and promising ivermectin trials in COVID-19 patients.

CONCLUSION

Indian Council of Medical Research (ICMR) is now reviewing the benefits of IVM and doxycycline as a potential therapy for COVID-19. There is an urgent need for a well-designed randomized controlled trial to assess the efficacy and validate the use of IVM against SARS-CoV-2. Under ideal circumstances, the answer would be yes. But, it's been 6-9 months since the start of the pandemic, and the number of COVID-19 positive cases and the related mortality appears to be out of control. We need to balance "Evidence-based medicine versus loss of human lives" while waiting for 9-12 months for a vaccine or an effective drug.

Table 2. Ongoing and Promising Clinical Trials on the Use of Ivermectin in Patients with COVID-19

Identifier Number	Title	Expected Participants	Starting Date	Completion Date	Length of Treatment	Dose of Ivermectin	Location
NCT 04373824	Max Ivermectin-COVID-19 Study versus Standard of Care Treatment for COVID-19 Cases. A Pilot Study	50	April 25, 2020	July 25, 2020	2 days	200-400 g/kg body weight + standard treatment	India
NCT 04374279	Trial to Promote Recovery from COVID-19 with Ivermectin or Endocrine Therapy	60	November 2020	November 2021	3 days or 6 days	600 g/kg (up to a maximum dose of 60 mg)	USA
NCT 04360356	Ivermectin and Nitazoxanide Combination Therapy for COVID-19	100	May 2020	October 2020	6 days	200 g/kg once orally on empty stomach plus nitazoxanide 500 mg twice daily orally with meal	Egypt
NCT 04343092	Ivermectin Adjuvant to hydroxychloroquine and Azithromycin in COVID-19 Patients	50	April 18, 2020	June 1, 2020	No information	12 mg/week + hydroxy-chloroquine 400 mg/day + azithromycin 500 mg daily	Iraq
NCT 04351347	The Efficacy of Ivermectin and Nitazoxanide in COVID-19 Treatment	60	June 16, 2020	December 1, 2030	No information	Combined with chloroquine (no information about dose)	Egypt
NCT 04374019	Novel Agents for Treatment of High-risk COVID-19 Positive Patients	240	May 1, 2020	May 2021	2 days for ivermectin + 14 days for Hydroxychloro-quine	First 2 days: Weight <75 kg: 4 tablets (12 mg total daily dose). Days 1-2: Weight >75 kg: 5 tablets (15 mg total daily dose) in combination with hydroxychloroquine. Days 1-14: 3 tablets (600 mg total daily dose)	USA
NCT 04345419	A Real-life Experience on Treatment of Patients with COVID-19	120	June 16, 2020	December 2029	No information	As a single dose	Egypt

Under these exceptional circumstances, "Do we have the time?" The cumulative loss of lives and economic loss may be humongous. Ivermectin appears to be the ideal choice as it shows the potential to exactly do that and the 5 A's make it the ideal drug in the scenario as listed in Figure 2. There is always scope of course correction as we learn from the rapidly changing circumstances and ensuing scientific results. Till then, these results raise hope and should be seen as light at the end of the tunnel to successfully manage the coronavirus pandemic till we get a safe and an efficient vaccine or drug against this deadly disease.

Assurance: Ivermectin has a well proven safety profile, with more than a trillion doses consumed every year.

Availability: Ivermectin is readily available; we have many manufacturers in India itself.

Administration: Ivermectin is easy to administer orally, and we already have experience of running a mass drug administration.

Accountability: Ivermectin, owing to its low toxicity and mostly Grade 1 adverse drug events, will not scare the stakeholders.

Affordability: Drug is cheap, which a normal Indian citizen can very well afford.

Figure 2. The Five A's which justify ivermectin as a pivotal drug for fighting coronavirus pandemic.

REFERENCES

1. Van Voorhis WC, Hooft van Huijsduijnen R, Wells TN. Profile of William C. Campbell, Satoshi Ōmura, and Youyou Tu, 2015 Nobel Laureates in Physiology or Medicine. Proc Natl Acad Sci U S A. 2015;112(52):15773-6.
2. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787.
3. Banerjee S, Bandyopadhyay K, Khan MF, Akkilagunta S, Selvaraj K, Tripathy JP, et al. Coverage of mass drug administration for elimination of lymphatic filariasis in urban Nagpur, Central India: A mixed method study. J Family Med Prim Care. 2019;8(9):3009-14.
4. Lehrer S, Rheinstein PH. Ivermectin Docks to the SARS-CoV-2 spike Receptor-binding Domain attached to ACE2. In Vivo. 2020;34(5):3023-6.
5. Doboszewska U, Wlaź P, Nowak G, Młyniec K. Targeting zinc metalloenzymes in coronavirus disease 2019. Br J Pharmacol. 2020 Jul 15:10.1111/bph.15199.
6. Juarez M, Cabrera AS, Gonzalez AD. The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug. Am J Cancer Res. 2018;8(2):317-31.
7. David S. Ivermectin for COVID-19 treatment: Clinical response at Quasi-threshold doses via hypothesized alleviation of CD147-mediated vascular occlusion (June 26, 2020). Available at: https://ssrn.com/abstract=3636557. Accessed on Oct 1, 2020.
8. Banerjee K, Nandy M, Dalai CK, Ahmed SN. The Battle against COVID 19 pandemic: What we need to know before we "Test Fire" ivermectin. Drug Res (Stuttg). 2020;70(8):337-40.
9. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. Biotechnol Biotechnolog Equip. 2020;34:469-74.
10. Bajpai J, Pradhan A, Singh A, Kant S. Hydroxychloroquine and COVID-19 - A narrative review. Indian J Tubercuc. 2020 July 3. https:// doi.org/10.1016/j.ijtb.2020.06.004
11. Patrì A, Fabbrocini G. Hydroxychloroquine and ivermectin: A synergistic combination for COVID-19 chemoprophylaxis and treatment? J Am Acad Dermatol. 2020;82(6):e221.
12. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol. 2002;42(10):1122-33.
13. Kircik LH, Del Rosso JQ, Layton AM, Schauber J. Over 25 years of clinical experience with ivermectin: An overview of safety for an increasing number of indications. J Drugs Dermatol. 2016;15(3):325-32.
14. Notes on the Design of Bioequivalence Study: Ivermectin. Available from: https://extranet.who.int/prequal/sites/default/files/documents/21%20BE%20ivermectin_Apr2019.pdf#:~:text=Administration%20of%2030%20mg%20ivermectin,an%20empty%20stomach%20with%20water.
15. Vernapalli SR, Chen Y, Ellingrod VL, Kitzman D, Lee Y, Hohl RJ. Orange juice decreases the oral bioavailability of ivermectin in healthy volunteers. Clin Pharmacol Therapeut. 2003;73(2):94-94.
16. Dixit A, Yadav R, Singh AV. Ivermectin: potential role as repurposed drug for COVID-19. Malays J Med Sci. 2020;27(4):154-8.
17. Drugs@FDA: FDA-Approved Drugs. STROMECTOL® (ivermectin) tablets [Internet]. [cited: 2020 July 19]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event1⁄4overview.process&ApplNo1⁄4050742.
18. Kant S. COVID 19 impact on health care workers. JIMA. 2020;118(09):64-9.
19. Vora A, Arora VK, Behera D, Tripathy SK. White paper on Ivermectin as a potential therapy for COVID-19. Indian J Tuberc. 2020;67(3):448-51.
20. COVID 19 Global literature on corona virus disease. [Internet]. [Cited 5 October 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov; July 2020.
21. Northern Indian State of Uttar Pradesh Drops Hydroxychloroquine & Replaces with Ivermectin for COVID-19 Patients [Cited 19 July 2020]. Available from: https://www.trialsitenews.com/northern-indian-state-of-uttar-pradesh-drops-hydroxychloroquine-replaces-with-ivermectin-for-covid-19-patients/
22. Delhi's COVID-19 Provider Lok Nayak Hospital Cuts Favipiravir & Adds Ivermectin & Remdesivir for COVID-19 Patients. [Internet]. [Cited 5october 2020]. Available from: https://www.trialsitenews.com/delhis-covid-19-provider-lok-nayak-hospital-cuts-favipiravir-adds-ivermectin-remdesivir-for-covid-19-patients; July 2020.
23. Tata Main Hospital Picks Up Ivermectin/Doxycycline Combo Regimen to Address COVID-19. [Internet]. [Cited 5 October 2020]. Available from: https://www.trialsitenews.com/tata-main-hospital-picks-up-ivermectin-doxycycline-combo-regimen-to-address-covid-19. August 2020.
24. Kalita K. Covid-19: Assam's positivity rate surges to 7.67%, 63 deaths in a Week. Available from: http://timesofindia.indiatimes.com/articleshow/77966058.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst
25. Peru's Universities Now Produce Ivermectin in Collaboration with Regional Health Authorities in a Fight for Survival. India e Trial Site News [Internet]. [Cited 28 September 2020]. Available from: https://www.trialsitenews.com/ Peru's Universities Now Produce Ivermectin in Collaboration with Regional Health Authorities in a Fight for Survival; 2020 July.
26. Bolivian Region Authorizes Ivermectin as Treatment Against COVID-19. Trial Site News [Internet]. [Cited 4

October 2020]. Available from: https://www.trialsitenews.com/ Bolivian Region Authorizes Ivermectin as Treatment Against COVID-19. 2020 May.

27. Dr. Alam Gets his Randomized Controlled Trial Approved by the Bangladesh Medical Research Council. Trial Site News [Internet]. [Cited 4 October 2020]. Available from: https://www.trialsitenews.com/. Dr. Alam Gets his Randomized Controlled Trial Approved by the Bangladesh Medical Research Council; July 2020.
28. Alam MT, Murshed R, Bhiuyan E, Saber S, Alam RF, Robin RC. A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline. J Bangladesh Coll Physic Surg. 2020;38:10-5.
29. Top California Gastroenterology Investigator Leads Phase 2 Ivermectin Clinical Trial Targeting COVID-19 Cases. Trial Site News [Internet]. [Cited 4 October 2020]. Available from: https://www.trialsitenews.com/ Top California Gastroenterology Investigator Leads Phase 2 Ivermectin Clinical Trial Targeting COVID-19 Cases. 2020 July.
30. Chowdhury AT, Shahbaz M, Karim MR, Islam J, Dan G, He S. A comparative observational study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients [Preprint] [Cited 2020 July 19]. Available from: https:// www.researchgate.net/publication/342159343; 2020.
31. Rajter JC, Sherman M, Fatteh N, Vogel F, Sacks J, Rajter JJ. ICON (Ivermectin in COvid Nineteen) study: use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19 [medRxiv Preprint]. [Cited July 19 2020] https:// doi.org/10.1101/2020.06.06.20124461; 2020 Jun.
32. India e Trial Site News [Internet]. President of Dominican Republic's largest private health group discusses the success of ivermectin as a treatment for early stage COVID-19. [Cited 19 July 2020]. Available from: https://www.trialsitenews.com/president-of-dominican-republics-largest-private-health-group-discusses-the-success-of-ivermectin-as-a-treatment-for-early-stage-covid-19/; 2020 Jun.
33. Rahman MA, Iqbal S, Islam MA, Niaz MK, Hussain T, Siddiquee T. Comparison of viral clearance between ivermectin with doxycycline and hydroxychloroquine with azithromycin in COVID-19 patients. J Bangladesh Coll Physic Surg. 2020;38:5-9.
34. Tanta University PI Sponsors Ivermectin Studies Targeting COVID-19 in up to 160 Patients While Safety is a Concern for Regulators. Trial Site News [Internet]. [Cited 4 October 2020]. Available from: https://www.trialsitenews.com/ Tanta University PI Sponsors Ivermectin Studies Targeting COVID-19 in up to 160 Patients While Safety is a Concern for Regulators; April 2020.
35. Chapin E. UK Launches Clinical Trial to Evaluate Novel Treatments for COVID-19. University of Kentucky news [Internet]. [Cited 3 October 2020]. Available from: http://www.http://uknow.uky.edu/research/uk-launches-clinical-trial-evaluate-novel-treatments-covid-19; May 2020.
36. Pilot Study to Evaluate the Potential of Ivermectin to Reduce COVID-19 Transmission. ClinicalTrials.gov [Internet]. [Cited 3 October 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT04390022; May 2020.
37. Combined Military Hospital Pakistan Launches Ivermectin Clinical Trial Investigating Efficacy in COVID-19 Patients. Trial Site News [Internet]. [Cited 4 October 2020]. Available from: https://www.trialsitenews.com/combined-military-hospital-pakistan-launches-Ivermectin-clinical-trial-investigating-efficacy-in-covid-19-patients; May 2020.
38. Argentinian Pharma Elea Laboratories Launches POC Clinical Trial Investigating Ivermectin in Hospitalized COVID-19 Patients. Trial Site News [Internet]. [Cited 4 October 2020]. Available from: https://www.trialsitenews.com/argentinian-pharma-elea-laboratories-launches-poc-clinical-trial-investigating-Ivermectin-in-hospitalized-covid-19-patients; May 2020.
39. Efficacy and Safety of Hydroxychloroquine and Ivermectin in Hospitalized no Critical Patients Secondary to COVID-19 Infection: Randomized Controlled Trial. ClinicalTrials.gov [Internet]. [Cited 3 October 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT04391127; May 2020.

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FDA to Look at 2 Months of Safety Data Before Considering COVID-19 Vaccine

The US Food and Drug Administration (FDA) has made it clear that it will see 2 months of follow-up data after volunteers are given their second vaccine doses for clinical trials testing potential COVID-19 vaccines.

This is going to make it difficult for any vaccine maker to apply for emergency use authorization by Election Day, as President Trump has suggested, or by the end of October. FDA posted new guidance for manufacturers stating that they need to provide at least 2 months of follow-up safety data following vaccination of volunteers before asking the FDA for emergency use authorization for a vaccine.

The guidance stated that data from Phase 3 studies must include a median follow-up duration of at least 2 months after completion of the full vaccination regimen in order to provide sufficient information for evaluating a vaccine's benefit-risk profile… (*CNN*)

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Flow Cytometer: The Need of Modern Hematology Laboratory

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ABSTRACT

Indeed, laboratory diagnosis is rapidly changing from what it was in the past to the present. Nowadays, flow cytometer (FCM) has become a novel introduction to the modern diagnostic technique, mainly in the field of hematology. In case of acute leukemia, peripheral blood, bone marrow examination, cytochemistry and immunohistochemistry for differentiation of myeloid or lymphoid lineage is required, which is feasible by flow cytometry. It has dramatically improved the diagnostic efficiency and reduced the duration of sampling along with better diagnostic outcomes as well as provided efficient therapeutic monitoring of any drug or drug regimen. It has also opened some more sensitive therapeutic plans, like monitoring "Minimal residual disease (MRD)", which is not possible without FCM. Detection of MRD has led to improved overall survival of patients. It has also opened up huge opportunities for research, which has become an important part of academic curriculum nowadays. Considering the importance and absolute necessity for better outcomes in hematology, the knowledge of basic principle of FCM becomes indispensable. Here, we try to elucidate the elementary components of this technique and also highlight its uses.

Keywords: Flow cytometer, hematology, immunohistochemistry

Flow cytometer (FCM) is a powerful technique for diagnosing multiple characteristics of a single cell. This technique is based on both qualitative and quantitative estimation. In the present era, FCM has made the transition from a research tool to a prerequisite in a laboratory dealing with hematolymphoid malignancy. It is useful not only in diagnosis for initiation of therapy, but also in therapeutic monitoring during follow-up. With the advent of prognostically useful antibodies, use of multicolor flow cytometry has become of utmost importance in the diagnosis and management of hematolymphoid diseases.[1] Looking at the importance of this equipment, we need to have an elementary knowledge of its principle.

Literally, the word 'flow' means to pass, 'cyto' means cell and 'metry' means measurement. Thus, flow cytometry translates to the passage of cells in a single file (line or row) in front of a laser beam to be detected, counted and sorted. The cells are labeled with fluorochromes and when excited by laser beams of appropriate wavelength, they emit light (fluorescence), which is filtered and collected. Specialized software converts the result into a digitalized (numerical) value.[1]

Integral Components of FCM: The key components are being described below:

Fluidics: Cells of interest flow through a liquid stream called the sheath fluid. The speed of cells is higher than the speed of sheath fluid. This results in streamlining of cells in a single line (linear file). This mechanism is called hydrodynamic focusing. Up to 50,000 cells/sec can be measured, but the normal throughput is 1,000-10,000 cells/sec.[2]

Interrogation point: Inside a FCM, cells in suspension are drawn into a stream created by a surrounding sheath of isotonic fluid. This creates a laminar flow which enables the cells to pass individually through an interrogation point. At this point, fluorochrome

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tagged cells pass through a laser beam causing its light (and that of the fluorochromes present) to scatter in all directions. These are collected through optics that direct the light to a series of filters and mirrors, which isolate particular wavelength bands.[3]

Scattering of light: Physical characteristics of a cell, such as size and internal complexity, like granularity, can help identify different cell populations like blasts, plasma cells, monocytes, etc. This diversity in different cell populations is identified using two parameters - forward and side scatter. Forward scatter (FSC) is based on two properties: size and refractive index. The FSC intensity is based on the particle's size and can also be used to distinguish between cellular debris and living cells. Side scatter (SSC) is based on the granularity or internal complexity. The more granular the cell, the more side scatter light is generated. Dead cells have lower FSC and higher SSC than living cells. The detector placed in the line of light beam measures forward scattering (FSC) [size] and that placed perpendicular to the light stream measures side scattering (SSC) [granularity, nuclear structure].[3-5]

Electronics: The light signals are detected by photomultiplier (PMT) tubes and undergo digitization for computer analysis. Figure 1 depicts a schematic diagram of the components of a FCM.

For all practical purposes, cells falling in the range of 3-20 μ diameter can be analyzed using this technique. Identification of cells at a frequency of as low as 0.0001% has been reported to be possible by flow cytometry. Fluorescent dyes may bind with different cellular components like DNA or RNA. Antibodies conjugated to fluorescent dye have the potential to bind specific proteins on cell membranes or inside the cells. When a fluorochrome labeled cell is passed through a light source, the fluorescent molecules get excited and achieve a higher energy state. As they return to their resting states, the fluorochromes emit light energy at different wavelengths.[3]

Several properties of a cell can be measured simultaneously by using multiple fluorochromes. Each fluorochrome with similar excitation wavelengths and different emission wavelengths (or colors) enables the measurement of several cell properties. Most commonly used dyes are propidium iodide, phycoerythrin, fluorescein, etc. Tandem dyes with internal fluorescence resonance energy transfer can create even longer wavelengths and more colors.[6]

Information about physical and chemical structure of cells gathered is used in diagnosis of diseases. Samples used are bone marrow aspirates, blood, body fluid and tissue. For tissue samples, dissociation to single cells is required. Equipment for tissue dissociation is available commercially.[7,8]

Getting numerical values: Photons collected by detectors get converted into electrical energy (current) to give a digitized value through "Analog to Digital Converter".[9] Common softwares used are Caluja, CellQuest, Flowjo, FCS Express (FCS: Fluorescence-activated cell sorting), etc.

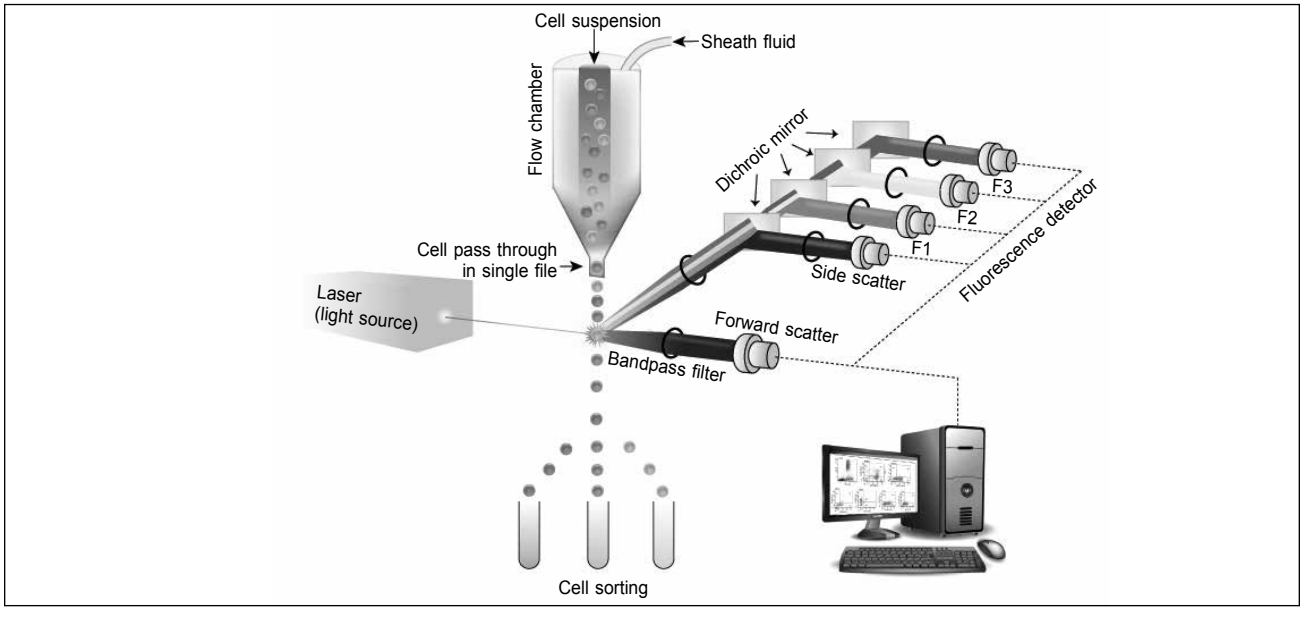

Figure 1. Schematic diagram of a flow cytometer.

Gating: This refers to the isolation of subsets of cells on a plot. Gates can be visualized as barriers placed around cell populations having common characteristics like scatter or cluster of differentiation (CD) marker expression to isolate, quantify and study these subpopulations. Initially, cells are gated on the basis of FSC and SSC properties. After initial isolation and quantification of the population of interest, further division into subpopulations based on surface (or intracellular) markers is done. Back gating is a method for elimination of nonspecific staining and false positives. Here, the population identified by a particular gate is gated again on entirely different parameters for confirmation.[3,5,10]

In Figure 2, we can understand the different cell clusters produced after running in FCM. Each cluster is gated using specialized software (caluja) and it is analyzed for any abnormality. Cluster of blasts can be identified in the image and its percentage can be used for analyzing presence or absence of malignancy.

COMPARISON OF FLOW CYTOMETRY WITH IMMUNOHISTOCHEMISTRY

Immunohistochemistry, in the past decade, has been popularly called as the brown revolution, due to its surmount importance in diagnosis.

However, the emergence of flow cytometry has made it possible to overcome the shortcomings of immunohistochemistry (IHC). It is a time-consuming technique restricted by the use of limited number of CD markers on a particular tissue section. The quantification of cells and enumeration of the different cell subtypes are also not possible via this technique. On the other hand, using flow cytometry, multicolor immunophenotyping is possible whereby large number of CD markers can be used simultaneously. This makes it possible to analyze numerous cells at the same time. Numerous parameters can be examined at once. Sometimes, the presence of two co-existent pathologies may be detected. Dead cells may also be gated using the analysis.

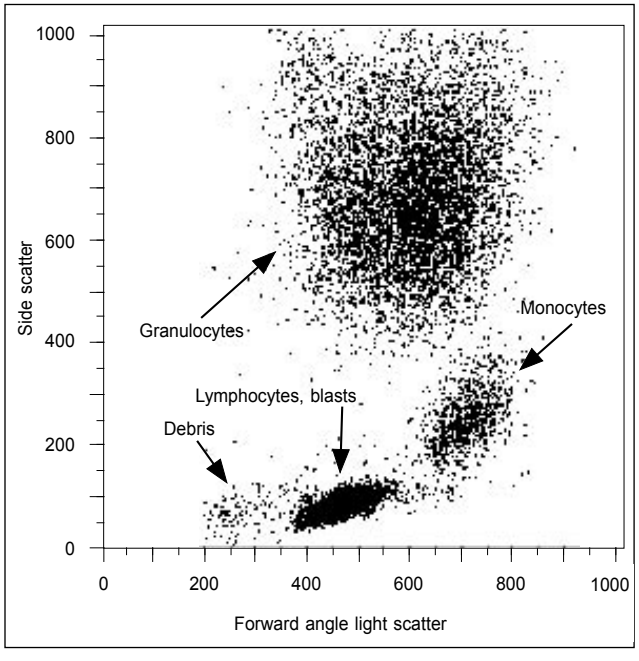

Figure 2. Dot plot of forward light scatter and side scatter.

Image source: Riley RS, Idowu M. Principles and applications of flow cytometry. Available at: http://www.flowlab-childrens-harvard.com/yahoo_site_admin/assets/docs/PRINCIPLESANDAPPLICATION.29464931.pdf

There is no need of a tissue biopsy. Even small quantities of samples such as body fluids, peripheral blood or fine needle aspirate specimens can be processed and identification of cells at a frequency as low as 0.001% is possible. Studies show that it is a rapid process requiring less effort. The only drawback of FCM as compared to IHC is that unlike in IHC, the localization of antigen (nuclear, cytoplasmic or membranous) is not possible in FCM.[9,11]

USES OF FLOW CYTOMETRY

Flow cytometer is used to detect the size of cells and also to incorporate various hematological parameters, like to enumerate red blood cell (RBC), platelets size and white blood cell (WBC) based on light scatter. Moreover, bone marrow aspirate, cerebrospinal fluid and peripheral blood are all specimens that can be analyzed using flow cytometry (only viable cells can be analyzed). If the sample does not carry viable cells, flow cytometry analysis does not seem to be an option.[12,13] FCM is also used in predicting leukemic cell lineages in peripheral blood of dogs and cats.[14]

Measurement of DNA content was one of the earliest uses of flow cytometry. A 67% increase in DNA content was noted in malignant cells compared to nonmalignant cells. Tumor cells that are not diploid have an abnormal number of chromosomes that lead to an aneuploidy cell. Moreover, flow cytometric analysis of nuclear DNA content will demonstrate histogram peaks for nuclei of the sample that is in different phases of the cell cycle - G_0/G_1, S-phase and G_2/M. Thus, it is used to determine the DNA content and ploidy of tumors. Retrospective studies examined the relationship between DNA abnormalities and duration of survival in patients with oncologic disease in an attempt to predict prognosis.[3,15-17]

Phenotyping, the identification of particular observable characteristics, is one of the uses of flow cytometry in

Table 1. The Basic CD and Immune Cells Designation

Immune cell type	CD designation
B-cell	CD19, CD20, CD22
T-cell	CD1, CD3, CD4, CD5, CD7, CD8
Myeloid cells	CD13, CD33, CD117
Blasts	CD34, CD38, HLA DR
Monocyte	CD14, CD64
Macrophage	CD68, CD14, CD64, CD11b
Granulocytes	CD13, CD15, CD16, MPO
Megakaryocytes	CD41, CD42, CD62
RBC	CD36, CD235a

oncology. There are many phenotypic designations to differentiate healthy cells from tumor cells. Table 1 provides basic CD specification for common immune cell phenotypes. In addition, flow cytometry is used to identify the lineage of leukemic blood cells or to classify a lymphoma or leukemia as either T or B cells, which provides prognostic information of the disease. It also examines functions of natural killer cells and T-cell, which have shown some correlation with psychological distress of patients.[10,18-21]

Flow cytometry is used for assessment of the affected lymphoid tissue which is important for staging and classification of malignant lymphomas. It is also used in laboratory diagnosis of immune-mediated cytopenias, like hemolytic anemia, thrombocytopenia and neutropenia, etc. Moreover, its sensitivity is more in comparison to conventional direct agglutination test (e.g., Coombs for immune-mediated hemolytic anemia [IMHA]). It is also used to monitor the progression of acquired immunodeficiency syndrome (AIDS) in humans with human immunodeficiency virus (HIV).[22,23]

CONCLUSION

To summarize, in the current scenario, flow cytometry forms an integral part of diagnosis, especially in hematolymphoid malignancies. It further aids in conducive disease management by guiding therapeutic protocols. Due to the accuracy and precision of this technique and its ability to use samples obtained from minimally invasive methods, like peripheral blood sampling, it is also widely used in assessing the response of the patient to treatment regimens. As of date, it can be said to be indispensable to the laboratory. In the times to come, FCMs can be expected to continue to decrease in energy consumption as well as size and increase in detection and precision measurements.

REFERENCES

1. Brown M, Wittwer C. Flow cytometry: principles and clinical applications in hematology. Clin Chem. 2000;46(8):1221-9.
2. Mittag A, Tárnok A. Perspectives in cytometry. In: Advanced Optical Flow Cytometry [Internet]. John Wiley & Sons, Ltd; 2011 [cited 2020 Apr 9]. p. 1-23. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9783527634286.ch1
3. Adan A, Alizada G, Kiraz Y, Baran Y, Nalbant A. Flow cytometry: basic principles and applications. Crit Rev Biotechnol. 2017;37(2):163-76.
4. Flow Cytometry-Definition, Principle, Parts, Steps, Types, Uses. May 11, 2020. Available at: https://microbenotes.com/flow-cytometry/. Accessed Sep. 25, 2020.
5. Bajgelman MC. Chapter 8 - Principles and applications of flow cytometry. In: Misra G. Data Processing Handbook for Complex Biological Data Sources. Elsevier Enhanced Reader. 2019. pp. 119-24. Available at: https://reader.elsevier.com/reader/sd/pii/B9780128165485000083?token=481A12913F603617F609F0D87D0758F574AA5C4E840CEFB0F6612BDD6A44216ECA191E85DCB8C75D389AB7B128978E36. Accessed Sep. 25, 2020.
6. McKinnon KM. Flow Cytometry: An overview. Curr Protoc Immunol. 2018;120:5.1.1-5.1.11.
7. Vembadi A, Menachery A, Qasaimeh MA. Cell cytometry: review and perspective on biotechnological advances. Front Bioeng Biotechnol. 2019;7:147.
8. Laerum OD, Farsund T. Clinical application of flow cytometry: a review. Cytometry. 1981;2(1):1-13.
9. Dunphy CH. Applications of flow cytometry and immunohistochemistry to diagnostic hematopathology. Arch Pathol Lab Med. 2004;128(9):1004-22.
10. Riley RS, Idowu M. Principles and applications of flow cytometry. Available at: http://www.flowlab-childrens-harvard.com/yahoo_site_admin/assets/docs/PRINCIPLESANDAPPLICATION.29464931.pdf
11. Matos LL, Trufelli DC, de Matos MG, da Silva Pinhal MA. Immunohistochemistry as an important tool in biomarkers detection and clinical practice. Biomark Insights. 2010;5:9-20.
12. Pati HP, Jain S. Flow cytometry in hematological disorders. Indian J Pediatr. 2013;80(9):772-8.
13. Brown M, Wittwer C. Flow cytometry: principles and clinical applications in hematology. Clin Chem. 2000;46(8 Pt 2):1221-9.
14. Fernandes PJ, Modiano JF, Wojcieszyn J, Thomas JS, Benson PA, Smith R 3rd, et al. Use of the Cell-Dyn 3500 to predict leukemic cell lineage in peripheral blood of dogs and cats. Vet Clin Pathol. 2002;31(4):167-82.

15. Snow CK. Flow cytometer electronics. Wiley Online Library. Cytometry Part A 2004;57A:63-9. Available at: https://onlinelibrary.wiley.com/doi/pdf/10.1002/cyto.a.10120. Accessed Sep. 26, 2020.
16. Darzynkiewicz Z, Huang X, Zhao H. Analysis of cellular DNA content by flow cytometry. Curr Protoc Cytom. 2017;82:7.5.1-7.5.20.
17. Culmsee K, Nolte I. Flow cytometry and its application in small animal oncology. In: Sobti RC, Krishan A (Eds.). Advanced Flow Cytometry: Applications in Biological Research. Dordrecht, Netherlands: Springer; 2003. pp. 49-54.
18. Wolniak K, Goolsby C, Choi S, Ali A, Serdy N, Stetler-Stevenson M. Report of the results of the International Clinical Cytometry Society and American Society for Clinical Pathology workload survey of clinical flow cytometry laboratories. Cytometry B Clin Cytom. 2017;92(6):525-33.
19. CD Markers. Ask Hematologist | Understand Hematology. Available at: https://askhematologist.com/cd-markers/. Accessed Sep. 28, 2020.
20. CD Marker Panel. Available at: Available at: https://www.antibodies-online.com/resources/18/1540/cd-marker-panel/. Accessed Sep. 28, 2020.
21. Haybar H, Maleki Behzad M, Shahrabi S, Ansari N, Saki N. Expression of blood cells associated CD markers and cardiovascular diseases: clinical applications in prognosis. Lab Med. 2020;51(2):122-42.
22. Henel G, Schmitz JL. Basic theory and clinical applications of flow cytometry. Lab Med. 2007;38(7):428-36.
23. Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. JAMA. 2002;288(2):222-35.

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CDC Updates 'How COVID is Spread' Webpage

The Centers for Disease Control and Prevention (CDC) has issued updated guidance to its 'How COVID-19 Spreads' website, which includes information about the potential for airborne spread of the virus.

CDC continues to believe, on the basis of current science, that people have increased likelihood of contracting the infection the longer and closer they are to a person infected with COVID-19. The latest update acknowledges certain published reports that show limited, rare circumstances where COVID-19 patients infected others who were more than 6 feet away or shortly after the COVID-19-positive person left an area. In these cases, transmission occurred in poorly ventilated and enclosed spaces that involved activities known to cause heavier breathing, such as singing or exercise.

It is possible for people to protect themselves by maintaining a distance of at least 6 feet from others, wearing a mask covering their nose and mouth, frequent handwashing, cleaning touched surfaces frequently and staying home when sick… (*CDC*)

Phrenic Nerve Stimulation for Central Sleep Apnea

Five-year data support the long-term safety and effectiveness of transvenous phrenic nerve stimulation (TPNS) for central sleep apnea (CSA), suggest researchers.

Investigators reported that CSA severity diminished in patients after device implantation and continued to stay that way up to 5 years. Over half of the patients maintained improvement of apnea hypopnea index (AHI) at both 1 year and 5 years. Central apnea index was below 1 event per hour at 1 year and 5 years alike, compared to a baseline of around 23 events per hour. Additionally, more than half of the patients achieved sustained improvement in arousals through 5 years, and the arousals added up to 19 per hour at both 1 year and 5 years, showing a decline from a baseline value of around 39 arousals per hour. Daytime sleepiness scores on the Epworth scale were at a median 6 points at 1 and 5 years, down from 9 points at baseline. The findings were presented at the virtual meeting of the Heart Failure Society of America… (*Medpage Today*)

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Transobturator Tape for Female Stress Incontinence: Our Experience

M GOPI KISHORE*, SAINADH AV†

ABSTRACT

Aim: The aim of this study was to evaluate the effectiveness of transobturator tape (TOT), patient satisfaction and morbidity in the treatment of female stress urinary incontinence (SUI). **Material and methods:** Forty-eight patients from January 2013 to December 2016 with SUI underwent TOT procedure by outside-in technique. Data related to operative time, postoperative complications and patient acceptance were assessed. **Results:** Mean age of the patients was 41.3 years and 46 (95.8%) were multiparous. The operative time was 26 ± 4 minutes and catheter was removed on 1 ± 2 days postoperatively. Hospital stay was 2 ± 3 days and return to normal activity was 4-7 days for 46 (95.8%) patients and 7-10 days for 2 (4.2%) patients. Of the 48 patients, 45 (93.75%) were continent postoperatively while 3 (6.25%) patients had occasional urine leak that did not influence daily activities. No major intra-/postoperative complication was reported. Quality of life improved significantly. A total of 45 (93.75%) patients were completely cured and satisfied, whereas 3 (6.25%) patients improved and partially satisfied with surgical outcome. **Conclusion:** The TOT sling procedure is an effective treatment for SUI with high success rate, high satisfaction rate, low morbidity and short hospital stay.

Keywords: Transobturator tape sling, stress urinary incontinence, complications, tension free

Stress urinary incontinence (SUI) is an involuntary urine loss due to increased intra-abdominal pressure during exertion, sneezing or coughing. In genuine stress incontinence, there will be hypermobility or lowering of the vesicourethral segment or a combination of two factors but the intrinsic sphincter itself is intact and normal. The estimated prevalence of urinary incontinence is nearly 25-30% in women aged 30-60 years, with approximately half of the cases attributed to SUI. Various factors that may increase the risk of developing incontinence include aging, obesity, smoking, straining, heavy manual labor and chronic obstructive pulmonary disease. The initial treatment for SUI is conservative therapies like lifestyle modifications, pelvic floor muscle training, bladder training and medical treatment. Surgery is indicated for those patients with no improvement in symptoms and quality of life (QOL) after initial treatment. Numerous surgical methods for stress incontinence have been described. The basic principle in treatment of SUI is proper suspension by creating functional kinking of the mid-urethra during increased intra-abdominal pressure. In the past two decades, two major minimally invasive sling procedures have been developed. In 1996, Ulmsten introduced the tension-free vaginal tape (TVT) procedure and reported an initial 2-year cure rate of 84%. TVT is a safe and successful procedure but serious, though rare, complications like bladder perforation, vascular and bowel injuries have been reported with this technique. In order to reduce these complications, Delorme in 2001 reported a transobturator vaginal tape (TOT) approach, which involved placing a mesh through the obturator foramen behind the mid-urethra. This approach is more anatomically correct and a theoretical advantage is less obstruction and postoperative voiding dysfunction. These minimally invasive mid-urethral sling techniques have become the standard procedures for the surgical treatment of SUI.

MATERIAL AND METHODS

This was a prospective study from January 2013 to December 2016, conducted on 48 patients diagnosed with genuine SUI, who were managed with

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transobturator sling in the Dept. of Urology, ESIC Super Speciality Hospital, Hyderabad. All patients attending urology OPD, who complained of involuntary passage of urine on coughing, laughing, straining, were subject to a thorough history taking, physical examination and local examination with Bonney's test. All baseline and special investigations, like urodynamic study and cystopanendoscopy were conducted on the patients. Diagnosis of SUI was based on typical subjective symptoms (i.e., involuntary leakage on effort, exertion, coughing, sneezing or laughing) as recommended in 2002 by the International Continence Society and on objective clinical data from the cough stress test, Q-tip test or urodynamic studies.

Excluded were women with recurrent urinary tract infections (UTIs), urge urinary incontinence or mixed urinary incontinence, post-voiding residual (PVR) urine of >150 mL, bladder capacity of <100 mL, co-existing pelvic organ prolapse or any other gynecological problem, previously corrective surgery for stress incontinence, pregnancy and physical or mental impairment.

All the patients diagnosed with SUI were explained about their disease, and the available modes of treatment, including nonsurgical and surgical options. Patients were managed initially with conservative therapies like lifestyle modifications, pelvic floor muscle training, bladder training and medical treatment (imipramine, duloxetine, estrogens) for 6 months. Patients, after failure or not satisfied with conservative management, were recruited in this study. TOT procedure was performed in all these patients.

Surgical Technique

The AMS Monarc TOT sling was inserted through outside-in route by using the technique recommended by Delorme in 2001. After spinal anesthesia, patient is placed in modified lithotomy position and Foley catheter is introduced to empty the bladder. After retracting the labial fold, an incision of 1.5 cm is made 1 cm proximal to the external urethral meatus in the anterior vaginal wall. On both sides, anterior vaginal wall is elevated laterally up to ischiopubic rami taking care of urethra and bladder. Two small skin incisions are made on both sides where the lateral edge of the ischiopubic bone is projected, on the horizontal line that runs through the clitoris. TOT needle is introduced from skin incision and tip of the TOT needle is brought out from the incision in the vaginal wall with finger acting as a guide. TOT tape is fixed to tip of the needle. TOT needle is withdrawn through the same path taking along with it one end of the TOT tape through the incision in groin. Same procedure is repeated on the other side also. The sling is placed under the middle of the urethra, tension-free with little finger gap, the two ends of the sling are sectioned at the level of groin skin incision and the vaginal incision is closed. The Foley catheter is kept 24-48 hours postoperatively and the patients are usually discharged 2 days after surgery.

Assessment

Postoperative assessment, including pain associated with surgery, lower urinary tract symptoms, infection, voiding problem and time to return to normal activity, was done at 1-week, 1-month and 6-month follow-up visits. At 6-month follow-up visit, the patients were evaluated for surgical outcome by cough stress test in full bladder, long-term complications, urinary flow rate, PVR urine, patient satisfaction, QOL index. QOL index was assessed by number of incontinence pads used per day or week (scale 1-5 – none, 1-3/week, >3/week, 1-3/day, >3/day), influence of urinary leak on daily activity (family life, social life, sleep and vacation), frequency of avoiding activities due to fear of urine leak and nonavailability of toilets (scale 1-5 – never, seldom, sometimes, often, always). The surgical outcome was divided into three groups, including cured, improved and failed. Patients were considered cured if they were extremely satisfied, with good QOL, no urine leak, negative cough stress test, no complications, good urine flow rate and <50 mL PVR. Patients were considered to have improved if they were satisfied, with satisfactory QOL, had occasional urine leakage that did not influence daily activities or require any further treatment, no leakage on the cough stress test, mild complications, satisfactory urine flow rate and post-void 50-100 mL. Treatment was considered to have failed if patient was not satisfied, had poor QOL, had urine leak, positive cough stress test, complications, poor urine flow and post-void >100 mL.

RESULTS

The total number of patients evaluated in our study was 48. The age of the patients was in the range of 35-48 years and mean age 41.3 years. Out of the total 48 patients, 46 (95.8%) were multiparous. All patients presented with involuntary loss of urine during straining, 41 (85.4%) patients had Grade 2 and duration of symptoms was more than 3 years in 44 (91.6%) patients. Twelve (25%) patients had mild cystocele preoperatively, which resolved after surgery. Associated problems, like diabetes mellitus/hypertension, were present in

9 (18%) patients. Bonney's test was positive in all cases. Abdominal leak point pressure varied from 96 to 112 cm water. All patients had maximum urine flow rate >20 mL/sec and PVR urine <50 mL. The operative time was 26 ± 4 minutes with minimal blood loss of 60 ± 20 mL, which was calculated by using pre-weighed swabs. No major intraoperative complications, like urethral or bladder injury, was observed. Catheter was removed on 1 ± 2 days postoperatively and hospital stay was 2 ± 3 days. Forty-six (95.8%) patients voided satisfactorily but 2 (4.2%) patients failed to void after catheter removal for which re-catheterization done for 3 more days and the patients voided satisfactorily after catheter removal. Various postoperative complications associated with the procedure, which gradually subsided over few days, are summarized in Table 1. Of the 48 patients, 45 (93.75%) were continent postoperatively while 3 (6.25%) patients had occasional urine leak that did not influence daily activities or require any further treatment and no leakage on the cough stress test. Return to normal activity was 4-7 days for 46 (95.8%) patients and 7-10 days for 2 (4.2%) patients. The QOL index improved from a mean value of 12.6 to a postoperative value of 2.1. Urine flow rate was >20 mL/sec in 39 (81.25%) patients postoperatively and 15-20 mL/sec in 9 (18.75%) patients that improved to >20 mL/sec after 3 months. PVR urine was <50 mL in 41 (85.4%) patients and 50-100 mL in 7 (14.6%) patients. A total of 45 (93.75%) patients were satisfied, whereas 3 (6.25%) patients were partially satisfied with surgical outcome at 6-month follow-up. Table 2 shows the surgical outcome of different patients at follow-up.

Table 1. Postoperative Complications

Complications	Number	Percentage (%)
Postoperative pain	4	8.3
Wound infection	1	2.08
UTI	2	4.16
LUTS - Urgency, dysuria	3	6.25
Hematoma, hematuria	0	0
Urinary retention	2	4.16
Mild obstructive voiding	9	18.75
Vaginal erosion, dyspareunia	0	0

UTI = Urinary tract infection; LUTS = Lower urinary tract symptoms.

Table 2. Surgical Outcome

Outcome	Number	Percentage (%)
Cured	45	93.75
Improved	3	6.25
Failed	0	0

DISCUSSION

The principal objective of the surgical treatment of SUI is to restore continence with minimal morbidity. Surgical procedures for stress incontinence are intended at lifting and supporting the urethrovesical junction. However, over the last few years, the focus has been on suburethral support at the mid-urethral level. Various procedures for suburethral support are TVT and TOT. Delorme in 2001 described the TOT procedure, which involved the tension-free insertion of a polypropylene tape *via* a tunneler in a horizontal plane under the mid-urethra between the two obturator foramina in an "outside-in" technique, which is an excellent alternative to the retropubic approach that reduces complications. There are two basic techniques for performing TOT: "outside-in" as described by Delorme and "inside-out" as described by de Leval. In our cases, trocars were placed from outside-in technique as described by Delorme. Subjective cure is usually regarded as the absence of incontinence during cough stress test.

In this study, the mean duration of surgery was 26 ± 4 minutes with minimal blood loss of 60 ± 20 mL. Taweel et al reported mean surgery duration of 18 minutes and average intra-operative blood loss of 57 mL, whereas Moore et al reported mean duration of 12.4 minutes and blood loss of 36 mL in their study. The average hospital stay of 48 patients in this study was 2.1 days. Isabelle et al reported the mean hospitalization as 2.2 days. Purnichescu et al from France reported mean duration of hospitalization as 1.25 days. In our series of 48 patients, there was no major intraoperative complication like urethral, bladder and neural or vascular injury. Achtari et al showed by cadaveric dissection that TVT-O runs more closely to the obturator canal, making TVT-O more prone to possible injury of the obturator nerve and vessels. Houwert et al prospectively studied 191 women and did not find any obturator nerve or vessel injury. Schanz et al reported 3-year experience with 200 patients, wherein 3 patients had intraoperative complications resulting in bladder injury. Two (4.2%) patients in our study, failed to void after catheter removal in 24 hours, probably due to urethral irritation but voided satisfactorily after 3 days. In the early part of our series, 9 (18.75%) patients showed decreased urine flow rate and 7 (14.6%) patients had 50-100 mL

PVR urine, which responded to conservative treatment. Sander et al observed the presence of the tape would decrease the urinary flow and offer increase in resistance to urethra, thus resulting in retention. Ingber et al and Romero-Nava et al have reported that there may be an improvement in the outcomes with time. Celik and Harmanlı have reported that voiding disturbance is known to be transient and resolve spontaneously as well. Kim et al reported a similar incidence of retention of urine and voiding dysfunction, which responded to conservative treatment. In our study, return to normal activity was 4-7 days for 46 (95.8%) patients and 7-10 days for 2 (4.2%) patients. Barry et al observed faster return to activity in TOT surgery due to short mean operation time, less dissection and natural suburethral suspension when compared with the TVT. Various postoperative complications were reported, like postoperative pain in 4 (8.3%), lower urinary tract symptoms in 3 (6.25%), wound infection in 1 (2.08%) and UTI in 2 (4.16%) patients that resolved after few days. Schanz et al, Taweel et al and Latthe et al showed similar low postoperative complications ranging from 3% to 8% following TOT surgery, which is comparable with our study. The QOL index in our study improved from a mean value of 12.6 to a postoperative value of 2.1, which is comparable with the study by Paul et al.

TOT application led to cure in 93.75% cases in this study and 6.25% cases improved. Delorme in 2001 reported on 40 patients in whom TOT was applied. Thirty-nine patients had no incontinence post-surgery and 1 patient had improvement in symptoms. In 2007, Latthe et al, quoting their experience in Britain in a series of 135 patients who were applied TOT, reported the subjective level of complete cure and improvement were 89.6% and 8.8%, respectively. In our study, 93.75% patients were satisfied and 6.25% were partially satisfied with the surgical outcome in 6-month follow-up. We found similar satisfaction rates in other studies but subjective cure rate detected in our study was better in comparison with other studies. The results of the present study have confirmed the optimal results in stress incontinence previously reported in short-term studies.

CONCLUSION

The TOT sling procedure is an effective treatment for SUI with high success rate, high satisfaction rate, low morbidity and short hospital stay. TOT surgery is well-tolerated and accepted by the patients and provides a long-term cure for patients of SUI. Considering safety, ease to perform, short operating time, quicker return to activities, minimal complications and high success rate, we recommend TOT as the primary choice for the treatment of SUI.

SUGGESTED READING

1. Ulmsten U, Henriksson L, Johnson P, Varhos G. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996;7(2):81-6.
2. Karram MM, Segal JL, Vassallo BJ, Kleeman SD. Complications and untoward effects of the tension-free vaginal tape procedure. Obstet Gynecol. 2003;101(5 Pt 1):929-32.
3. Delorme E. Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women. Prog Urol. 2001;11(6):1306-13.
4. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol. 2002;187(1):116-26.
5. Paul F, Jose A, Giridhar A, Mampatta J, Shetty S, Bhat S. Impact of transobturator tape procedure on quality of life in female stress urinary incontinence. IJARS. 2017;6(1):SO06-SO09.
6. Minaglia S, Ozel B, Hurtado E, Klutke CG, Klutke JJ. Effect of transobturator tape procedure on proximal urethral mobility. Urology. 2005;65(1):55-9.
7. de Leval J. Novel surgical technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out. Eur Urol. 2003;44(6):724-30.
8. Latthe PM, Patodi M, Constantine G. Transobturator tape procedure in stress urinary incontinence: UK experience of a district general hospital. J Obstet Gynaecol. 2007;27(2):177-80.
9. Taweel WA, Rabah DM. Transobturator tape for female stress incontinence: follow-up after 24 months. Can Urol Assoc J. 2010;4(1):33-6.
10. Moore RD, Miklos JR, Cervigni M, Davila W, Mellier G, Jacquetin B. Transobturator sling: combined analysis of 1 year follow-up in 9 countries with 266 patients: XV Congress of the International Society for Gynecologic Endoscopy. April 1. Argentina: Buenos Aires; 2006. pp. 101-4.
11. Purnichescu V, Cheret-Benoist A, Eboué C, Von Theobald P. Surgical treatment for female stress urinary incontinence by transobturator tape (outside in). Study of 70 cases. J Gynecol Obstet Biol Reprod (Paris). 2007;36(5):451-8.
12. Achtari C, McKenzie BJ, Hiscock R, Rosamilia A, Schierlitz L, Briggs CA, et al. Anatomical study of the obturator foramen and dorsal nerve of the clitoris and their relationship to minimally invasive slings. Int Urogynecol J Pelvic Floor Dysfunct. 2006;17(4):330-4.
13. Houwert RM, Renes-Zijl C, Vos MC, Vervest HA. TVT-O versus Monarc after a 2-4-year follow-up: a prospective

comparative study. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(11):1327-33.

14. Schanz JP, Arriola PR, Fernández XT, Ortiz EB. Trans obturator tape (TOT) for female stress incontinence. Experience with three years follow-up in 200 patients. Actas Urol Esp. 2007;31(10):1141-7.
15. Sander P, Møller LM, Rudnicki PM, Lose G. Does the tension-free vaginal tape procedure affect the voiding phase? Pressure-flow studies before and 1 year after surgery. BJU Int. 2002;89(7):694-8.
16. Ingber MS, Krlin RM, Vasavada SP, Firoozi F, Goldman HB. Outcomes of midurethral slings in women with concomitant preoperative severe lower urinary tract voiding symptoms. Ochsner J. 2015;15(3):223-7.
17. Romero-Nava LE, Gómez-Cardoso R. Stress urinary incontinence treatment with modified technique tension-free vaginal tape obturator. Ginecol Obstet Mex. 2015;83(9):537-44.
18. Celik H, Harmanlı O. Evaluation and management of voiding dysfunction after midurethral sling procedures. J Turk Ger Gynecol Assoc. 2012;13(2):123-7.
19. Kim S, Bae J, Cho M, Lee K, Lee H, Jun T. Effect of preoperative flow rate on postoperative retention and voiding difficulty after transobturator tape operation. Korean J Urol. 2014;55(3):190-5.
20. Barry C, Lim YN, Muller R, Hitchins S, Corstiaans A, Foote A, et al. A multi-centre, randomised clinical control trial comparing the retropubic (RP) approach versus the transobturator approach (TO) for tension-free, suburethral sling treatment of urodynamic stress incontinence: the TORP study. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(2):171-8.

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COVID-19 Positivity Rate in India Shows Marginal Decline

The positivity rate of COVID-19 infections in India has seen a marginal decline, reveal government data. The government has stated that aggressive testing helped authorities carry out effective treatment and maintain a low fatality rate. Over the past month, the positivity rate of COVID-19 infections came down from 8.52% to 8.32% on Saturday (Oct 4), which has been attributed to significant scaling up of testing. Government data till Saturday (Oct 4) reported that the total number of cases and deaths in the country stood at 55,09,966 and 101,782 respectively. The national case fatality rate is reported to be 1.84%.

The country's testing capacity has been increased to conduct about 1.5 million tests per day and on average, about a million COVID-19 tests have been done per day over the past 1 month… (*HT*)

Olive Oil as HFpEF Treatment

Extra virgin olive oil (EVOO) appears promising as a secondary prevention therapy for heart failure with preserved ejection fraction (HFpEF), reported a small uncontrolled study.

Nine participants with HFpEF and obesity were supplemented with unsaturated fatty acid-rich foods and their EVOO intake was estimated over 12 weeks according to their dietary recall. Daily EVOO intake increased from zero at baseline to 23.6 g on average during the study period. Greater EVOO intake was associated with small but significant improvements in cardiorespiratory fitness on cardiopulmonary exercise testing (CPET). A statistical model indicated that a 40-g increase in EVOO intake resulted in an increased peak VO_2 by just under 2 mL/kg/min, translating to a nearly 6% improvement compared with predicted peak VO_2; oxygen uptake efficiency slope also increased by about 0.1. The findings were presented at the virtual Heart Failure Society of America meeting… (*Medpage Today*)

Remdesivir Effective, Well-tolerated: Final Trial Report

A final report from the multinational ACTT-1 trial has confirmed that remdesivir is effective and well-tolerated for reducing the time to recovery from COVID-19 infection. The newly published ACTT-1 trial data revealed that the median time to recovery was 10 days for those on active therapy compared to 15 days for those on placebo. With a rate ratio of 1.29 ($p < 0.001$), the recovery was about one-third faster. In the final report, the significant advantage of remdesivir over placebo for the trial's primary endpoint was strengthened by efficacy on several secondary endpoints. The benefits on secondary endpoints included a 50% greater odds ratio (OR, 1.5; 95% CI, 1.2-1.9) of significant clinical improvement by Day 15 after adjusting for baseline severity, a shorter initial length of hospital stay (12 vs. 17 days) and fewer days on oxygen supplementation (13 vs. 21 days) for the subgroup on oxygen therapy at enrollment. The findings were published in the *New England Journal of Medicine…* (*Medscape*)

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

ARCHANA JORIGE*, LOHITHA B, LAVANYA SL

ABSTRACT

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

Keywords: Pediatrics, prescribing indicators, antibiotics, demographic characters

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

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

MATERIAL AND METHODS

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

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

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

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

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

RESULTS

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

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

Table 1. Summary of Drugs per Prescription

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

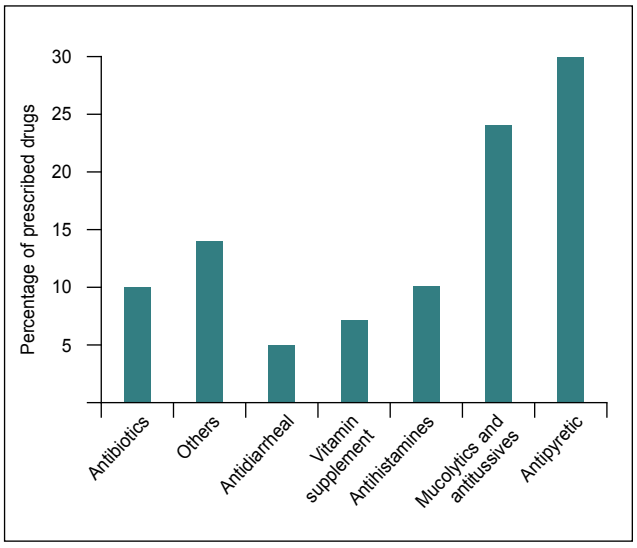

Figure 1. Percentage of prescribed drugs from various therapeutic classes.

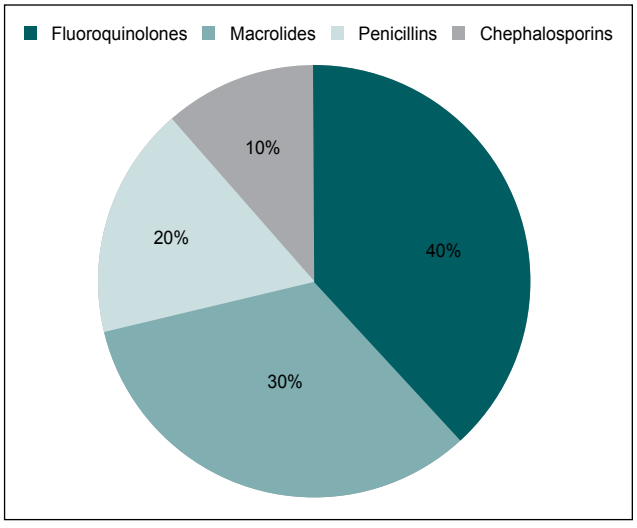

Figure 2. Relative percentage of prescribed antibiotics.

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

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

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

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

DISCUSSION

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

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

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

CONCLUSION

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

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SUGGESTED READING

1. Lalan BK, Hiray RS, Ghongane BB. Drug prescription pattern of outpatients in a tertiary care teaching hospital in Maharashtra. Int J Pharm Bio Sci. 2012;3(3): 225-9.
2. Foliaki S, Pearce N, Björkstén B, Mallol J, Montefort S, von Mutius E; International Study of Asthma and Allergies in Childhood Phase III Study Group. Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: International Study of Asthma and Allergies in Childhood Phase III. J Allergy Clin Immunol. 2009;124(5):982-9.
3. Murphy R, Stewart AW, Braithwaite I, Beasley R, Hancox RJ, Mitchell EA; ISAAC Phase Three Study Group. Antibiotic treatment during infancy and increased body mass index in boys: an international cross-sectional study. Int J Obes (Lond). 2014;38(8):1115-9.
4. WHO Model List of Essential Medicines for Children: First List, WHO. 2007. Available at: https://www.who.int/medicines/publications/essentialmedicines/en/
5. World Health Organization Model List of Essential Medicines for Children: 7th List. 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1.
6. World Health Organization. How to Investigate Drug use in Health Facilities: Selected Drug use Indicators. WHO/DAP. Vol. 1. Geneva: World Health Organization; 1993. pp. 1-87.
7. Akhtar MS, Vohora D, Pillai K, Dubey K, Roy M, Najmi A, et al. Drug prescribing practices in paediatric department of a North Indian university teaching hospital. Asian J Pharm Clin Res. 2012;5(1):146-9.
8. Malpani AK, Waggi M, Rajbhandari A, Kumar GA, Nikitha R, Chakravarthy AK. Study on prescribing pattern of antibiotics in a pediatric out-patient department in a tertiary care teaching and non-teaching hospital. Indian J Pharm Pract. 2016;9(4):253-9.
9. Pandey AA, Thakre SB, Bhatkule PR. Prescription analysis of pediatric outpatient practice in Nagpur city. Indian J Community Med. 2010;35(1):70-3.
10. Vallano A, Montané E, Arnau JM, Vidal X, Pallarés C, Coll M, et al. Medical speciality and pattern of medicines prescription. Eur J Clin Pharmacol. 2004;60(10): 725-30.
11. Roy V, Gupta U, Gupta M, Agarwal AK. Prescribing practices in private health facilities in Delhi (India). Indian J Pharmacol. 2013;45(5):534-5.

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Hospital Course and Comorbidity Profile of Swine Flu (H1N1) Deaths in a Tertiary Care Hospital, Southern Rajasthan

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ABSTRACT

Introduction: Influenza is an acute respiratory tract infection caused by influenza virus. There has been resurgence since 2009 pandemic in India. Rajasthan, being one of the worst hit states and the fact that clinico-epidemiological profile of swine flu positive deaths varies from place to place and from time to time, it becomes important to conduct audit of cases in each resurgence phase. **Methods:** A hospital-based retrospective descriptive study done in MB Government Hospital, Udaipur on 61 swine flu positive deaths for a year (September 2018 to August 2019). All relevant details were noted in the preformed performa, analyzed and results were attributed a statistical significance of $p < 0.05$. **Results:** Out of 61 deaths, 27.9% deaths were in the 41-50 age group. About 63.9% were males and 50.8% belonged to rural areas. Only 21.3% patients seeked hospital care within 72 hours of onset of symptom. Fifty-three had comorbidities. Type 2 diabetes mellitus (30.1%) was the most common comorbidity. **Conclusion:** Our study showed that most patients had multiple comorbidities. Those with comorbidities and delayed hospitalization from the onset of symptoms (>3 days delay) showed less survival time in the hospital. People with a comorbid condition should be vaccinated with influenza vaccine prior to outbreak of the disease.

Keywords: Swine flu, acute respiratory distress syndrome, comorbidities

Influenza is an acute respiratory tract infection caused by influenza virus. There are four types of influenza virus, namely A, B, C and D, with influenza A often causing pandemics. Influenza A undergoes frequent antigenic variation, termed shifts and drifts. This antigenic shift leads to sudden key change, giving rise to new epidemics or pandemics. Influenza is known to spread from person to person through droplet infection and the risk of transmission is heightened in overcrowded places, thereby facilitating the spread of the infection in times of epidemic. Influenza affects all age groups and both sexes; however, children, those aged 65 years and above as well as immunocompromised individuals are at high risk of infection.[1]

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In June 2009, the World Health Organization (WHO) declared the first influenza pandemic of the century following the spread of new influenza A (H1N1) virus.[2]

In India, the first confirmed case was reported in May 2009 and from Gujarat state in June 2009.[3-5] In 2017, 38,811 confirmed influenza cases were reported with 2,270 deaths in India.[6]

The pandemic influenza A (H1N1) started in southern part of Rajasthan in August 2009 and lasted until November 2010. Two thousand four hundred sixty-two patients were screened for influenza-like illness in a study and 1,022 throat swabs were taken for reverse transcription-polymerase chain reaction (RT-PCR). Of these, 297 (29.06%) patients were found positive for H1N1.[7] Thereafter, there have been resurgences in 2015, 2017 and now in 2019.

Rajasthan, being one of the worst hit states and the fact that clinico-epidemiological profile of the H1N1-infected patients varies from place to place and from time to time, it becomes important to conduct audit of cases in each resurgence phase.

The objectives of the present study were to explore the demographic profile of H1N1 positive deaths, to know

the onset-to-hospitalization (OH) time, hospitalization-to-death time, to study the comorbidities associated and to study the effect of delayed hospitalization (>3 days) on mortality.

METHODOLOGY

This was a hospital-based retrospective descriptive study done in the Swine Flu Block of RNT Medical College and attached MB Government Hospital, Udaipur, Rajasthan for a period of 1 year from September 2018 to August 2019. All 61 laboratory confirmed (RT-PCR) H1N1 swine flu positive deceased were included in the study. A semi-structured self-designed performa was used to collect the details pertaining to socio-demographic details, presenting complaints, time interval since onset of symptoms and seeking healthcare, receiving oseltamivir, events after hospitalization, throat or nasal swab collection, shifting to ICU and death. Details of radiological features were recorded from the case sheets and any relevant information missing was taken *via* telephonic conversation wherever necessary.

Data Analysis and Interpretation

Data entry and analysis was done using Microsoft Excel 2010, Open Epi version 3 software. Descriptive statistics, mean with standard deviation values and percentages were used to interpret the results. Tests of significance, like students *t*-test, Chi-square test, were used to find out the association between various variables and significance attributed to $p < 0.05$. Results were interpreted in the form of simple tables and graphs wherever necessary.

RESULTS

Out of 512 laboratory confirmed swine flu positive cases, 240 (46.9%) were admitted in the swine flu block and 61 (11.9%) expired among them. One hundred ninety-five cases (38.1%) and 16 deaths (3.12%) were reported in the month of February, 2019, followed by 178 cases (34.8%) and 15 deaths (2.9%) in January, 2019 (Fig. 1).

Out of 61 deaths, 17 (27.9%) deaths were in the 41-50 years age group, followed by 14 (23%) in >60 years age group, with mean age being 48.3 ± 17.5 years. Thirty-nine (63.9%) were males and mean age of males was 49.4 ± 15.4 years and that of females was 46.3 ± 20.9 years. Thirty-one (50.8%) belonged to rural areas (Table 1).

Out of 61 deaths, only 13 (21.3%) patients seeked hospital care within 72 hours (3 days) of onset of symptom, while 19 (31.1%) seeked hospital care on 5th day of onset of symptoms (range 1-30 days). Mean duration between onset of symptoms and hospitalization was 5.9 ± 4.5 days.

The common presenting symptoms were - all (100%) had fever, 60 (98.4%) had common cold, 55 (90.2%) had cough, 52 (85.2%) had breathlessness/shortness of breath.

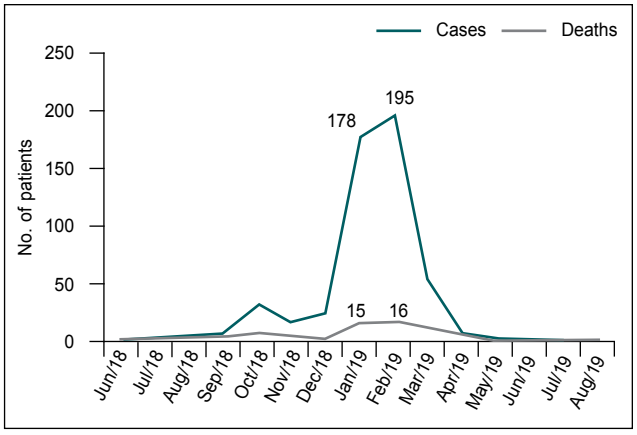

Figure 1. Month-wise distribution of swine flu positive cases and deaths.

Table 1. Socio-demographic Details of Swine Flu Positive Deaths

Socio-demographic variables	Age group	N	%
Age (years)	0-10	1	1.6
	11-20	3	4.9
	21-30	8	13.1
	31-40	6	9.8
	41-50	17	27.9
	51-60	12	19.7
	>60	14	23.0
	Total	**61**	**100**
Overall mean age: 48.3 ± 17.5 years Male: 49.4 ± 15.4 years Female: 46.3 ± 20.9 years			
Gender	Male	39	63.9
	Female	22	36.1
	Total	**61**	**100**
Location	Urban	25	41
	Rural	31	50.8
	Tribal	5	8.2
	Total	**61**	**100**

Only 4 (6.5%) received drug oseltamivir within 24 hours of onset of symptoms while upon admission, all (100%) patients received it, either in the form of 75 or 150 mg BID.

Fifty-eight (95.08%) had bilateral atypical consolidation feature on chest X-ray.

Among 61 deaths, 53 (86.9%) had comorbidities. Among these 53, 16 (30.1%) had single comorbidity and 37 (69.9%) had multiple (≥2) comorbidities.

Among 53 who had comorbidities, 16 (30.1%) had type 2 diabetes mellitus, 12 (22.6%) were hypertensive, 11 (20.7%) had chronic obstructive pulmonary disease (COPD), 9 (16.9%) had chronic kidney disease (CKD), and 8 (15.1%) were morbidly obese (Table 2).

One (4.5%) among 22 deceased females were pregnant. The complications were - 9 (14.7%) had acute kidney injury (AKI), 61 (100%) had acute respiratory distress syndrome (ARDS), 14 (22.9%) had ARDS with multiple organ dysfunction syndrome (MODS), 3 (4.9%) had septicemia, 2 (3.3%) had CO_2 narcosis.

All (100%) patients who died required ventilatory support in the form of mechanical ventilation and couldn't be weaned off from ventilator till death.

Table 2. Distribution of Comorbidity among Swine Flu Positive Deaths

List of comorbidity	N = 53* (%)
Type 2 diabetes mellitus	16 (30.1)
Hypertension	12 (22.6)
Chronic obstructive pulmonary disease	11 (20.7)
Chronic kidney disease	9 (16.9)
Morbid obesity	8 (15.1)
Chronic liver disease	6 (11.3)
Coronary artery disease	4 (7.5)
Severe anemia	4 (7.5)
Cerebrovascular disease	2 (3.8)
Rheumatic heart disease	2 (3.8)
Pulmonary tuberculosis	2 (3.8)
Carcinoma lung	1 (1.9)
Dengue fever	1 (1.9)
HIV AIDS (Retroviral disease)	1 (1.9)

*53 out of 61 had comorbidity(s).

The mean duration of hospital stay (mean survival time after admission) was 3.85 ± 2.8 days (median: 3 days, range: 1-14 days).

Seventeen (27.9%) survived for only 24 hours, 6 (9.8%) survived for 2 days, 9 (14.8%) survived for 3 days and 9 (14.8%) for 5 days.

Various factors affected the mean survival time of swine flu positive patients. Those who were hospitalized within 3 days of onset of symptoms survived for 4.3 ± 3.4 days and those without any comorbidities survived for 5.6 ± 3.02 days (Table 3).

Overall, 47 (77%) survived for <5 days after admission. Among 48 patients who were admitted to hospital after 3 days delay from onset of symptoms, 37 (77.1%) survived for less than 5 days. This difference among delayed hospitalization from onset of symptom on mean survival time wasn't statistically significant (P-0.9) (Table 4).

Table 3. Factors Influencing the Mean Survival Time of Swine Flu Positive Deaths

Factors	Criteria	N = 61	Mean (SD) survival time (days)	P value
Delay in hospitalization from onset of symptoms	<3 days	13	4.3 ± 3.4	0.5
	>3 days delay	48	3.7 ± 2.6	
Presence of comorbidity(s)	Yes	53	3.6 ± 2.6	0.05*
	No	8	5.6 ± 3.02	

*P < 0.05 is significant.

Table 4. Effect of Time of Hospitalization on Survival Time

		Survival time (days)		Total (%)	P value
		<5 days (%)	>5 days (%)		
Hospitalization time from onset of symptoms	<3 days	10 (76.9)	3 (23.1)	13 (100)	P value* (Chi-square) - 0.9
	>3 days delay	37 (77.1)	11 (22.9)	48 (100)	
	Total	**47 (77)**	**14 (23)**	**61 (100)**	

P < 0.05 is significant.

DISCUSSION

In our study, out of 512 laboratory confirmed swine flu positive cases, maximum cases (38.1%) and deaths (3.12%) were reported in the month of February 2019, followed by 34.8% cases and 2.9% deaths in January 2019. The epidemic propagated from October to April with peaks in January and February. A similar propagation was seen in a study by Choudhary et al.[5]

A study in Nagpur in 2015 showed peak rise in mid-week of February and first week of March.[8]

The H1N1 epidemic in Hyderabad from December 2014 to April 2015 saw a peak in January 2015.[9] A swine flu epidemic in North Karnataka in the year 2012 noted a peak rise in cases from July to September 2012.[5,10]

Though influenza is more common in winter months, it can be seen that since the 2009 H1N1 epidemic, the occurrence of epidemic is seen round the year in different places across India.

The case fatality ratio (CFR) was 11.9% (61/512). It is only an approximate value as it does not include the cases that were tested positive at this hospital but opted to go to other places for treatment and died there. Other studies during previous outbreaks in Rajasthan have reported CFR to be 7.18% in Bikaner (2015),[11] 17.9% in Jaipur (2015)[12] and 19.1% in Jodhpur (2012).[13]

Among total deaths, majority i.e., half (50.9%) the deaths were in age group of 41-50 years and >60 years. Jain et al[14] showed the majority (92.5%) of deceased persons were almost equally distributed in 20-40 years and 40-60 years age groups, while Singh et al[13] have reported 51.7% deaths in 15-30 years age group and 22.4% in 30-45 years age group in Jodhpur in 2012. Mean age of deceased in our study was 48.3 ± 17.5 years. Similar finding was found in Arbat et al[8] (mean age: 47 years) and Sonkar et al[15] (47 years), while it was more compared to Taparia et al[16] (36.5 years), and less compared to Kshatriya et al[17] (51.0 years).

People in these age groups are working actively and are more prone to exposure to the virus. The difference of age might be due to severity change of epidemic or less of pediatric age group in our study.

In our study, majority (63.9%) deceased were males with male:female ratio being 1.8:1.

Similarly, Arbat et al showed male predominance.[8] This explains that males have more exposure to the infected, which may be due to more contact and outdoor exposure. Jain et al[14] showed almost equal number of deceased persons among males and females. Contrary to this, higher female mortalities have been reported in previous resurgences from Rajasthan.[11,13]

Males or females are not susceptible only by virtue of gender. The differences in male or female preponderance of cases could be due to increased exposure of the individuals to the host and also the environmental factors. It also could be due to differences of reporting due to accessibility to healthcare and treatment seeking behavior of individuals due to which the cases may not have come in contact with the health system.

The proportion of deceased was higher in rural area (50.8%) compared to urban (41%). Rural predominance was found in studies by Arbat et al[8] and Jain et al.[14] During 2015 resurgence, rural predominance was reported in North-West Rajasthan[11] while predominantly urban mortalities (63.5%) were reported from Jaipur.[18]

Out of 61 deaths, only 21.3% patients seeked hospital care within 72 hours (3 days) of onset of symptom. While 59% seek hospital care between 3 and 7 days. Mean duration between onset of symptoms and hospitalization was 5.9 ± 4.5 days. Once hospitalized, all 61 patients received oseltamivir immediately and their throat swab was taken and sent for testing within 24 hours. This suggests prompt diagnosis and management of H1N1 influenza cases once they reported to this hospital.

Similar mean onset to hospitalization time was seen in study by Jain et al[14] (5.8 days), but Taparia et al[16] showed 4.8 median days. In a study in Hyderabad, 42.04% patients reported to the hospital within 48 hours while 52.27% patients reported from 3 to 7 days after symptom onset.[5,9]

Majority presented to hospital with fever (100%) along with common cold (98.4%), cough (90.2%) and breathlessness (85.2%). Another study in Udaipur, Rajasthan showed breathlessness as major presenting symptom,[14] while Kshatriya et al[17] showed cough followed by fever as major presenting feature.

Overall, there has been no change in the presentation of H1N1 cases since the 2009 epidemic. The clinical presentation has been the same whether in 2009 or 2015, or 2019 swine flu outbreak.

Majority (95.08%) had bilateral atypical consolidation feature on chest X-ray which is similar to Jain et al,[14] Arbat et al[8] and Kshatriya et al.[17] Findings on chest radiograph were consistent with ARDS in all patients requiring mechanical ventilation and all (100%) patients who died required ventilatory support in form of

mechanical ventilation and couldn't be weaned off from ventilator till death which is similar to Taparia et al[16] and Sonkar et al.[15] Mehta et al also showed bilateral pneumonia as independent risk factor associated with mortality or need of mechanical ventilation and poor prognosis.[19]

Majority (86.9%) of the deceased had comorbidities/ risk factors. Among these, 69.9% had more than one (multiple) comorbidities. This is similar to other studies in Rajasthan.[11,14] Amaravathi et al[9] and Sonkar et al,[15] found through their study that the severity of the disease (Category C), occurrence of pneumonia and mortality were higher among patients with comorbid conditions, while Arbat et al[8] showed 75% among deceased had comorbidities.

Diabetes mellitus type 2 was most common comorbidity (30.1%) followed by hypertension (22.6%), COPD (20.7%), CKD (16.9%) and morbid obesity (15.1%). Others were chronic liver disease (CLD), coronary artery disease (CAD) and anemia.

Other studies[11,14,20] have also reported high existence of diabetes mellitus in H1N1 positive mortalities. Kshatriya et al[17] reported high existence of hypertension (37%) in their study followed by diabetes mellitus (27%).

Mortality in pregnancy was 4.5% (1 out of 22). Jain et al[14] showed mortality as high as 26.3% in pregnancy.

In few studies,[11,21] female gender and pregnancy and postpartum state were important risk factors for mortality. Studies in Rajasthan[13] and Telangana[9] showed that mortality was higher among pregnant women compared to nonpregnant women. Weaker immune system, reduced tidal volume, congestion and localized edema, make a woman more susceptible to complications, such as pneumonia and ARDS.[22]

Most common complication was ARDS (100%) followed by ARDS with MODS (22.9%). Taparia et al showed in their study that 28.8% of the patients died of MODS with ARDS.[16]

The mean duration of hospital stay was 3.85 ± 2.8 days (median: 3 days, range: 1-14 days). Approximately 27.9% survived for only 24 hours, which shows that patients presented to our center in critical condition and 14.8% survived for 5 days.

In a study conducted in Chandigarh, out of the 28 deaths, 46% of the deaths occurred within 48 hours of hospital admission, of which 7 were within 24 hours of admission.[23]

A study in Solapur showed a high average hospital stay of 9.6 days (range 1-37)[8] and a study in Lucknow showed it to be 4.93 days (range 1-9).[15]

A previous study in Udaipur showed that 27.5% fatalities occurred within 24 hours of hospitalization with mean survival time of 4.02 days.[14] Other studies from Rajasthan during past outbreaks showed higher mortalities within first 2-3 days of hospitalization - 53.4% deaths within 48 hours of admission at Jodhpur, of which 77.4% deaths were within 24 hours of admission.[13]

Patients who were admitted to the hospital after 3 days delay from onset of symptoms showed more mortality (77.1%), though this difference among delayed hospitalization wasn't statistically significant (P-0.9). Choudhary et al showed higher proportion of deaths (6.8%) in the patients who were hospitalized late (i.e., after 48 hours of onset of symptoms).[5]

This study has tried to identify the clinical and epidemiological profile of H1N1 mortalities and comorbidities during current (2019) resurgence in Southern region of Rajasthan. The results will add to the pool of literature on impact of post pandemic outbreaks and aid in public health research in this direction.

CONCLUSION

In our study, higher mortality was seen in late winters. Majority of deceased were males, in the age group of 41-50 years, from rural background. Fever followed by cold and cough was the most common presenting symptom. Most had multiple comorbidities and diabetes mellitus was the most common comorbidity followed by hypertension, COPD, CKD and morbid obesity. Those with comorbidities and delayed hospitalization from the onset of symptoms (>3 days delay) showed less survival time in the hospital compared to others. Also, higher proportion of mortality was seen in those who were hospitalized late. More audit studies of current and future resurgences will give better insight in morbidity and mortality profile. People with comorbid condition should be vaccinated with influenza vaccine prior to outbreak of the disease. Suspected cases should be promptly treated with oseltamivir within 48 hours of illness to prevent complication and fatality.

LIMITATIONS

This was a retrospective study. It has a selection bias as positive patients admitted only in our hospital were studied for a short period and the size of the cohort (number of patients) is relatively small. The

laboratory investigations and other tests were carried as per the clinical requirement and not according to the standardized protocol. Also, study was confined to small geographical area.

REFERENCES

1. Park K. Epidemiology of communicable diseases. In: Park's Textbook of Preventive and Social Medicine. 25th Edition, Jabalpur: M/s Banarsidas Bhanot; 2019. pp. 166-72.
2. World Health Organization. World now at the start of 2009 influenza pandemic. Media Centre. 11th June, 2009. Available at: https://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/
3. Government of India (MoHFW). Situation update on H1N1. 2010. Ministry of Health and Family Welfare. 2010.
4. Choudhry A, Singh S, Khare S, Rai A, Rawat DS, Aggarwal RK, et al. Emergence of pandemic 2009 influenza A H1N1, India. Indian J Med Res. 2012;135(4):534-7.
5. Choudhary SR, Momin MH, Chauhan NT, Chhaya J. Profile of influenza A (H1N1) positive patients of Surat district. Int J Contemp Med Res. 2017;4(2):504-6.
6. Seasonal Influenza A (H1N1): State/UT- wise number of cases & deaths from 2016 to 2020* (As on 31.08.2020). Available from: https://ncdc.gov.in/showfile.php?lid=280
7. Sharma CP, Keerti, Sharma S, Kumar A, Gupta MK. Demographic correlates of swine flu cases attending a tertiary care hospital in Rajasthan. Indian J Prev Soc Med. 2012;43(2):224-8.
8. Arbat S, Dave M, Niranjane V, Rahman I, Arbat A. Analyzing the clinical profile of swine flu/influenza A H1N1 infection in central India: a retrospective study. Virusdisease. 2017;28(1):33-8.
9. Amaravathi KS, Sakuntala P, Sudarsi B, Manohar S, Nagamani R, Rao SR. Clinical profile and outcome of recent outbreak of influenza A H1N1 (swine flu) at a tertiary care center in Hyderabad, Telangana. Ann Trop Med Public Health. 2015;8:267-71.
10. Kashinkunti MD, Gundikeri SK, Dhananjaya M. Study of clinical profile of patients with H1N1 Influenza in a teaching hospital of North Karnataka. IJRRMS. 2013;3:53-5.
11. Kumar S. A study of outbreak of swine flu (H1N1) in North-West zone of Rajasthan (Current Status - 2015). J Assoc Physicians India. 2016;64(7):46-9.
12. Sharma R, Agarwal S, Mehta S, Nawal CL, Bhandari S, Rathore M, et al. Profiling the Mortality due to Influenza A (H1N1) pdm09 at a tertiary care hospital in Jaipur during the current season - January & February 2015. J Assoc Physicians India. 2015;63(4):36-9.
13. Singh M, Sharma S. An epidemiological study of recent outbreak of Influenza A H1N1 (Swine Flu) in Western Rajasthan region of India. J Med Allied Sci. 2013;3(2):48-52.
14. Jain A, Sharma R, Nagar MK, Kaushik PB. A death audit of H1N1 influenza cases in a tertiary care hospital in Southern Rajasthan (Current Out Break- 2017). Natl J Community Med. 2018;9(5):380-4.
15. Sonkar SK, Kumar S, Atam V, Chaudhary SC, Kumar A, Kumar A, et al. Clinical, biochemical and radiological features of swine flu pandemic in a tertiary care centre of northern India In 2017-2018. Assam Int J Recent Sci Res. 2019;10(08):34338-42.
16. Taparia NB, Jeurkar VN, Rudrakshi SM, Singhal PJ. Clinical aspects and outcome of patients with swine flu among survivors and non-survivors. Int J Adv Med. 2018;5(5):1151-7.
17. Kshatriya RM, Khara NV, Ganjiwale J, Lote SD, Patel SN, Paliwal RP. Lessons learnt from the Indian H1N1 (swine flu) epidemic: Predictors of outcome based on epidemiological and clinical profile. J Family Med Prim Care. 2018;7(6):1506-9.
18. Malhotra B, Singh R, Sharma P, Meena D, Gupta J, Atreya A, et al. Epidemiological & clinical profile of influenza A (H1N1) 2009 virus infections during 2015 epidemic in Rajasthan. Indian J Med Res. 2016;144(6):918-23.
19. Mehta AA, Kumar VA, Nair SG, K Joseph F, Kumar G, Singh SK. Clinical profile of patients admitted with swine-origin influenza A (H1N1) virus infection: an experience from a tertiary care hospital. J Clin Diagn Res. 2013;7(10):2227-30.
20. Sardar JC, Sau A, Mandal PK. Clinico-epidemiological profile of confirmed swine flu (H1N1) cases admitted at an infectious disease hospital in Kolkata, India. Int J Community Med Public Health 2016;3(8):2340-3.
21. Bhatt KN, Jethw SC, Bhadiyadar D, Patel D, Joshi K. Study of clinical profile in patients with H1N1 influenza in Surat district, June 2009-March 2010. J Assoc Physicians India. 2012;60:15-9.
22. Lim BH, Mahmood TA. Influenza A H1N1 2009 (swine flu) and pregnancy. J Obstet Gynaecol India. 2011;61(4):386-93.
23. Siddharth V, Goyal V, Koushal VK. Clinical-epidemiological profile of influenza A H1N1 cases at a tertiary care institute of India. Indian J Community Med. 2012;37(4):232-5.

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A Comparative Study to Analyze the Association of Metabolic Syndrome in Females with Diagnosed Polycystic Ovarian Syndrome

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ABSTRACT

Objectives: Polycystic ovarian syndrome (PCOS) is a common female endocrinopathy affecting 5-6% of women within the age group 12-45 years. This study was contemplated with the aim to study the prevalence of metabolic syndrome in patients of PCOS and to study the spectrum of clinical features of metabolic syndrome in patients of PCOS. **Material and methods:** This case-controlled study was conducted on 50 cases of diagnosed PCOS females and compared with 50 healthy age and body mass index (BMI) matched controls. **Results:** The prevalence of metabolic syndrome in PCOS patients was found to be 24% and in control group it was 6%. Among patients with metabolic syndrome 14% of patients had high blood pressure, 12% had impaired fasting glucose, 38% had high waist-hip ratio, 14% had raised serum triglycerides and 44% had decreased high-density lipoprotein (HDL). **Conclusion:** It is observed that metabolic syndrome manifests at an early age in women with PCOS. In order to prevent metabolic syndrome one should maintain BMI <25 and waist circumference <35 inches.

Keywords: Metabolic syndrome, polycystic ovarian syndrome, hyperinsulinemia

Polycystic ovarian syndrome (PCOS) is one of the most common female endocrinopathies affecting 5-6% of women within the age group 12-45 years. These patients are at high-risk of developing infertility, dysfunctional uterine bleeding, endometrial carcinoma and a number of metabolic disorders including insulin resistance, hyperinsulinemia, type 2 diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease. Due to these facts, early diagnosis of the syndrome should be emphasized.

This background knowledge demands the necessity to work out the prevalence of metabolic syndrome in women with PCOS in our society and to measure the strength of their association in the Indian scenario.

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AIMS AND OBJECTIVES

- To study the prevalence of metabolic syndrome in patients of PCOS.
- To study the spectrum of clinical features of metabolic syndrome in patients of PCOS.

MATERIAL AND METHODS

This study was conducted on 50 cases of diagnosed PCOS coming to our hospital and was compared with 50 healthy age and body mass index (BMI) matched women (control group) over a period of 1 year.

Inclusion Criteria

Around 50 cases diagnosed to have PCOS by the Rotterdam European Society of Human Reproduction Embryology/The American Society of Reproductive Medicine (ESHRE/ASRM) PCOS group's revised 2003 criteria, with presence of any two of the three criteria, were recruited for the study. These criteria are:

- Oligo and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (as confirmed by USG)

The criteria for metabolic syndrome in women with PCOS.

According to National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III) 2001, three out of these five will qualify for the syndrome:

- Abdominal obesity (waist circumference ≥88 cm or 35 inches) and ≥80 cm for Asian females
- Triglycerides ≥150 mg/dL
- High-density lipoprotein (HDL) cholesterol ≤50 mg/dL
- Blood pressure ≥130/85 mmHg
- Fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes.

After taking careful history from the patient and conducting examination, following investigations were carried out - hemogram, fasting blood sugar, oral glucose tolerance test (OGTT), fasting insulin, fasting lipid profile, hormonal estimations for leuteinizing hormone, follicle-stimulating hormone, testosterone, estrogen, progesterone and ultrasound abdomen.

In these women, fasting blood was drawn for glucose, insulin and lipid profile, which included triglycerides, total cholesterol, HDL and low-density lipoprotein (LDL) cholesterol. A 2-hour 75 g glucose tolerance test was done in all PCOS patients.

Two markers for obesity, such as BMI and waist-hip ratio, which depict central obesity, were used to study the relationship of obesity to lipid parameters. Height (m) and weight (kg) measurements can be used to calculate the BMI (BMI = Weight in kg/height in m^2). Waist-hip ratio can be calculated after measuring waist circumference between pelvic brim and costal margin, while hip circumference is taken at the level of the greater trochanter. Waist-hip ratio >0.85 is considered abnormal, while <0.85 normal.

The results were subjected to statistical analysis wherever applicable.

RESULTS

The profile of patients included in the study is shown in Table 1. The distribution of cases and controls according to BMI (kg/m^2) is shown in Table 2.

It is seen that 68% of patients included in the study were overweight or obese. Table 3 shows distribution of cases according to fasting insulin levels. Fasting insulin levels were raised in 24% of cases and 10% of controls.

Table 1. Patient Profile

	Age group			Socioeconomic status	
	15-25	26-35	Total	Low	High
Cases					
No.	21	29	50	20	30
%	42	58	100	40	60
Controls					
No.	16	34	50	22	28
%	32	68	100	44	56

P value < 0.04.

Table 2. Distribution of Cases and Controls according to BMI (kg/m^2)

Category according to BMI (kg/m^2)	Cases		Controls	
	No.	%	No.	%
Underweight (≤19.9)	3	6	2	4
Normal (20-24.9)	13	26	15	30
Overweight (25-29.9)	30	60	28	56
Obese (≥30)	4	8	5	10
Total	**50**	**100**	**50**	**100**

Table 3. Distribution of Cases according to Fasting Insulin Levels

Category	Cases		Controls	
	No.	%	No.	%
Normal	38	76	45	90
Increased	12	24	5	10

Table 4. Distribution of Cases according to Components of Metabolic Syndrome in Patients of PCOS

Clinical components	Cases		Controls	
	Positive	%	Positive	%
BP >130/85 mmHg	7	14	2	4
Impaired fasting blood glucose (>100 mg/dL)	6	12	2	4
Waist-hip ratio >0.85 cm	19	38	7	14
↑S. TG (>150 mg/dL)	8	16	5	10
↓HDL-C (<50 mg/dL)	22	44	6	12

PCOS = Polycystic ovarian syndrome; BP = Blood pressure; S. = Serum; TG = Triglyceride; HDL-C = High-density lipoprotein cholesterol.

Distribution of cases according to components of metabolic syndrome in patients of PCOS is shown in Table 4. It was seen that ↓HDL-C levels were seen

Table 5. Comparative Evaluation of Clinical Spectrum of Metabolic Syndrome in Cases and Controls

Clinical parameters	Controls (50)	Cases (50)	P value
Age (years)	26	25	0.52
BMI	23.75	24.25	0.78
SBP (mmHg)	110	120	0.06
DBP (mmHg)	70	74	0.06
S. cholesterol (mg/dL)	175.2	201.2	0.02
S. TG (mg/dL)	110.7	133.3	0.03
HDL (mg/dL)	35.2	25.4	0.04
LDL (mg/dL)	105.2	130.8	0.04
VLDL (mg/dL)	12.2	18.12	0.02
Insulin (μIU/mL)	5.1	6.5	0.04
Fasting glucose (mg/dL)	77	86	0.04

ANOVA test is used for calculating p value.

BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; S = Serum; TG = Triglyceride; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; VLDL = Very low-density lipoprotein.

Table 6. Prevalence of Metabolic Syndrome in Various Studies

Study	Year	Prevalence of metabolic syndrome (%)
Our study	2012-13	24
Glueck et al (USA)[1]	2003	43-46
Dey (India)[2]	2011	42
Ehrmann et al[3]	2006	33.4
Dokras et al[4]	2005	47.3

in 44% of cases and 12% of controls. Waist-hip ratio >0.85 cm was seen in 38% of cases and 14% of controls. Comparative evaluation of clinical spectrum of metabolic syndrome in cases and controls is depicted in Table 5. The prevalence of metabolic syndrome in various studies is shown in Table 6.

DISCUSSION

This was a cross-sectional case-control study of 100 females attending our OPD over a period of 1 year.

If we compare BMI matched cases and controls, then also lipid profile derangement is associated more with PCOS obese than non-PCOS obese ($p < 0.04$). This is in accordance with the study of Macut et al[5] who found that overweight and normal weight women with PCOS have higher incidence of lipid profile derangement than their controls. Wild et al[6] found that dyslipidemia is more common in PCOS. In our study, among patients with lipid profile derangement, 44% had decreased HDL as compared to 12% of controls ($p < 0.05$). Low HDL is having more detrimental effect on lipid profile derangement predictions among cases, which is in accordance with a study in Teharian women by Moini et al,[7] where low HDL was found in 96.9% of cases of metabolic syndrome in PCOS. Study by Dey et al[2] showed decreased HDL in 50% cases. In our study, waist circumference, which depicts central obesity ≥80 cm was found in 38% of cases and 14% of controls ($p < 0.05$). It is different from the study done by Ehrmann et al,[3] which supports high value of waist circumference by citing 80% of subjects above 88 cm.

In our study, fasting insulin level showed increase in 24% of cases and 10% of controls ($p < 0.05$). It shows a significant difference among women with metabolic syndrome in comparison to those without metabolic syndrome as supported by Dokras et al[4] in 2005.

We observed that, while USA women and Indian women have similar androgen levels, similar blood pressure, similar total cholesterol and LDL, USA women have higher body weight, higher fasting insulin, higher fasting glucose level, lower HDL and raised triglycerides. Most of these differences occurred as a result of higher prevalence of obesity in USA group, but other factors including characteristics of diet may also be responsible.

Thus, in our study, prevalence of metabolic syndrome was 24% among cases and 6% among age and BMI matched controls, which shows a statistically significant difference ($p < 0.05$) and thus, PCOS, *per se*, is responsible for prevalence of metabolic syndrome.

CONCLUSION

It is observed that metabolic syndrome manifests at an early age in women PCOS. Hyperinsulinemia, a central factor in the pathogenesis of PCOS, also appears to be a critical link between PCOS and metabolic syndrome. Thus, there is an urgent necessity to assess the rising trend of metabolic syndrome among the women with PCOS and to take early measures for primary prevention of its long-term sequel.

In order to prevent metabolic syndrome maintain BMI <25 and waist circumference <35 inches to prevent the development of metabolic syndrome or cardiovascular disease. An independent panel convened by the National Institutes of Health has recommended that well-designed, multicentric studies be conducted to determine factors such as obesity, that exacerbate a

genetic predisposition. The panel also determined the need for additional research to identify risks and treatments for complications and how to manage the common symptoms.

REFERENCES

1. Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. Metabolism. 2003;52(7):908-15.
2. Dey R, Mukherjee S, Roybiswas R, Mukhopadhyay A, Biswas SC. Association of metabolic syndrome in polycystic ovarian syndrome: an observational study. J Obstet Gynaecol India. 2011;61(2):176-81.
3. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN; PCOS/Troglitazone Study Group. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91(1):48-53.
4. Dokras A, Bochner M, Hollinrake E, Markham S, Vanvoorhis B, Jagasia DH. Screening women with polycystic ovary syndrome for metabolic syndrome. Obstet Gynecol. 2005;106(1):131-7.
5. Macut D, Damjanovic S, Panidis D, Spanos N, Glisic B, Petakov M, et al. Oxidised low-density lipoprotein concentration - early marker of an altered lipid metabolism in young women with PCOS. Eur J Endocrinol. 2006;155(1):131-6.
6. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril. 2011;95(3):1073-9.e1-11.
7. Moini A, Javanmard F, Eslami B, Aletaha N. Prevalence of metabolic syndrome in polycystic ovarian syndrome women in a hospital of Tehran. Human Reprod Med. 2012;10(2):127-30.

■■■■

Corticosteroid Use Tied to Lower Risk of Condition Worsening in Non-ICU Patients with COVID-19 Pneumonia

- A study published in *PLOS ONE* has revealed that early use of moderate-dose systemic corticosteroids in patients admitted to the general ward with COVID-19 pneumonia complicated by acute hypoxic respiratory failure (AHRF) resulted in a significantly lower rate of the primary composite outcome of ICU transfer, intubation or in-hospital death.
- The single-center retrospective cohort study assessed 265 patients consecutively admitted to non-ICU wards with laboratory-confirmed COVID-19 pneumonia between March 16 and April 30, 2020.
- Overall, 205 patients who developed AHRF (SpO_2/FiO_2 ≤440 or PaO_2/FiO_2 ≤300) were included in the final study.
- The mean age of the patients was 57 years; 74.63% were male, 73.04% patients were of Hispanic ethnicity/race. Among these 205 patients, 29.27% received systemic corticosteroids.
- Patients received methylprednisolone (n = 29, 48.33%), prednisone (n = 10, 16.67%), hydrocortisone (n = 1, 1.67%) and dexamethasone (n = 20, 33.33%).
- Corticosteroid treatment was started at a median of 2 days (IQR, 1-5) following admission, on a median or equivalent dose of 80 mg/day (IQR, 60-107) of methylprednisolone (equivalent to 12 (IQR, 9-16) mg of dexamethasone) for a median duration of 5 days (IQR, 4-7).
- Among the 202 eligible patients, 13 (22.41%) patients in the corticosteroid cohort developed the primary composite outcome, compared to 54 (37.5%) patients in the noncorticosteroid group (p = 0.039). The adjusted hazard ratio (HR) for developing the composite primary outcome was 0.15 (95% confidence interval [CI], 0.07-0.33; p < 0.001).
- Early administration of moderate-dose systemic corticosteroid (oral or intravenous) for a shorter duration in COVID-19 viral pneumonia may not be as harmful as initially believed. Additionally, it may be more beneficial than shown by the RECOVERY trial, whose early results revealed that low-dose (6 mg) dexamethasone decreased the risk of death among COVID-19 patients who required oxygen, with or without invasive mechanical ventilation.

With input from Dr Monica Vasudev

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Accidental Instillation of Superglue in External Ear: A Unique Foreign Body

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ABSTRACT

Foreign bodies in the ear are not an uncommon clinical entity; however, we hereby report a unique case of cyanoacrylate glue or superglue, accidentally instilled by a child into the external auditory canal of a young adult. Complete removal of the glue manually under microscope while preserving the normal anatomy of the ear canal and tympanic membrane is described.

Keywords: Superglue, cyanoacrylate, foreign body, external ear canal

Numerous types of foreign bodies are usually encountered in the external auditory canal (EAC) in day-to-day otological practice. Superglue or cyanoacrylate glue is an excellent bonding agent, which can even bind with the skin and when tried to be removed from EAC, could cause undesirable symptoms like pain, bleeding, mucosal irritation, conductive hearing loss, anxiety and injury to the tympanic membrane. Removal of the cyanoacrylate glue from the EAC and tympanic membrane, without damaging it, is a real challenge. This case highlights one such situation, wherein superglue got accidentally instilled into the EAC and was removed successfully without any damage to the underlying skin and the tympanic membrane under local anesthesia.

CASE REPORT

A 21-year-old male presented to the otology clinic with history of instillation of superglue into his right ear by his 5-year-old nephew, while he was sleeping. He presented to the clinic within 6 hours of instillation along with glue tube. He complained of slight itching and blockage on affected side. The patient denied any history of pain, bleeding, discharge and hearing loss. Upon microscopic examination, affected side revealed a hard glistening white substance filling the right EAC, slightly adherent to it and occluding the view of tympanic membrane (Fig. 1). Patient was taken up for

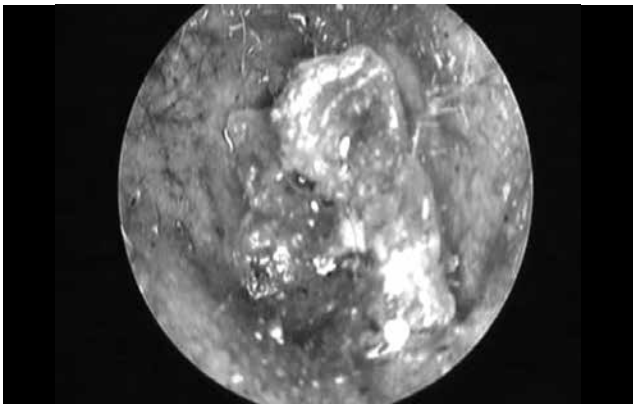

Figure 1. External auditory canal occluded with cyanoacrylate.

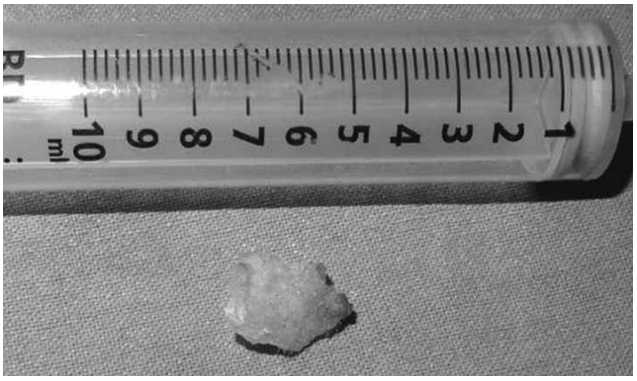

Figure 2. Cyanoacrylate mold removed *in toto*.

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removal of foreign body under local anesthesia. After giving local anesthesia, the glue was peeled off gently *in toto* from the EAC skin and tympanic membrane using Rosen's dissector and crocodile forceps without any significant injury (Fig. 2). Mucosa had slight ooze that stopped eventually. Re-examination revealed intact tympanic membrane.

DISCUSSION

Superglue is an easily available adhesive for domestic use in India, used to bond plastic, wood and metal at homes. Human skin may also get exposed to superglue sometimes, during its use. Superglue is a cyanoacrylate monomer obtained from formaldehyde and cyanoacetate. The main constituent is cyanoacrylate which undergoes rapid polymerization, forming a hard structure in the presence of basic substances.[1] The main hardener for cyanoacrylate is water and on coming into contact with a mucosal surface such as human skin, the molecules of the glue form close-fitting chains between the surfaces, being bonded within just seconds.

Review of literature revealed a few reported cases of superglue as the foreign body in the ear with various approaches for its removal. Wight and Bull removed superglue in the EAC with an endaural incision under general anesthesia.[1,2] Pollock used the permeatal approach under general anesthesia. The most superficial layers of the tympanic membrane were removed, but no perforation was reported.[3] White and Broner reported the use of organic solvent acetone for dissolving polystyrene impacted in the EAC of a 6-year-old child.[4] Abadir et al removed superglue from the ear canal of 2 patients with the help of pure acetone.[5] Persaud used warm peroxide (3%) for removal of superglue from external auditory meatus of a patient without causing any damage to the meatus or the tympanic membrane.[6]

The removal should be carried out by a trained otologist using a microscope who has a lot of patience. Possible complications such as perforation or total avulsion of the eardrum and sometimes even ossicle must be explained to the patient and a written consent should be taken when dealing with such a situation. The patient could also develop otitis externa or media and may require future reconstructive surgery.

CONCLUSION

Removal of the cyanoacrylate glue from the EAC and tympanic membrane is a challenging situation. In the reported case, the glue was peeled off *in toto* from the EAC skin and tympanic membrane using Rosen's dissector and crocodile forceps, under local anesthesia, without causing any significant injury. Being available easily, it is recommended that superglue should be kept away from the reach of the children.

REFERENCES

1. Gogia S, Agarwal A. Removal of superglue from the external ear using acetone: A case report. Egypt J Otolaryngol. 2016;32(20:116-7.
2. Wight RG, Bull PD. Superglue ear. J Laryngol Otol. 1987;101(7):706-7.
3. Pollock HD. Glue ear - cyanoacrylic. Arch Otolaryngol Head Neck Surg. 1988;114(10):1188.
4. White SJ, Broner S. The use of acetone to dissolve a Styrofoam impaction of the ear. Ann Emerg Med. 1994;23(3):580-2.
5. Abadir WF, Nakhla V, Chong P. Removal of superglue from the external ear using acetone: case report and literature review. J Laryngol Otol. 1995;109(12):1219-21.
6. Persaud R. A novel approach to the removal of superglue from the ear. J Laryngol Otol. 2001;115(11):901-2.

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Caffeine and Parkinson's Disease

According to new research, published in *Neurology*, individuals with Parkinson's disease had lower plasma caffeine levels compared to those without Parkinson's, and the levels were even lower for Parkinson's patients having the *LRRK2* gene mutation.

Researchers reported that plasma caffeine concentration was found to be lower among Parkinson's patients compared to healthy controls, which was considerably more among *LRRK2* carriers (by 76%) compared to noncarriers (by 31%). The findings prompt future research investigating caffeine and caffeine-related therapies to decrease the odds that people with this gene develop Parkinson's. Investigators further suggest that it might be a possibility that caffeine levels in the blood could be used as a biomarker to ascertain which people with this gene will go on to develop the disease, assuming that caffeine levels remain relatively stable… (*Medpage Today*)

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An Enigma of Lower Airway Mucormycosis Infection

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ABSTRACT

Saprophytic zygomycetes (e.g., Mucor, Rhizopus) are occasionally found in tissues of compromised hosts, in persons suffering from diabetes mellitus (particularly acidosis), extensive burns, leukemia, lymphoma or other chronic illness or immunosuppression. Rhizopus species, Mucor species and other zygomycetes invade the walls of blood vessels, producing thrombosis. This occurs commonly in paranasal sinus, the lungs and result in ischemic necrosis of surrounding tissue with an intense polymorphonuclear infiltrate. The organisms are rarely cultured during life but are seen in histologic preparations of tissues as broad nonseptate, irregular hyphae in thrombosed vessels or sinuses with surrounding leukocyte and giant cell response.

Keywords: Zygomycosis, *Rhizopus arrhizus*, posaconazole, coronary artery disease, hyperuricemia, dyselectrolytemia, bronchogram, hemodialysis

Cell wall of fungus contains chitin, a polymer of N-acetylglucosamine, rather than peptidoglycan. Mucormycosis refers to a fungal infection caused by fungi in the order Mucorales. Species in genera Mucor, Rhizopus, Absidia and Cunninghamella are often the cause of infection. Mucormycosis commonly infects the sinuses, brain or lungs. Uncontrolled diabetes is a focal point in accelerating mucormycosis. Zygomycosis and mucormycoses occur in soil and their airborne spores often contaminate food and laboratory specimens and produce infections. Common symptoms include thrombosis and tissue necrosis. The diagnosis can be confirmed by staining with toluidine blue, silver stain, periodic acid-Schiff stain or an immunofluorescence assay shows the characteristic cysts. Antifungal drug therapy and surgery help in removing the infected tissue. Mucormycosis occurs in patients with increased serum iron. Improvements in therapeutic and diagnostic options are helping clinicians prevent invasive fungal infection. The mold is unaffected by antibiotics. The degree of infection varies in different sites of the body, like lungs, skin, gastrointestinal tract and brain. The invasive mold causes serious mucormycosis disease in immunocompromised patients.

Posaconazole is the drug of choice in the management of pulmonary mucormycosis in diabetic patients. Fever, hemoptysis and tissue infarction is characteristic of pulmonary mucormycosis. Fungus enters into lung and produces mucormycosis. Fungi will enter into sinonasal cavities by spores inhalation. Neutropenia, glucocorticoid therapy and diabetes are the risk factors for invasive mucormycosis. In immunocompromised patients, mucormycosis is a life-threatening condition. The incidence of pulmonary mucormycosis is up to 24% among all cases of mucormycosis. Most fungi are harmless saprophytes, but some species may, in certain circumstances, infect human tissue or promote damaging allergic reactions. The term mycosis is applied to disease caused by fungal infection. Predisposing factors include metabolic disorders, such as diabetes mellitus, toxic states such as chronic alcoholism,

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diseases such as leukemia and myelomatosis in which immunological responses are disturbed. Treatment is done with corticosteroids and immunosuppressive drugs, and radiotherapy.

The damage or necrosis and the elimination of the competitive influence of a normal bacterial flora by antibiotic may also facilitate fungal infection. The pulmonary mycoses are difficult to treat. The administration of antibacterial drugs should be stopped, and antifungal agents substituted. Nystatin or natamycin by inhalation may control the more superficial respiratory mycoses involving the trachea and bronchi. For grave pulmonary infections, amphotericin, a potent but highly toxic antifungal agent may have to be given intravenously. Flucytosine and the antifungal imidazoles may also be useful. The effective dose of amphotericin, and thus its toxic effects on the kidney, can reduced by combining it with flucytosine. Surgical treatment may have to be considered if severe hemoptysis occurs.

Presented here is the case of a 65-year-old man with poorly controlled diabetes who was diagnosed with mucormycosis.

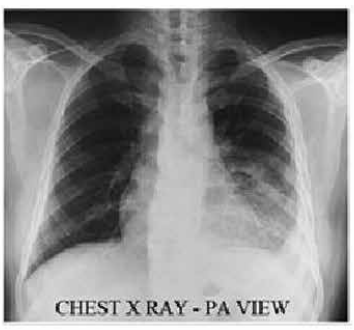
CASE REPORT

A 65-year-old male patient with complaints of fever and cough associated with hemoptysis since 1 week presented to the emergency. He was on medical management for diabetes mellitus, hypertension and coronary artery disease. He was evaluated with relevant investigations which showed – Hyperglycemia (614 mg%), poorly controlled diabetes (HbA1c - 12.8%), anemia (Hb - 9.1 gm%), elevated TLCs - 24,600/mm^3, azotemia (creatinine - 3.21 mg% and urea - 212 mg%), hyperkalemia (7. 6 mEq/L), hyponatremia (123 mEq/L), hyperuricemia (uric acid - 10.2 mg%), CUE-1 + Protein,1 + Glucose. Chest X-ray showed homogenous opacity in left lower zone and left CP angle with fluid tracking along left lateral chest wall – Pleural effusion with underlying lung collapse (Fig. 1).

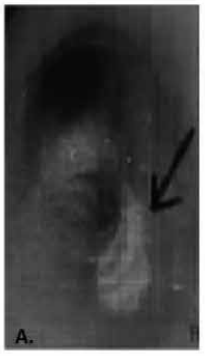
There were no significant changes in ECG. 2D Echo high-resolution CT chest (Fig. 1) showed - patchy parenchymal opacity with few areas of cystic changes and air bronchogram in the superior and inferior lingular segments; vague ground-glass opacities in lower lobe and medial basal segments of right lower lobe; atelectatic bands in the basal segments of left lower lobe; left pleural effusion. Features were suggestive of infective etiology. Sputum cultures grew multidrug-resistant Klebsiella. Bronchoscopy was done which revealed – whitish membranes present in the left lingular orifice; endobronchial biopsy suggestive of mucormycosis (Fig. 1); bronchoalveolar lavage (BAL) fungal stain showed fungal elements and galactomannan was not detected; BAL cultures grew Klebsiella. USG-guided pleural fluid tapping done for microbiology, reports were inconclusive. He was managed with glycemic control, hemodialysis, dyselectrolytemia, specified antibiotics, antifungals, stress ulcer prophylaxis, comorbidity management, oxygen and supportive care.

Patient's attendants were counseled about the infection – regarding management, and prognosis with (~70-90% mortality) and without surgery (~100% mortality) was explained. Patient developed arrhythmia (AF). Cardiologist's opinions were taken and posaconazole was switched to amphotericin B. Lobectomy/pneumonectomy was planned, explained to attendants in detail and consents were taken. Left upper lobe wedge resection was done, biopsy was sent for histopathological examination, implantable cardioverter-defibrillator (ICD) was placed and was uneventful. Post-op recovery was good and patient was extubated. On post-op Day 2, patient became drowsy and hypertensive. Inotrope supports were given, chest X-ray showed new opacities; antibiotics were escalated. He was intubated and bronchoscopy was done which revealed thick white color mucus plaques adherent to mucosa, present in the left upper lobe and BAL was collected from the left lower lobe and upper lobe. Surgical tissue biopsy revealed mucormycosis with angioinvasion. He developed empyema; ICD drained around 600 mL pus.

Patient gradually deteriorated, family was prognosticated. Patient vitals worsened further and he developed cardiac arrest. Cardiopulmonary resuscitation (CPR) was started immediately according to the advanced cardiac life support (ACLS) protocol and continued. In spite of all the efforts, return of spontaneous circulation (ROSC) was not achieved, pupils became dilated, BP was not recordable, ECG showed flat line. Patient was declared dead at 9:37 pm on 14/11/2019 due to cardiorespiratory arrest, secondary to pulmonary mucormycosis, uncontrolled diabetes mellitus, acute kidney injury and sepsis. Pathology slides showed broad, nonseptate, irregular hyphae in contrast to *Aspergillus fumigatus*, a group of mycoses, in tissues, exudates or sputum. Aspergillus species occur as filamentous, septate structures that usually branch dichotomously.



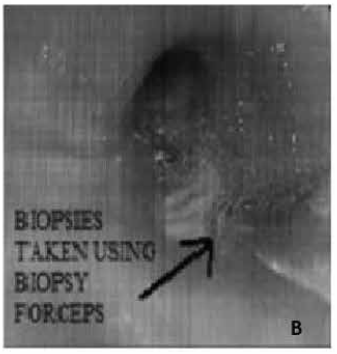
Left-sided effusion with collapse consolidation

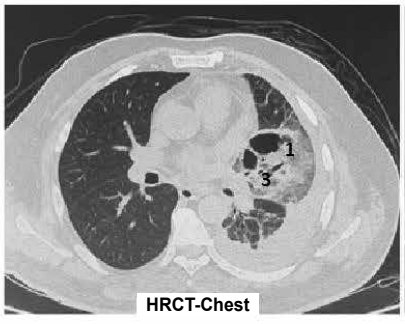


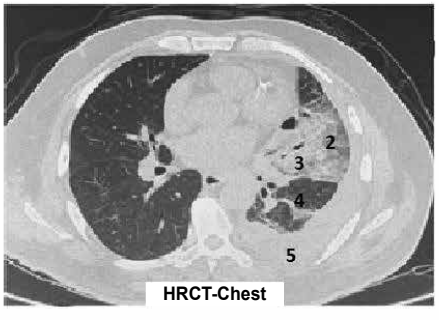
Bronchoscopy-

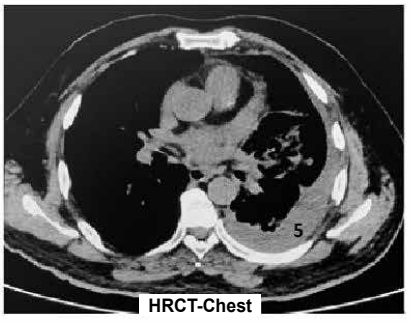
A. Whitish membranes in the left lingular orifice

B. Biopsies taken from the whitish membranes using biopsy forceps

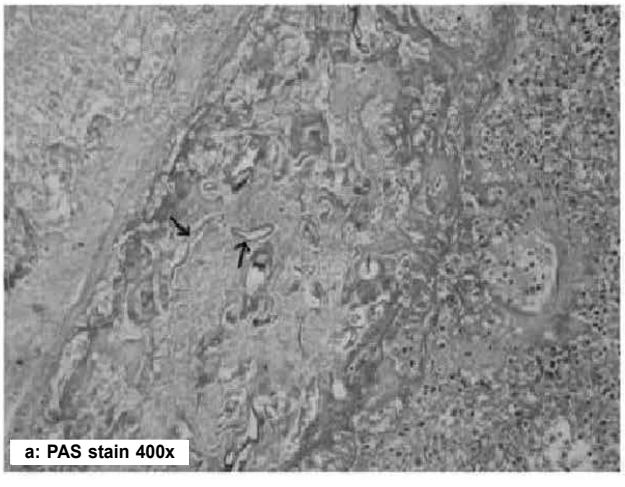


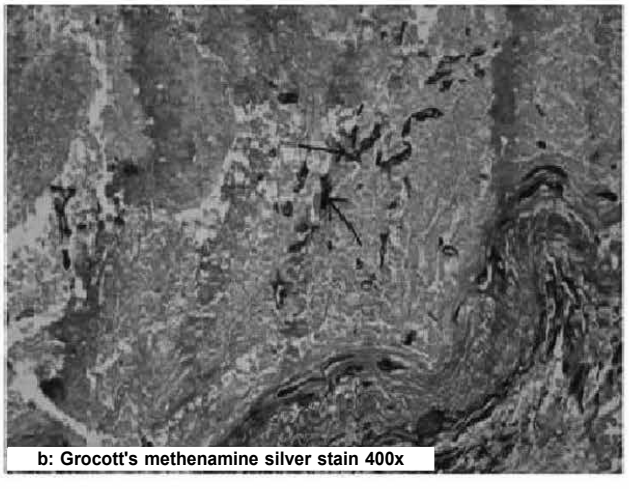






HRCT-Chest – Patchy parenchymal opacity with areas of necrosis with cavity changes (1), ground-glass opacities (2) consolidation (3) in the superior and inferior lingular segments, atelectatic band (4) in the basal segments of left lower lobe and left pleural effusion (5).





Microscopy – a. PAS stain b. Grocott's methenamine silver stain

Angioinvasive mucormycosis showing nonseptate broad fungal hyphae in the blood vessel.

Figure 1. Findings on various investigations.

DISCUSSION

Several factors contribute to the predisposition to Mucor infection in patients with diabetes mellitus. Impaired neutrophil function and high blood glucose concentration favor fungal growth. Adequate treatment of Mucor infection is dependent on early diagnosis. Mucor should be suspected when a patient with diabetes mellitus has orbital cellulitis or sudden visual changes. The underlying disease process must be aggressively controlled, correcting hyperglycemia and acidosis. Medical therapy also includes intravenous antifungal agents, usually amphotericin. Hyperbaric oxygen was shown in two small studies to be effective by decreasing tissue hypoxia and tissue acidosis. Early recognition increases the chance of successful medical and surgical treatment. Patients with high HbA1c levels, poor clinic attendance and risk-taking behaviors, are at greater risk for developing this devastating infection. A multimodality treatment approach with antifungal

agents and surgical debridement has been shown to improve outcomes. Other immunocompromised patients at risk include those using corticosteroids or deferoxamine, or long-term voriconazole prophylaxis, or with iron overload.

The organisms are normally saprophytic and phycomycetous, usually Absidia, Rhizopus or Mucor. The infection develops into cellulitis with the organism showing a predilection for blood vessels as Aspergillus does when invading the lungs. Sinus infections spread rapidly to the orbit and brain and most cases have been fatal. The phycomycetous are common free living fungi with nonseptate hyphae and reproduce asexually by the production of large number of spores within a sporangium, which develops at the end of an aerial hyphae. They grow and sporulate rapidly. Wounds very rarely become infected with filamentous fungi. Though mucormycosis exhibits several syndromes with isolated involvement of the gastrointestinal system, skin, kidney and central nervous system, the commonest and most devastating manifestations are rhino-orbital cerebral and pulmonary syndromes. These fungi have a ketone reductase enzyme that permits a high-glucose environment. Concomitant sinusitis and voriconazole prophylaxis are significantly associated with development of pulmonary mucormycosis. Cavitary lesions with the air crescent sign are rare. The high mortality observed in pulmonary mucormycosis may be related to delays in the diagnosis, poor host response (e.g., neutropenia) and limited available therapy.

CONCLUSION

Mucormycosis refers to a fungal infection caused by fungi in the order Mucorales. Uncontrolled diabetes is a focal point in accelerating mucormycosis. The diagnosis can be confirmed by staining with toluidine blue, silver stain, periodic acid-Schiff stain or an immunofluorescence assay shows the characteristic cysts. Antifungal drug therapy and surgery help in removing the infected tissue.

The present case represents the enigma associated with mucormycosis infection in a patient with underlying diabetes mellitus, hypertension and coronary artery disease. The case report emphasizes the significance of adequately controlling hyperglycemia in diabetes patients and the importance of early diagnosis in Mucor infection.

SUGGESTED READING

1. Staff Springfield News-Leader. Aggressive Fungus Strikes Joplin Tornado Victims PI. Seattle, Wash, USA: Hearst Communications Inc; 2011.
2. James WD, Berger TG, Elston DM, Odom RB. Andrews' Diseases of the Skin: Clinical Dermatology. 10th Edition, Philadelphia: Saunders Elsevier; 2006.
3. Nancy F Crum-Cianflone; MD MPH. "Mucormycosis". eMedicine. Retrieved May 19, 2008.
4. Nakada M, Tanaka C, Tsunewaki K, Tsuda M. RFLP analysis for species separation in the genera Bipolaris and Curvularia. Mycoscience. 1994:35:271-8.
5. Draper B, Suhr J. Survivors of Joplin tornado develop rare infection. Seattle Post-Intelligencer. Associated Press, June 11, 2011.
6. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18(3):556-69.
7. Supplementary Information: Microscopic appearance of *Pneumocystis jiroveci* from bronchial washings. Available at: https://web.archive.org/web/20090718235617/http://www.bmb.leeds.ac.uk/mbiology/ug/ugteach/icu8/std/pcp.html.
8. Larsen K, von Buchwald C, Ellefsen B, Francis D. Unexpected expansive paranasal sinus mucormycosis. ORL J Otorhinolaryngol Relat Spec. 2003;65(1):57-60.
9. Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. Future Microbiol. 2012;7(5):639-55.
10. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634-53.
11. Lamoth F, Calandra T. Early diagnosis of invasive mould infections and disease. J Antimicrob Chemother. 2017;72(Suppl 1):i19-i28.
12. Dorin J, D'Aveni M, Debourgogne A, Cuenin M, Guillaso M, Rivier A, et al. Update on *Actinomucor elegans*, a mucormycete infrequently detected in human specimens: how combined microbiological tools contribute efficiently to a more accurate medical care. Int J Med Microbiol. 2017;307(8):435-42.
13. Panigrahi MK, Manju R, Kumar SV, Toi PC. Pulmonary mucormycosis presenting as nonresolving pneumonia in a patient with diabetes mellitus. Respir Care. 2014;59(12):e201-e205.
14. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. CDC. 2009;58(4):1-198.
15. Soler ZM, Schlosser RJ. The role of fungi in diseases of the nose and sinuses. Am J Rhinol Allergy. 2012;26(5):351-8.
16. Khorvash F, Reza Abtahi SH, Hakamifard A, Derakhshan M, Zarghami L. Mucormycosis of middle ear in a diabetic patient. Indian J Otol. 2018;24(1):60-2.
17. Sharma S, Mohapatra S, Patel N. Case report on pulmonary mucormycosis. J Med Sci and Clin Res. 2019;7(10): 514-7.

18. Hamilos G, Samonis G, Kontoyiannis DP. Pulmonary mucormycosis. Semin Respir Crit Care Med. 2011;32(6): 693-702.
19. John Macleod. Davidson's Principles and Practice of Medicine. 14th Edition, ELBS.
20. Rangel-Guerra RA, Martínez HR, Sáenz C, Bosques-Padilla F, Estrada-Bellmann I. Rhinocerebral and systemic mucormycosis. Clinical experience with 36 cases. J Neurol Sci. 1996;143(1-2):19-30.
21. Weprin BE, Hall WA, Goodman J, Adams GL. Long-term survival in rhinocerebral mucormycosis. Case report. J Neurosurg. 1998;88(3):570-5.
22. Agrawal R, Yeldandi A, Savas H, Parekh ND, Lombardi PJ, Hart EM. Pulmonary mucormycosis: risk factors, radiologic findings, and pathologic correlation. Radiographics. 2020;40(3).
23. Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am. 2000;33(2):349-65.
24. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54 Suppl 1:S23-S34.
25. Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol. 2006;44(4):335-42.
26. Ajith Kumar AK, Gupta V. Rhino-orbital cerebral mucormycosis. [Updated 2020 May 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-
27. Di Carlo P, Cabibi D, La Rocca AM, De Luca D, La Licata F, Sacco E. Post-bronchoscopy fatal endobronchial hemorrhage in a woman with bronchopulmonary mucormycosis: a case report. J Med Case Rep. 2010; 4:398.
28. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis. 2005;41(1):60-6.
29. Spellberg B, Kontoyiannis DP, Fredricks D, Morris MI, Perfect JR, Chin-Hong PV, et al. Risk factors for mortality in patients with mucormycosis. Med Mycol. 2012;50(6):611-8.
30. E. Jawetz, J. L. Malnick, E.A. Adelberg. A Lange Medical Book Review of Medical Microbiology. 17th Edition.

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Pregnant Women Show Fewer COVID-19-related Symptoms

DG Alerts: According to new findings published in the *British Medical Journal*, pregnant and recently pregnant women with COVID-19 have lesser odds of exhibiting COVID-19-related symptoms of fever and myalgia. However, they may have a higher risk for admission to intensive care units (ICUs) and invasive ventilation, in comparison with nonpregnant women of reproductive age.

The living systematic review and meta-analysis also suggested that mothers with pre-existing comorbidities appeared to have a greater risk for severe COVID-19, along with those who were obese and of older maternal age. Preterm birth rates seem to be higher in pregnant women with COVID-19, compared to those without it, and their neonates have a higher likelihood of being admitted to a neonatal unit.

Overall, 77 cohort studies, including 55 comparative and 22 noncomparative, were included in the systematic review. The studies included 13,118 pregnant and recently pregnant women with COVID-19, and 83,486 nonpregnant women of reproductive age with the disease. Forty cohort studies, including 13,018 pregnant and 85,084 nonpregnant women, reported on clinical manifestations; 45 studies, involving 14,094 pregnant and 85,169 nonpregnant women, reported on COVID-19-related maternal outcomes and 35 studies, with 6,279 women and 2,557 neonates, reported on pregnancy-related maternal and perinatal outcomes.

Reference: https://www.bmj.com/content/370/bmj.m3320

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

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

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

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

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

About Sameer Malik Heart Care Foundation Fund

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

Objectives

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

Activities of the Fund

Financial Assistance

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

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

Drug Subsidy

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

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

Who is Eligible?

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

Important Notes

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

Check List of Documents to be Submitted with Application Form

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

Free Diagnostic Facility

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

Free Education and Employment Facility

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

Laboratory Subsidy

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

Help Us to Save Lives

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

Donate Now...

About Heart Care Foundation of India

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

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

Objectives

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

Heart Care Foundation Blood Donation Camps

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

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

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

Governing Council Members

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

Advisors

Mukul Rohtagi
Ashok Chakradhar

Executive Council Members

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

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

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

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Multifocal Intracerebral Hemorrhages: A Rare Presentation in a Patient of Cerebral Venous Sinus Thrombosis

MAHESH DAVE*, ANIRUDDHA BURLI†, NAGARAJ‡, AYUSH AGARWAL#

ABSTRACT

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease, accounting for 1% of all strokes occurring when a blood clot forms in any of the venous sinuses of the brain. CVST commonly presents as severe headache, seizures, focal neurological deficit, nausea and vomiting. Presentation of CVST in the form of multifocal intracerebral hemorrhage (ICH) is an extremely rare occurrence. We report a case of a 29-year-old male presenting with multifocal ICH and seizures with underlying CVST. The finding of multifocal ICH was incidentally found on brain radio imaging and further workup revealed underlying CVST. This case report underscores the importance of brain radio imaging in an otherwise normal patient presenting with seizure disorder. CVST as an etiology for multifocal ICH is a very rare yet significant phenomenon.

Keywords: Multifocal intracerebral hemorrhage, cerebral venous sinus thrombosis, seizures, metabolic syndrome

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease, accounting for 1% of all strokes, but with a mortality rate as high as 10%. There are many causes and risk factors of CVST, such as pregnancy, oral contraceptive use, infection, trauma, central nervous system (CNS) tumor, metabolic syndrome and coagulopathies. Initial presentation of CVST as intracerebral hemorrhage (ICH) is rare and further as multifocal ICH is rarest. Few common clinical features of CVST may be in the form of headache, giddiness, nausea, vomiting, seizure and focal neurological deficit, out of which, headache is the commonest presentation, found in up to 77% in some studies.

Despite the advances in the recognition of CVST in recent years, the diagnosis and treatment may be difficult because of the diversity of underlying risk factors.

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The reported incidence of spontaneous solitary ICH in CVST is around 33%; however, multifocal (at 2 or more sites within 48 hours) ICH is much more uncommon.

Hence, we are reporting a case of multifocal ICH in a patient with underlying CVST.

CASE REPORT

A 29-year-old male, taxi driver by occupation, was admitted to medical ward with history of first episode of abnormal body movements in the form of generalized tonic-clonic type with frothing from mouth and loss of consciousness, which remained for 20 minutes. There was a history of postictal confusion and headache, which persisted for 2 hours. He had no significant history of alcohol intake and head injury. Past history and family history were unremarkable.

General physical examination at the time of admission revealed that he was drowsy, not oriented to time, place and person, with Glasgow Coma Scale (GCS) $E_3V_2M_5$. His blood pressure was 160/104 mmHg and rest of the vitals were normal. After recovery from postictal confusion state, patient was examined thoroughly and found to have a height of 199 cm weighing 100 kg. His body mass index (BMI) was 25.25 kg/m^2. His waist circumference was 118 cm and hip circumference was 96 cm, with waist-hip ratio of 1.23. CNS examination revealed no focal neurological deficit.

So, a clinical diagnosis of seizure disorder with hypertension was suspected and an urgent noncontrast computed tomography (NCCT) head was ordered.

The NCCT head showed multiple hyperdense focal areas in right frontal and parietal lobes suggestive of multifocal ICH (Fig. 1). The patient was subjected to further extensive workup.

His hemogram showed hemoglobin level of 14.4 g% with erythrocyte sedimentation rate (ESR) of 25.

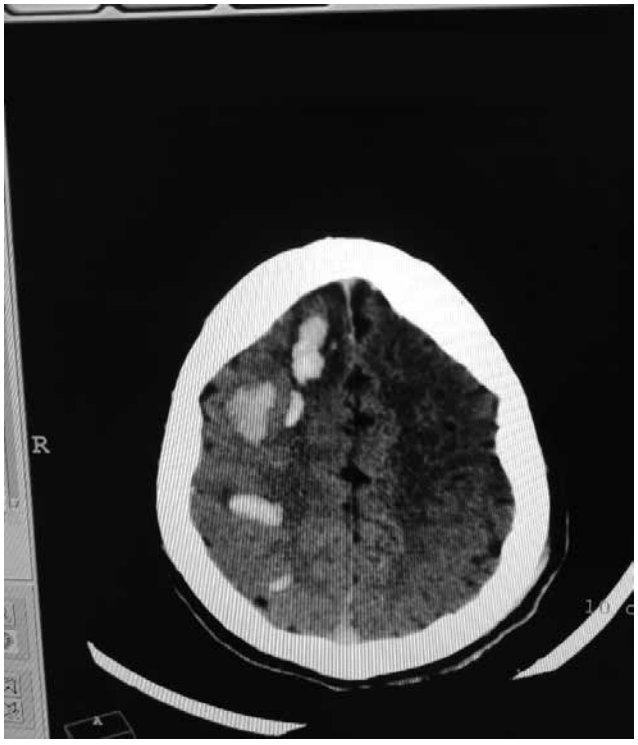

Figure 1. NCCT showing multifocal ICH in right cerebral hemisphere.

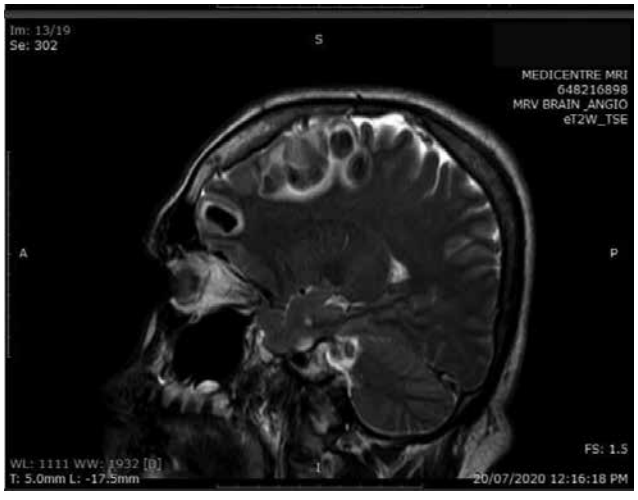

Figure 2 a. MR brain sagittal section showing multifocal ICH.

The total leukocyte count (TLC) and platelet counts were within normal limits. Other routine investigations like renal function test (RFT), liver function test (LFT), serum electrolytes and urine examination were within normal limits. His fever profile consisting of MP QBC, dengue and scrub typhus came out negative. His C-reactive protein (CRP) level was elevated to 14.74 mg/L. His coagulation profile, consisting of activated partial thromboplastin time (aPTT), prothrombin time-international normalized ratio (PT-INR), bleeding time (BT) and clotting time (CT), were normal. Fasting lipid profile revealed an elevated triglyceride level of 183 mg/dL and fasting blood sugar level was 114 mg/dL. His serum homocysteine level was 24.66 μmol/L (Normal reference range 5.46-16.2).

A diagnosis of metabolic syndrome or syndrome X was also established.

X-ray chest and electrocardiogram (ECG) were normal. Ultrasonography (USG) abdomen showed fatty liver.

Considering the atypical presentation and the nature of bleed, further radio imaging of the brain in the form of magnetic resonance (MR) brain, MR angiogram and MR venogram were ordered.

MR brain showed multiple acute intraparenchymal hemorrhages in cortical and subcortical aspect of right frontal and parietal lobes with mild perilesional edema. Largest measuring 2.8 × 1.5 cm. Figure 2 shows MR brain findings.

MR venography revealed acute cerebral venous thrombosis in superior sagittal sinus, right transverse sinus and right sigmoid sinus. On post contrast study, filling defect was noted.

MR angiography appeared normal.

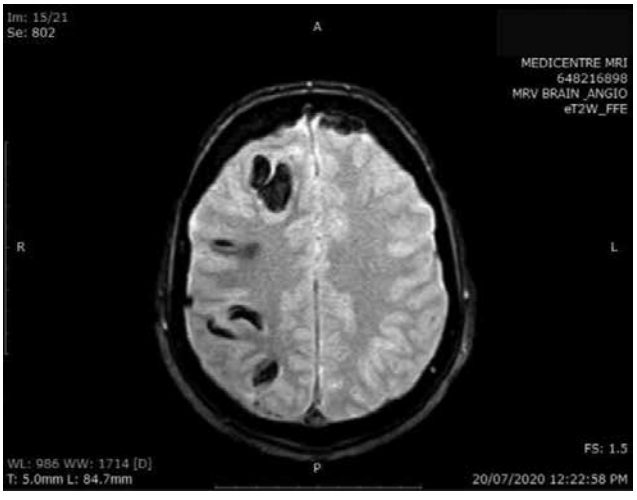

Figure 2b. MR brain transverse section showing multifocal ICH in right cerebral hemisphere.

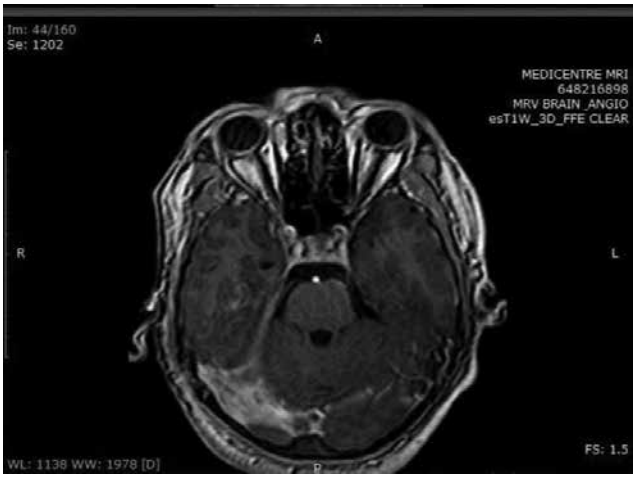

Figure 2c. MR brain showing right side cerebral venous sinus thrombosis.

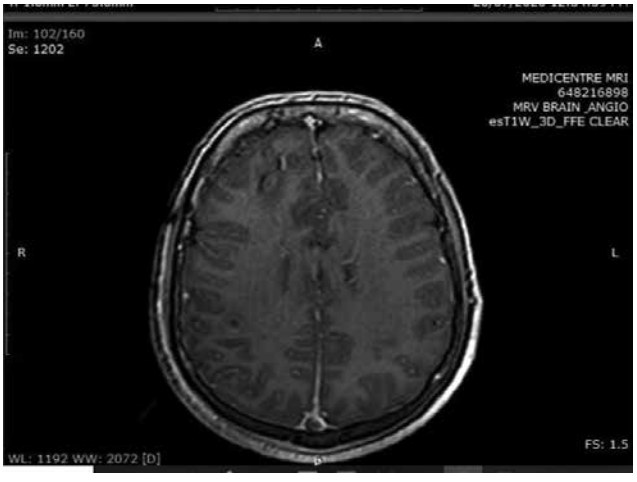

Figure 2d. MR brain showing filling defect in venous sinuses.

Patient was treated with antiepileptic medications for seizure control. Parenteral anticoagulant enoxaparin was given for 5 days with oral warfarin overlap. Patient was discharged after satisfactory management and asked to follow-up at Medical OPD with INR report.

DISCUSSION

Cerebral venous sinus thrombosis occurs when a blood clot forms in any of the venous sinuses of the brain. Approximately 5 people per million are affected by CVST and it accounts for approximately 1% of all stroke events. There may be a lot of risk factors of CVST, such as female gender, pregnancy, oral contraceptive use, infection, trauma, CNS tumor, metabolic syndrome and coagulopathies. CVST is extremely rare in young adult males. The probable risk factor in our patient may be metabolic syndrome. Although CVST is observed with increasing frequency in daily practice and has a variety of non-specific clinical symptoms, its presentation with an associated ICH *via* CT and magnetic resonance imaging (MRI) is infrequent. In patients with CVST, spontaneous intracranial hemorrhage accounts for 30-40% of ICH. ICH induced by CVST encompasses simple cerebral hemorrhage and venous infarction hemorrhage. The distribution of venous infarction hemorrhages does not agree with the normal distribution of simple cerebral hemorrhage. The hematoma is usually seen closer to the surface of the brain, with a large area of low-density around the focal point. The earliest presentation of CVST with ICH is intramedullary or subcortical meniscus hemorrhage; zebra striated hemorrhage is also a common feature of this combination. Increased venous and capillary pressure lead to diapedesis of red blood cells, followed by rupture of small vessels. ICH might therefore represent an extension of this sequence of events. Among patients with lobar ICH of otherwise unclear origin or with cerebral infarction that crosses typical arterial boundaries, imaging of the cerebral venous system should be carried out.

Multiple simultaneous ICH is an uncommon event and has been observed in only 2% of hemorrhagic strokes. Yen et al reported an incidence of 0.8% for simultaneous multiple ICH among intracranial hemorrhages. In simultaneous multiple ICHs, it is most commonly seen in the bilateral thalami followed by the putamen. Due to the limited number of reported cases, the underlying pathology is still unclear. The causative factors include hypertension, multiple micro-bleeding, cerebral amyloid angiopathy, vasculitis, administration of intravenous tissue plasminogen activator, asphyxiation, deep cerebral vein thrombosis and neoplasm. These causative factors appear to be similar to those for single spontaneous ICH

CONCLUSION

Cerebral venous sinus thrombosis is an uncommon disorder in young adult males. A CVST presenting with multifocal hemorrhages on radio imaging and seizure episode is very rare. Like other risk factors, metabolic syndrome is a significant cause for CVST. This case report underlines the importance of an urgent radio imaging in an otherwise normal patient presenting with seizure disorder. CVST as an etiology for multifocal ICH is a very rare, yet significant phenomenon.

SUGGESTED READING

1. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, et al; American

Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2011;42(4):1158-92.

2. Iurlaro S, Beghi E, Massetto N, Guccione A, Autunno M, Colombo B, et al. Does headache represent a clinical marker in early diagnosis of cerebral venous thrombosis? A prospective multicentric study. Neurol Sci. 2004;25 Suppl 3:S298-9.
3. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352(17):1791-8.
4. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010;9(2):167-76.
5. Jin-Suk Seo, Taek-Kyun Nam, Jeong-Taik Kwon, Yong-Sook Park. Multiple spontaneous simultaneous intracerebral hemorrhages. J Cerebrovasc Endovasc Neurosurg. 2014;16(2):104-11.
6. Sun J, He Z, Nan G. Cerebral venous sinus thrombosis presenting with multifocal intracerebral hemorrhage and subarachnoid hemorrhage: A case report. Medicine (Baltimore). 2018;97(50):e13476.
7. Minami K, Iida M, Iida H. Case report: central venous catheterization via internal jugular vein with associated formation of perioperative venous thrombosis during surgery in the prone position. J Anesth. 2012;26(3): 464-6.
8. Tanno H, Ono J, Suda S, Karasudani H, Yamakami I, Isobe K, et al. Simultaneous, multiple hypertensive intracerebral hematomas: report of 5 cases and review of literature. No Shinkei Geka. 1989;17(3):223-8.
9. Chanda A, Nanda A. Multiple cavernomas of brain presenting with simultaneous hemorrhage in two lesions: a case report. Surg Neurol. 2002;57(5):340-4; discussion 344-5.
10. Kase CS, Pessin MS, Zivin JA, del Zoppo GJ, Furlan AJ, Buckley JW, et al. Intracranial hemorrhage after coronary thrombolysis with tissue plasminogen activator. Am J Med. 1992;92(4):384-90.
11. Ooneda G, Yoshida Y, Suzuki K, Sekiguchi T. Morphogenesis of plasmatic arterionecrosis as the cause of hypertensive intracerebral hemorrhage. Virchows Arch A Pathol Pathol Anat. 1973;361(1):31-8.

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85% of a Seattle Fishing Boat Crew Got Infected on Board with COVID-19 in May

The crew had tested negative for infection and had blood drawn before departure.

On return, the three people who had neutralizing antibodies prior to departure were not infected on the ship.

- How long are COVID-19 antibodies protective? It is based on the titers, or the concentration of antibodies, in a person's blood.
- Individuals with more severe COVID-19 infection probably have more antibodies, which could possibly protect them from reinfection for a year or beyond. Milder infections lead to fewer antibodies and could possibly protect for up to 6 months.
- Nearly 10% of people don't exhibit a very strong immune response in mild infection. Those people would have a much higher risk for reinfection. Those reinfections are usually milder and the people are asymptomatic.
- Virus is always mutating. It undergoes two mutations a month. COVID-19 has been around for 10 months in people. Influenza, respiratory syncytial virus (RSV), other respiratory viruses and have been circulating in people for hundreds of years or in different animal hosts that can infect people.
- Across the whole antibody and clinical lab spectrum, there are two different antigens - the nucleocapsid, which wraps the genome, and the spike protein, which binds the cells.
- Most of the tests done in the United States are done against the nucleocapsid, as it is the most sensitive assay.
- We need antibody tests that show that spike, the outside glycoprotein from the virus that is associated with attachment and entry.
- But this is not what current labs are doing. The market is 75-80% nucleocapsid, and only 20% spike.
- For the receptor-binding domain, we look at the outside of the spike, the part that binds the receptor.

(*Source: Medscape*)

Indian Journal of Clinical Practice, Vol. 31, No. 5, October 2020

An Unusual Presentation of Bickerstaff Brainstem Encephalitis

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ABSTRACT

Bickerstaff brainstem encephalitis (BBE) is diagnosed by progressive, relatively symmetrical ophthalmoplegia, ataxia, disturbance of consciousness and/or hyperreflexia. Positive anti-GQ1b are found in 66% and abnormal brain MRI in 30% of patients. The classical triad seen in Fisher syndrome is ataxia, ophthalmoplegia and areflexia. If there is associated alteration in the level of consciousness and/or hyperreflexia, a diagnosis of Bickerstaff encephalitis is made due to possible involvement of the central nervous system. Here we report a case of BBE presenting with hyperreflexia without drowsiness as a sign of CNS involvement.

Keywords: Bickerstaff brainstem encephalitis, ophthalmoplegia, GQ1b

Bickerstaff brainstem encephalitis (BBE) is diagnosed by progressive, relatively symmetrical ophthalmoplegia, ataxia, disturbance of consciousness and/or hyperreflexia. Positive anti-GQ1b are found in 66% and abnormal brain magnetic resonance imaging (MRI) in 30% of patients. The classical triad seen in Fisher syndrome is ataxia, ophthalmoplegia and areflexia. If there is associated alteration in the level of consciousness and/or hyperreflexia, a diagnosis of Bickerstaff encephalitis is made due to possible involvement of the central nervous system (CNS). A Japanese survey estimated the annual incidence of Bickerstaff encephalitis as 0.078/1,00,000. The majority of case reports of Bickerstaff encephalitis have described the typical features of confusion or drowsiness as a sign of CNS involvement. However, this is the case report of a patient with BBE presenting with hyperreflexia without drowsiness as a sign of CNS involvement.

CASE REPORT

A 22-year-old male patient presented with history of headache and fever 7 days before admission. Fever recovered in next 2 days and was followed by acute onset double vision. Double vision was present in all the directions. Attendants noticed history of diminished movement of both eyeballs in all the directions. There was history of difficulty in walking in the form of swaying to either direction. There was no history of altered sensorium, drooping of eyelids, facial numbness or weakness, swallowing difficulty, sensory symptoms or weakness.

On examination, patient was conscious, oriented, speech was normal, pupils bilateral dilated and nonreactive with restricted extraocular movements in all directions. Other cranial nerves were normal. Motor system - bulk, tone, power - normal, deep tendon reflexes (DTR) were brisk, plantar extensor bilaterally; sensory system - normal, ataxia on tandem gait, extrapyramidal and peripheral nerves were normal, no signs of meningeal irritation, no involuntary movements. In view of acute-onset progressive bilateral complete ophthalmoplegia with pupillary involvement, brisk DTR in all 4 limbs, and ataxia on tandem walking, possibilities of Bickerstaff encephalitis, atypical Miller-Fisher and botulism were considered. MRI brain was normal and nerve conduction studies (NCS) in all limbs were normal. Botulism was unlikely due to absence of gastrointestinal (GI) symptoms and bulbar affection and no increment on repetitive nerve stimulation test (RNST) >20 Hz. Cerebrospinal fluid (CSF) showed albuminocytological dissociation with raised proteins. CSF GQ1b was; however, negative in our patient. As NCS was normal, atypical Miller-Fisher syndrome (MFS) was unlikely. Diagnosis of Bickerstaff was satisfied in view of ataxia,

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ophthalmoplegia and hyperreflexia. Patient was given injection IVIG 0.4 mg/kg for 5 days and showed complete recovery at 1 month follow-up.

DISCUSSION

Bickerstaff encephalitis was described initially by Edwin Bickerstaff in 1950s with clinical features of ophthalmoplegia, ataxia and drowsiness, preceded by infection. Similarities with MFS and Guillain-Barré syndrome (GBS) include areflexia, ophthalmoplegia and a raised protein in the CSF. This shows a shared etiology of the common association with antecedent infection. Odaka et al proposed clinical diagnostic criteria for the purpose of distinguishing BBE and MFS. Bickerstaff encephalitis is diagnosed as ophthalmoplegia and ataxia with disturbed consciousness and/or pyramidal signs. MFS is diagnosed as acute ophthalmoplegia and ataxia with areflexia or hyporeflexia. Our patient presented with complaints of ataxia, ophthalmoplegia with pyramidal signs but without altered sensorium.

CNS manifestations include drowsiness (45%), stupor, semi-coma or coma (29%), hyperreflexia (34%), Babinski's sign (40%) and deep sensory impairment (16%). Other common neurological features included ptosis, mydriasis, facial weakness, bulbar palsy and nystagmus. In our patient, mydriasis was present. Patients with GBS, MFS and BBE contain antibodies against gangliosides in there serum. Anti-GQ1b antibodies are present in 60-70% of BBE and 83-100% of MFS patients. GBS is associated with anti-GM1 antibodies except in 8%, where it is associated with anti-GQ1b positive.

The GQ1b antigen is highly expressed in the oculomotor, trochlear and abducens nerves, muscle spindles in the limbs and reticular formation in the brainstem. Infection by microorganism having GQ1b epitope may induce production of immunoglobulin G (IgG) anti-GQ1b antibodies in susceptible patients. The binding of anti-GQ1b antibodies to GQ1b antigens expressed on the cranial nerves and muscle spindles induces Fisher syndrome. Whereas, sometimes, the anti-GQ1b antibodies may also enter the brainstem and bind to GQ1b, inducing BBE. A continuous spectrum exists between these conditions, presenting with variable CNS and peripheral nervous system (PNS) involvement. Our patient was anti-GQ1b negative with preserved reflexes, which is predictable in light of the above evidence.

Bickerstaff encephalitis is usually associated with antecedent pathogens like herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, measles virus, *Salmonella typhi*, *Mycoplasma pneumoniae* and *Campylobacter jejuni* enteritis, substantiating evidence that antiganglioside antibodies work through molecular mimicry with infectious agents.

In MFS patients, ataxia improves by 3-41 days after onset, at a median of 32 days and ophthalmoplegia (between 3 and 46 days) at a median of 88 days. In Bickerstaff encephalitis, most patients achieve complete remission by 6 months.

The majority of cases are self-limiting. A definitive treatment for BBE is yet to be found. The established treatment is the same as that used in GBS: IVIg and plasmapheresis, although more clinical trials are required to determine its effectiveness.

CONCLUSION

Bickerstaff encephalitis can be diagnosed clinically with the triad of ataxia, complete ophthalmoplegia and pyramidal signs of hyperreflexia without evidence of impaired consciousness.

SUGGESTED READING

1. Koga M. A nationwide survey of patients with Bickerstaff brainstem encephalitis: diversity of underlying mechanism. Rinsho Shinkeigaku. 2013;53(11):1322-4.
2. Koga M. Bickerstaff brainstem encephalitis: epidemiology, diagnosis, and therapy. Nihon Rinsho. 2013;71(5):898-903.
3. Bickerstaff E. Brain-stem encephalitis; further observations on a grave syndrome with benign prognosis. Br Med J. 1957;1(5032):1384-7.
4. Bickerstaff E, Cloake PCP. Mesencephalitis and rhombencephalitis. BMJ. 1951;2(4723):77-81.
5. Odaka M, Yuki N, Hirata K. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. J Neurol Neurosurg Psychiatry. 2001;70(1):50-5.
6. Odaka M, Yuki N, Yamada M, Koga M, Takemi T, Hirata K, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barre syndrome. Brain. 2003;126(Pt 10):2279-90.
7. Kim JK, Bae JS, Kim DS, Kusunoki S, Kim JE, Kim JS, et al. Prevalence of anti-ganglioside antibodies and their clinical correlates with Guillain-Barré syndrome in Korea: a nationwide multicenter study. J Clin Neurol. 2014;10(2):94-100.
8. Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. Neurology. 2001;56(8):1104-6.

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Indian Journal of Clinical Practice, Vol. 31, No. 5, October 2020

Paraparesis Following Spinal Anesthesia in a Patient After Cesarean Section: A Rare Entity

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ABSTRACT

Paraparesis, as a complication after spinal anesthesia, is very rare. It may occur due to presence of undiagnosed spinal tumor or spinal shock after lumbar puncture. We describe a 22-year-old mother who had cesarean section under spinal anesthesia and developed paraparesis in postoperative period. She had history of facial palsy and hearing impairment for last 9 years. Magnetic resonance imaging (MRI) revealed spinal space-occupying lesion (extramedullary meningioma) at D-5/D-6 level. Careful observation and examination in postoperative period after regional anesthesia is necessary for early diagnosis and management.

Keywords: Spinal anesthesia, meningioma, paraparesis, cesarean section

Post-spinal paraparesis is an uncommon complication after applying spinal anesthesia. It may occur due to neuronal injury at lumbar vertebrae level or spinal shock. This type of incidence may happen with history of previous neurological morbidity or presence of previously undiagnosed spinal tumor.[1]

CASE REPORT

Mrs CD, a 22-year-old female P_{1+0} with previous history of lower-segment cesarean section (indications: Severe pre-eclampsia with scar tenderness in post-cesarean pregnancy with 39 weeks 5 days gestational age) presented at Eden Hospital, Kolkata. Her blood pressure (BP) was 174/112 mmHg during admission. Labetalol and prophylactic magnesium sulfate was administered. Spinal anesthesia was given for cesarean section. A healthy girl baby weighing 2.5 kg was delivered with Apgar score 8 and 10 at 1 minute and 5 minutes, respectively after birth. The vital signs were normal throughout cesarean section. Total operative time was 50 minutes. She was kept in observation ward for observation and transferred to postoperative ward after 6 hours. During postoperative follow-up, the patient developed paraparesis in both lower limbs with loss of sensory response to pain and temperature. The degree of motor block was scale 2 (according to Bromage scale). The patient had right-sided Bell's palsy and hearing impairment for the last 9 years and history of 3-4 episodes of generalized convulsions during the last antenatal period. She subsequently developed urinary retention after removal of Foley's catheter. Her BP was gradually normalized with medications and investigations were done to rule out renal, liver, cardiac dysfunctions, whose levels were found within normal limits. Hemoglobin - 12.8 g/dL, TC - 14,900/mm^3, D/C - $N_{78}L_{10}M_7E_5B_0$, platelet count - 3.2 lac/mm^3, total bilirubin - 0.5 mg/dL, postprandial blood sugar (PPBS) - 139 mg/dL, blood urea - 33 mg/dL, creatinine - 0.7 mg/dL. She was referred to Anesthesiologists and Dept. of Neuromedicine for opinion and they advised magnetic resonance imaging (MRI) of dorsal and lumbosacral spine for diagnosis. MRI features were suggestive of marginated isotense extramedullary lesion involving posterior and left side of spinal canal at D-5/D-6 level (Fig. 1) favoring meningioma that almost blocked the spinal cord canal with dorsal cord thinned out and shifted towards right side with cord edema. Figure 2 shows the lateral view of dorsolumbar spine showing the space-occupying lesion. A small marginated lesion was also seen intraspinally at L-3 level likely to be small meningioma or neurogenic tumor. Then, the patient was

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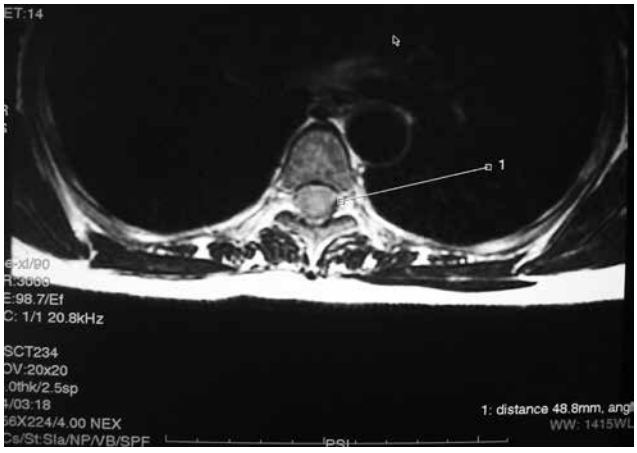

Figure 1. Marginated isotense extramedullary lesion involving posterior and left side of spinal canal at D-5/D-6 level.

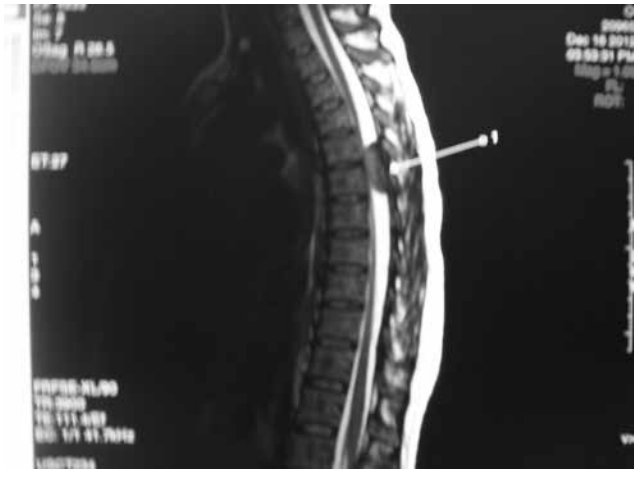

Figure 2. Lateral view of dorsolumbar spine showing the space-occupying lesion.

referred to a neurosurgeon for specific management. Laminectomy with resection of the tumor was done in the Dept. of Neurosurgery. She attended Gynecology OPD after 3 months without any paraparesis.

DISCUSSION

Spinal or epidural anesthesia is commonly given during cesarean section or related procedures. It may be associated with variety of complications. Immediate complications may be in the form of high neuronal block causing hypotension, bradycardia, respiratory insufficiency, apnea, unconsciousness or even cardiac arrest. The delayed complications may be post-dural puncture headache or neuronal injury. Neurological injury may occur due to direct accidental injury to the spinal cord or damage to the conus medullaris leading to paraplegia, isolated sacral dysfunctions, etc. Transient neurological symptoms may occur in the form of back pain without sensory or motor deficit. In some patients, intraspinal or epidural hematoma or abscess may lead to neurological deficit as a result of compression effect.[2-4] But paraparesis as a complication of spinal anesthesia is very rare. It may be due to presence of space-occupying lesion (intradural extramedullary tumor) or spinal shock. In our case, though some neurological morbidity was present previously, no clinical signs or symptoms were found suggestive of compressive spinal cord tumor before the incident. The diagnosis of meningioma was revealed after developing post-operative paraparesis.

Probably, the space-occupying lesion created a pressure gradient above and below the level of nearly obliterated spinal cord canal. When the lumbar puncture was done in the lower compartment, the cerebrospinal fluid continued to leak-out through the puncture site causing spinal-coning. MRI, a better diagnostic procedure in the present case, revealed the space-occupying lesion and the patient was referred to a neurosurgeon for definitive management (laminectomy for the resection of the tumor mass).

For spinal anesthesia, 0.5% hyperbaric bupivacaine is commonly used. It's duration of action is 90-120 minutes. During postoperative follow-up of our patient, there was motor and sensory deficit even after 6 hours. The case report suggested that close postoperative monitoring with special emphasis on motor or sensory dysfunctions (neurological assessment) is needed and immediate investigations are needed to rule out spinal pathology. During preoperative anesthetic check-up, any pre-existing neurological disorders should be enquired.[5]

REFERENCES

1. Dureja J, Singh I, Kad N, Bhai V, Lal J. Paraparesis following spinal anesthesia in a patient with an undiagnosed metastatic spinal tumor. The Indian Anaesthesists Forum, 2013.
2. Gerancher JC, Waterer R, Middleton J. Transient paraparesis after postdural puncture spinal hematoma in a patient receiving ketorolac. Anesthesiology. 1997;86(2):490-4.
3. Kane RE. Neurologic deficits following epidural or spinal anesthesia. Anesth Analg. 1981;60(3):150-61.
4. Morgan GE, Mikhail MS, Murray MJ. Clinical Anaesthesiology. 4th Edition, Tata McGraw-Hill Education Private Limited; 2009. pp. 316-21.
5. Cherng YG, Chen IY, Liu FL, Wang MH. Paraplegia following spinal anesthesia in a patient with an undiagnosed metastatic spinal tumor. Acta Anaesthesiol Taiwan. 2008;46(2):86-90.

Indian Journal of Clinical Practice, Vol. 31, No. 5, October 2020

Clinical Aspect to Admit a Patient Under MBBS Doctors and Specialist

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Question No. 1: Can a general MBBS doctor admit patients under his/her self?

Answer No. 1:

Yes, a general MBBS doctor can admit patient under his/her self.

The provisions of Section 15 of the Indian Medical Council Act, 1956 deals with right of persons possessing qualifications in the schedules to be enrolled which is reproduced hereunder:

"(15) (1) Subject to the other provisions contained in this Act, the medical qualifications included in the Schedules shall be sufficient qualification for enrolment on any State Medical Register.

(2) Save as provided in Section 25, no person other than a medical practitioner enrolled on a State Medical Register:

(a) shall hold office as physician or surgeon or any other office (by whatever designation called) in Government or in any institution maintained by a local or other authority;

(b) shall practice medicine in any State;

(c) shall be entitled to sign or authenticate a medical or fitness certificate or any other certificate required by any law to be signed or authenticated by a duly qualified medical practitioner;

(d) shall be entitled to give evidence at any inquest or in any court of law as an expert under Section 45 of the Indian Evidence Act, 1872 on any matter relating to medicine.

(3) Any person who acts in contravention of any provision of Sub-section (2) shall be punished with imprisonment for a term which may extend to one year or with fine which may extend to one thousand rupees, or with both."

Also, the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 enumerates the duties and responsibilities of Physician in general. The provisions of Regulation 1 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 are reproduced hereunder:

"B. Duties and responsibilities of the Physician in general:

***1.1: Character of Physician** (Doctors with qualification of MBBS or MBBS with post graduate degree/diploma or with equivalent qualification in any medical discipline):*

***1.1.1** A physician shall uphold the dignity and honour of his profession.*

***1.1.2** The prime object of the medical profession is to render service to humanity; reward or financial gain is a subordinate consideration. Who-so-ever chooses his profession, assumes the obligation to conduct himself in accordance with its ideals. A physician should be an upright man, instructed in the art of healings. He shall keep himself pure in character and be diligent in caring for the sick; he should be modest, sober, patient, prompt in discharging his duty without anxiety; conducting himself with propriety in his profession and in all the actions of his life.*

***1.1.3** No person other than a doctor having qualification recognised by Medical Council of India and registered with Medical Council of India/State Medical Council (s) is allowed to practice Modern System of Medicine or Surgery. A person obtaining qualification in any other system of Medicine is not allowed to practice Modern System of Medicine in any form.*

***1.3:** Maintenance of medical records:*

***1.3.1** Every physician shall maintain the medical records pertaining to his/her indoor patients for a period of 3 years from the date of commencement of the treatment in a standard proforma laid down by the Medical Council of India and attached as Appendix 3.*

***1.3.2** If any request is made for medical records either by the patients/authorised attendant or legal authorities involved, the same may be duly*

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acknowledged and documents shall be issued within the period of 72 hours.

1.3.3 *A Registered medical practitioner shall maintain a Register of Medical Certificates giving full details of certificates issued. When issuing a medical certificate he/she shall always enter the identification marks of the patient and keep a copy of the certificate. He/She shall not omit to record the signature and/or thumb mark, address and at least one identification mark of the patient on the medical certificates or report. The medical certificate shall be prepared as in Appendix 2.*

1.3.4 *Efforts shall be made to computerize medical records for quick retrieval.*

Further, as per the Schedules of Indian Medical Council Act, 1956 the qualification in MBBS is a recognized qualification and the person who undertakes the MBBS qualification is entitled to be registered as registered medical practitioner practicing modern system of medicine as per the provisions of Indian Medical Council Act, 1956. Further, the provisions of Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 enumerates the code of ethics to be observed by physician who is a doctor with qualification of MBBS or MBBS with post graduate degree/diploma or with equivalent qualification in any medical discipline. Thus, once a person has obtained a degree in MBBS and is registered under the Indian Medical Council Act, 1956, then he/she is entitled to practice the modern system of medicine.

Also, as per the provisions of Section 15 of the Indian Medical Council Act, 1956 the registered medical practitioner has a right to sign, issue and authenticate medical or fitness certificate or other certificates to his/her patient.

Also, as per the provisions of Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002, the physical is required to maintain the medical records of his/her indoor patients. The indoor patients are those patients who have been admitted by the physician for treatment.

Hence, a patient can be admitted under the physician who is a qualified MBBS doctor and who has been registered with the Indian Medical Council or any State Medical Council for treatment of the patient as admission of a patient is essential for treatment of the patient which is the paramount duty of the registered medical practitioner.

As per the provisions of Regulation 1.4.2 of Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulation, 2002, the physician shall display as suffix to their names only recognized medical degrees or such certificates/diplomas and memberships/honours which confer professional knowledge or recognizes any exemplary qualifications/achievements. Thus, the MBBS cannot claim himself specialist.

Further, in the matter tilted as "Surinder Kumar (Laddi) versus Dr. Santosh Menon & Others, 2000 (III) CPJ 517 (Punj. SCDRC)", the Hon'ble Punjab State Consumer Disputes Redressal Commission held that MBBS doctor having obtained degree from the University was competent to practice medicines, surgery and obstetrics. Caesarean operation is a part of surgery. It may be that the persons obtaining diploma like D.G.O may be more qualified to conduct Caesarean operation but it cannot be said that such persons who had obtained such training only were eligible to conduct Caesarean operation. Further, doctor was qualified as well as eligible for conducting Caesarean operation, on the basis of her experience also.

Thus, in view of the above, it is opined that the MBBS doctor can admit patients.

Question No. 2: If a patient is admitted under MBBS doctor and having specific complains in that case is it acceptable?

Answer No. 2:

If a patient is admitted under MBBS doctor and having specific complaint, the MBBS doctor should refer the patient to the specialist or any other physician for consultation and treatment. The MBBS doctor cannot practice which is detrimental to his/her patient. Also, in case of serious illness or in doubtful or difficult condition, it is duty of the MBBS doctor to consult the specialist.

The Chapter 2 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 deals with the duties of the physician to their patients.

As per the provisions of Regulation 2.1.1, the physician can advise the patient to seek another physician's advise. Also, if a patient is suffering from any ailment which is not within the range of the physician, then the physician can refuse to treat the patient and refer the patient to another physician.

Further, as per the provisions of Regulation 2.1.2 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002, the physician having any incapacity which is detrimental to his/her patient is not entitled to practice.

The provisions of which are reproduced hereunder:

"CHAPTER 2

2. DUTIES OF PHYSICIANS TO THEIR PATIENTS

2.1 Obligations to the Sick

2.1.1 Though a physician is not bound to treat each and every person asking his services, he should not only be ever ready to respond to the calls of the sick and the injured, but should be mindful of the high character of his mission and the responsibility he discharges in the course of his professional duties. In his treatment, he should never forget that the health and the lives of those entrusted to his care depend on his skill and attention. A physician should endeavour to add to the comfort of the sick by making his visits at the hour indicated to the patients. A physician advising a patient to seek service of another physician is acceptable, however, in case of emergency a physician must treat the patient. No physician shall arbitrarily refuse treatment to a patient. However for good reason, when a patient is suffering from an ailment which is not within the range of experience of the treating physician, the physician may refuse treatment and refer the patient to another physician.

2.1.2 Medical practitioner having any incapacity detrimental to the patient or which can affect his performance vis-à-vis the patient is not permitted to practice his profession."

Further, as per the provisions of the Chapter 3 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 deals with the duties of the physician in consultation.

As per the provisions of Regulation 3.1.1 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002, it is the duty of the physician to request consultation in case of serious illness and in doubtful or difficult conditions.

"CHAPTER 3

3. DUTIES OF PHYSICIAN IN CONSULTATION

3.1 Unnecessary consultations should be avoided:

3.1.1 However in case of serious illness and in doubtful or difficult conditions, the physician should request consultation, but under any circumstances such consultation should be justifiable and in the interest of the patient only and not for any other consideration."

In the matter titled as "Martin F D'Souza versus Mohd. Ishfaq, Civil Appeal 3541/2002 vide judgement dated 17.2.2009", the Hon'ble Supreme Court of India has held that:

"54.*……Precautions which Doctor/Hospitals/Nursing Homes should take:*

(a) Current practices, infrastructure, paramedical and other staff, hygiene and sterility should be observed strictly. Thus, in Sarwat Ali Khan vs. Prof. R. Gogi and others Original Petition No.181 of 1997, decided on 18.7.2007 by the National Consumer Commission, the facts were that out of 52 cataract operations performed between 26th and 28th September, 1995 in an eye hospital 14 persons lost their vision in the operated eye. An enquiry revealed that in the Operation Theatre two autoclaves were not working properly. This equipment is absolutely necessary to carry out sterilization of instruments, cotton, pads, linen, etc., and the damage occurred because of its absence in working condition. The doctors were held liable.

(b) No prescription should ordinarily be given without actual examination. The tendency to give prescription over the telephone, except in an acute emergency, should be avoided.

(c) A doctor should not merely go by the version of the patient regarding his symptoms, but should also make his own analysis including tests and investigations where necessary.

(d) A doctor should not experiment unless necessary and even then he should ordinarily get a written consent from the patient.

*(e) **An expert should be consulted in case of any doubt**. Thus, in Smt. Indrani Bhattacharjee, Original Petition No. 233 of 1996 decided by the National Consumer Commission on 9.8.2007, the patient was diagnosed as having 'Mild Lateral Wall Ischemia'. The doctor prescribed medicine for gastroenteritis, but he expired. It was held that the doctor was negligent as he should have advised consulting a Cardiologist in writing.*

(f) *Full record of the diagnosis, treatment, etc. should be maintained."*

Question No. 3: As above condition is same (If a patient is admitted under MBBS doctor and having specific complains) but Specialist visits are done 1 or 2 times now in this scenario can treatment is carry on by MBBS doctors (but specialist is not looking or taking round for patient in regular manner)?

Answer No. 3:

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

*"**CHAPTER 3***

***3.** DUTIES OF PHYSICIAN IN CONSULTATION*

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

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

*"**CHAPTER 4***

***4.** RESPONSIBILITIES OF PHYSICIANS TO EACH OTHER*

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

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

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

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

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

Question No. 4: If a patient is admitted under MBBS doctor, so what are the limitations and scope of treatment which are ok or acceptable for MBBS doctor?

Answer No. 4:

The MBBS doctor has to provide treatment to his patient and to practice medical professions as per the Code of Ethics as enshrined in Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 and also as per the provisions of Indian Medical Council Act, 1956.

The Chapter 2 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 enumerates the provisions relating to the duties of the physician towards their patients which are reproduced hereunder:

*"**CHAPTER 2***

***2.** DUTIES OF PHYSICIANS TO THEIR PATIENTS*

2.1 Obligations to the Sick

***2.1.1** Though a physician is not bound to treat each and every person asking his services, he should not only be ever ready to respond to the calls of the sick and the injured, but should be mindful of the high character of his mission and the responsibility he discharges in the course of his professional duties. In his treatment, he should never forget that the health and the lives of those entrusted to his care depend on his skill and attention. A physician should endeavour to add to the comfort of the sick by making his visits at the hour indicated to the patients. A physician advising a patient to seek service of another physician is acceptable,*

however, in case of emergency a physician must treat the patient. No physician shall arbitrarily refuse treatment to a patient. However for good reason, when a patient is suffering from an ailment which is not within the range of experience of the treating physician, the physician may refuse treatment and refer the patient to another physician.

***2.1.2** Medical practitioner having any incapacity detrimental to the patient or which can affect his performance vis-à-vis the patient is not permitted to practice his profession.*

***2.2 Patience, Delicacy and Secrecy**: Patience and delicacy should characterize the physician. Confidences concerning individual or domestic life entrusted by patients to a physician and defects in the disposition or character of patients observed during medical attendance should never be revealed unless their revelation is required by the laws of the State. Sometimes, however, a physician must determine whether his duty to society requires him to employ knowledge, obtained through confidence as a physician, to protect a healthy person against a communicable disease to which he is about to be exposed. In such instance, the physician should act as he would wish another to act toward one of his own family in like circumstances.*

***2.3 Prognosis**: The physician should neither exaggerate nor minimize the gravity of a patient's condition. He should ensure himself that the patient, his relatives or his responsible friends have such knowledge of the patient's condition as will serve the best interests of the patient and the family.*

***2.4 The Patient must not be neglected**: A physician is free to choose whom he will serve. He should, however, respond to any request for his assistance in an emergency. Once having undertaken a case, the physician should not neglect the patient, nor should he withdraw from the case without giving adequate notice to the patient and his family. Provisionally or fully registered medical practitioner shall not willfully commit an act of negligence that may deprive his patient or patients from necessary medical care.*

***2.5 Engagement for an Obstetric case**: When a physician who has been engaged to attend an obstetric case is absent and another is sent for and delivery accomplished, the acting physician is entitled to his professional fees, but should secure the patient's consent to resign on the arrival of the physician engaged."*

Also, the Chapter 3 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 enumerates the provisions relating to the duties of the physician in consultation towards their patients which are reproduced hereunder:

"CHAPTER 3

***3.** DUTIES OF PHYSICIAN IN CONSULTATION*

3.1 Unnecessary consultations should be avoided:

***3.1.1** However in case of serious illness and in doubtful or difficult conditions, the physician should request consultation, but under any circumstances such consultation should be justifiable and in the interest of the patient only and not for any other consideration.*

***3.1.2** Consulting pathologists/radiologists or asking for any other diagnostic Lab investigation should be done judiciously and not in a routine manner.*

***3.2 Consultation for Patient's Benefit**: In every consultation, the benefit to the patient is of foremost importance. All physicians engaged in the case should be frank with the patient and his attendants.*

***3.3 Punctuality in Consultation**: Utmost punctuality should be observed by a physician in making themselves available for consultations.*

3.4 Statement to Patient after Consultation:

***3.4.1** All statements to the patient or his representatives should take place in the presence of the consulting physicians, except as otherwise agreed. The disclosure of the opinion to the patient or his relatives or friends shall rest with the medical attendant.*

***3.4.2** Differences of opinion should not be divulged unnecessarily but when there is irreconcilable difference of opinion the circumstances should be frankly and impartially explained to the patient or his relatives or friends. It would be opened to them to seek further advice as they so desire.*

***3.5 Treatment after Consultation:** No decision should restrain the attending physician from making such subsequent variations in the treatment if any unexpected change occurs, but at the next consultation, reasons for the variations should be discussed/explained. The same privilege, with its obligations, belongs to the consultant when sent for in an emergency during the absence of attending physician. The attending physician may prescribe medicine at any time for the patient, whereas the consultant may prescribe only in case of emergency or as an expert when called for.*

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

***3.7 Fees and other charges**:*

***3.7.1** A physician shall clearly display his fees and other charges on the board of his chamber and/or the hospitals he is visiting. Prescription should also make clear if the Physician himself dispensed any medicine.*

***3.7.2** A physician shall write his name and designation in full along with registration particulars in his prescription letterhead.*

***Note:** In Government hospital where the patient–load is heavy, the name of the prescribing doctor must be written below his/her signature."*

In the matter titled as "P. B. Desai versus State of Maharashtra, AIR 2014 SC 795", the Hon'ble Supreme Court of India has held that:

***"(1)** The Doctor-Patient relationship*

***36.** Since ancient times, certain duties and responsibilities have been cast on persons who adopt the sacred profession as exemplified by Charak's Oath (1000 BC) and the Hippocratic Oath (460 BC).*

***37.** It is the responsibilities that emerge from the doctor-patient relationship that forms the cornerstone of the legal implications emerging from medical practice. The existence of a doctor-patient relationship presupposes any obligations and consequent liability of the doctor to the patient.*

***38.** It was Talcott Parsons, a social scientist, who first theorized the doctor-patient relationship. He worked on the hypothesis that illness was a form of dysfunctional deviance that required re-integration with social organism. Maintaining the social order required the development of a legitimized sick role to control this deviance, and make illness a transitional state back to normal role performance. In this process, the physician, who has mastered a body of technical knowledge, on a functional role to control the deviance of sick persons who was to be guided by an egalitarian universalism rather than a personalized particularism. While this basic notion has remained robust, over a period of time there have been numerous qualifications to the theory of Parsons. For instance, physicians and the public consider some illnesses to be the responsibility of the ill, such as lung cancer, AIDS and obesity.*

***39.** It is not necessary for us to divulge this theoretical approach to the doctor-patient relationship, as that may be based on model foundation. Fact remains that when a physician agrees to attend a patient, there is an unwritten contract between the two. The patient entrusts himself to the doctor and that doctor agrees to do his best, at all times, for the patient. Such doctor-patient contract is almost always an implied contract, except when written informed consent is obtained. While a doctor cannot be forced to treat any person, he/she has certain responsibilities for those whom he/she accepts as patients. Some of these responsibilities may be recapitulated, in brief:*

(a) to continue to treat, except under certain circumstances when doctor can abandon his patient;

(b) to take reasonable care of his patient;

(c) to exhibit reasonable skill: The degree of skill a doctor undertakes is the average degree of skill possessed by his professional brethren of the same standing as himself. The best form of treatment may differ when different choices are available. There is an implied contract between the doctor and patient where the patient is told, in effect, "Medicine is not an exact science. I shall use my experience and best judgment and you take the risk that I may be wrong. I guarantee nothing."

(d) Not to undertake any procedure beyond his control: This depends on his qualifications, special training and experience. The doctor must always ensure that he is reasonably skilled before undertaking any special procedure/treating a complicated case.

(e) Professional secrets: A doctor is under a moral and legal obligation not to divulge the information/ knowledge which he comes to learn in confidence from his patient and such a communication is privileged communication.

***Conclusion:** The formation of a doctor-patient relationship is integral to the formation of a legal relationship and consequent rights and duties, forming the basis of liability of a medical practitioner. Due to the very nature of the medical profession, the degree of responsibility on the practitioner is higher than that of any other service provider. The concept of a doctor - patient relationship forms the foundation of legal obligations between the doctor and the patient.*

In the present case, as already held above, doctor-patient relationship stood established, contractually, between the patient and the appellant.

(2) Duty of Care which a doctor owes towards his patient.

***40.** Once, it is found that there is 'duty to treat' there would be a corresponding 'duty to take care' upon the doctor qua/his patient. In certain context, the duty acquires ethical character and in certain other situations, a legal character. Whenever the principle of 'duty to*

take care' is founded on a contractual relationship, it acquires a legal character. Contextually speaking, legal 'duty to treat' may arise in a contractual relationship or governmental hospital or hospital located in a public sector undertaking. Ethical 'duty to treat' on the part of doctors is clearly covered by Code of Medical Ethics, 1972. Clause 10 of this Code deals with 'Obligation to the Sick' and Clause 13 cast obligation on the part of the doctors with the captioned "Patient must not be neglected". Whenever there is a breach of the aforesaid Code, the aggrieved patient or the party can file a petition before relevant Disciplinary Committee constituted by the concerned State Medical Council."

Question No. 5: What are the criteria or situation in which patients can/should transfer from admission under MBBS doctor to admission under Specialist?

Answer No. 5:

If a patient is admitted under MBBS doctor and having specific complaint, the MBBS doctor should refer the patient to the specialist or any other physician for consultation and treatment. The MBBS doctor cannot practice which is detrimental to his/her patient. Also, in case of serious illness or in doubtful or difficult condition, it is duty of the MBBS doctor to consult the specialist.

The Chapter 2 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 deals with the duties of the physician to their patients.

As per the provisions of Regulation 2.1.1, the physician can advise the patient to seek another physician's advise. Also, if a patient is suffering from any ailment which is not within the range of the physician, then the physician can refuse to treat the patient and refer the patient to another physician.

Further, as per the provisions of Regulation 2.1.2 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002, the physician having any incapacity which is detrimental to his/her patient is not entitled to practice.

The provisions of which are reproduced hereunder:

"CHAPTER 2

2. DUTIES OF PHYSICIANS TO THEIR PATIENTS

2.1 Obligations to the Sick

***2.1.1** Though a physician is not bound to treat each and every person asking his services, he should not only be ever ready to respond to the calls of the sick and the injured, but should be mindful of the high character of his mission and the responsibility he discharges in the course of his professional duties. In his treatment, he should never forget that the health and the lives of those entrusted to his care depend on his skill and attention. A physician should endeavour to add to the comfort of the sick by making his visits at the hour indicated to the patients. A physician advising a patient to seek service of another physician is acceptable, however, in case of emergency a physician must treat the patient. No physician shall arbitrarily refuse treatment to a patient. However for good reason, when a patient is suffering from an ailment which is not within the range of experience of the treating physician, the physician may refuse treatment and refer the patient to another physician.*

2.1.2 Medical practitioner having any incapacity detrimental to the patient or which can affect his performance vis-à-vis the patient is not permitted to practice his profession"

Further, as per the provisions of the Chapter 3 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 deals with the duties of the physician in consultation.

As per the provisions of Regulation 3.1.1 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002, it is the duty of the physician to request consultation in case of serious illness and in doubtful or difficult conditions.

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***3.** DUTIES OF PHYSICIAN IN CONSULTATION*

3.1 Unnecessary consultations should be avoided:

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Question No. 6: If patient is admitted under MBBS doctor and having specific complains but not seen by specialist and happens anything wrong – is it the part of medical negligence? and what are the legal actions can take against Doctor or Hospital?

Answer No. 6:

Yes, it is a part of medical negligence, if the patient is admitted under MBBS doctor and is having specific complaint but is not seem by specialist and something wrong happens to the patient as it is the duty of the MBBS doctor to refer the patient to the specialist or any other physician for consultation and treatment. The MBBS doctor cannot practice which is detrimental

to his/her patient. Also, in case of serious illness or in doubtful or difficult condition, it is duty of the MBBS doctor to consult the specialist.

The Chapter 2 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002 deals with the duties of the physician to their patients.

As per the provisions of Regulation 2.1.1, the physician can advise the patient to seek another physician's advise. Also, if a patient is suffering from any ailment which is not within the range of the physician, then the physician can refuse to treat the patient and refer the patient to another physician.

Further, as per the provisions of Regulation 2.1.2 of the Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulations, 2002, the physician having any incapacity which is detrimental to his/her patient is not entitled to practice.

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In such situation, the patient and/or his/her relatives can take appropriate legal remedy against doctor and hospital for medical negligence by lodging a police complaint, consumer complaint, civil suit for damages, complaint before MCI.

The role of the specialist/consultant has to be very clear and there should be transparency.

Question No. 7: What is the age limit for pediatric patients?

Answer No. 7

As per government hospital, the age is up to 12 years, but the physician and pediatricians can treat the patient between the age group of 12 to 18 years.

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Indian Journal of Clinical Practice, Vol. 31, No. 5, October 2020

Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Minutes of Virtual Meeting of CMAAO NMAs on "COVID-19 Update"

29th August, 2020 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Marthanda Pillai, Member-World Medical Council; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Prakash Budhathoky, Nepal

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

Key points from the discussion

- Three acute phase reactants–C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and interleukin (IL)-6. In a resource-limited country, CRP is the best choice amongst the three. It is an indicator of intensity of inflammation. CRP cannot rise without increase in IL-6. When CRP is raised, presume that the D-dimer is high.
- We do not know how China with a higher population density than India has managed to control the disease. Mortality is 3 per million; new cases are 9.
- Antigens of various diseases such as typhoid, malaria, chikungunya and dengue are false-positive in coronavirus disease 2019 (COVID-19).
- "*All overseas players and support staff underwent two COVID-19 reverse transcription polymerase chain reaction (RT-PCR) tests before flying into the UAE and could fly only if the tests were negative. If not, then the same 14-day quarantine period and two negative tests was needed to be able to fly to the UAE. The players and support staff will be tested on Day 1, Day 3 and Day 6 of their quarantine in the UAE and after clearing that, they will be tested every fifth day during the 53-day event*." Instead of three tests, pooled testing of the teams can be done daily.
- Oxygen administered without anticoagulation has no significance. Aspirin/anticoagulation must be given. For cases under home care, rivaroxaban (10 mg prophylaxis) can be given in place of low molecular weight heparin (LMWH); it is cheaper, can be taken by the patient, onset of action is 10 hours.
- According to a Times of India report, 87,000 healthcare workers (HCWs) in India are infected with COVID-19; there have been 573 deaths; 74% cases and over 86% deaths are from six states: Maharashtra, Tamil Nadu, Delhi, West Bengal, Gujarat and Karnataka. The numbers projected seem to be very high and need to be checked.
- Doctors have a high viral load so have higher chances of developing hypercoagulable state. Should prophylactic anticoagulation be initiated on Day 1 of the illness itself for doctors/HCWs?
- There are three phases of the illness: COVID (1-9 days, infectious phase), post-COVID (after 9 days, noninfectious, persistent inflammation) and non-COVID (after 3 months). After 3 months, the patient should be treated as non-COVID, instead of post-COVID. However, this comes laced with medicolegal aspects.
- In Hong Kong, the third wave is partly controlled. There have been less than 20 cases per day for the last week or more. One-third of confirmed cases have no known source of origin; so, the chain of spread of infection is not known. Universal community testing scheme will start from 1st September to find out silent carriers. The Hong Kong government has agreed to expand to high-risk group tracing and testing even with universal testing. With opening up of economy, better monitoring of industries is mandatory, to ensure there is no fourth wave. The third wave began with 9 cases with mutated virus strain (d614g). At that time, sailors coming to Hong Kong had been exempted from testing and quarantine; also restrictions of social distancing were relaxed. This created the third wave.
- Reinfection: A person from Spain tested positive in March then became negative reached Hong Kong and tested positive again in July. This raises a question whether this virus can re-infect. It was a mutated virus with 24 gene differences. It formed antibodies quickly, caused no symptoms and no

serious manifestations and disappeared early. We need to be vigilant about this. People in post-COVID phase getting recurrent corona-like illness may be getting reinfection with a different strain.

- Another case of reinfection reported in the US; a young person who had severe symptoms and required oxygen and assisted breathing in the second infection.
- A study from Mumbai has reconfirmed the US study that antibodies do not last for more than 3 months.

With input from Dr Monica Vasudev

Round Table Expert Zoom Meeting on "Role of Thymus in Enhancing Immunity Against COVID-19"

29th August, 2020 (Saturday, 11 am-12 noon)

Participants: Dr KK Aggarwal, Dr AK Agarwal, Dr Suneela Garg, Dr Jayakrishnan Alapet, Dr DR Rai, Dr Tripathi, Dr Angeli Misra, Dr Atul Pandya, Prof Bejon Misra, Dr Anil Kumar, Mrs Upasana Arora, Ms Ira Gupta, Dr S Sharma

Faculty: Dr Jagat Kaul, Director Prof and Former Head, Dept. of Anatomy, Maulana Azad Medical College, New Delhi; Consultant Academics and Advisor, Baba Saheb Ambedkar Medical College, Govt. of Delhi

Key points from the discussion

- Thymus is the primary lymphoid organ besides bone marrow and provides T lymphocytes to the whole body. It provides specificity of T-cell responses and immune tolerance to self.
- It influences and is influenced by products of neuroendocrine axis of the body.
- Thymus varies at different stages of life under the influence of different physiological and pathological states.
- The shape of thymus is molded to the adjacent structures and weighs about 20 g in adults. It is reddish in color and becomes yellowish with advancing age due to adipose infiltration at the cost of active lymphoid tissue. The older thymus can be distinguished from surrounding mediastinal fat only by the presence of the capsule, which covers the gland.
- The thymic microstructure consists of cortex (thymocytes) and the medulla (epithelial cells, lymphocytes). The blast cells in the subcapsular cortex do not express any marker.
- Type 1 cells are subcapsular and attract blast cells from bone marrow by way of their negative surface charge. Type 6 cells are commonest and form thymic hormone.
- Hassall's corpuscles start to form in the intrauterine life and are very well-established by the 5th month of intrauterine life; they increase with age.
- The T lymphocytes carry out cell-mediated defense actions by their effector and controlling actions.
- Via the effector action, they directly kill by cytotoxic substances (which release toxic lysosomal proteins) and indirectly by cytotoxins. Through the controlling action, they induce or suppress immune responses in B and T lymphocytes or any other variety of cells derived from the bone marrow. It can also cause delayed hypersensitivity response causing release of cytokines, which stimulate phagocytosis and chemotaxis.
- The natural killer cells are devoid of T-cell receptors and are not restricted by MHC protein.
- Suppression cells are certain T cells, which when stimulated, suppress the activity of B cells and other T cells.
- There is a fine balance between positive and negative controls in the T-cell system, which is lost in COVID-19.
- The thymic hormones (thymulin, thymosin, thymopentin, thymic humoral factor) exert immunomodulatory effects on maturation of lymphocytes and induce markers of early differentiation on lymphoid cells and enhance function of T cells. Thymulin relies on zinc for its biological action.
- Thymocytes secrete IL-1, 2, 4, 6; thymic epithelium secretes IL-1, 3, 4, 6 and 7.
- Nonlymphocytic thymic cells are cells of mononuclear phagocytic system in the form of monocytes and interdigitating cells. They present antigens to T cells as they move from cortex to medulla.
- Hormones can affect thymic function and thymic factors often affect other endocrine organs.
- Thymocytes have receptors for corticosteroids, oxytocin and estrogens.
- High levels of corticosteroids kill cortical lymphocytes and low steroid levels have a thymopoietic effect.
- The thymus increases in weight up to the first year of life, then the weight remains fairly constant at around 20 g until the 6th decade of life, and then the weight starts reducing.

- Pathogens may be more infective and prevalent in the elderly, yet may affect the young also; these are gerophilic in nature.
- Infections including COVID-19 are gerolavic. It has been seen that older adults were at greater risk of serious illness due to COVID-19 compared to children.
- Emerging research has shown that there is a marked decrease in the number of T cells in some seriously ill patients.
- It seems that the entire process of COVID-19 (T cells, IL-6, CD4) is directly or indirectly linked to the thymus.
- The role of T and B lymphocytes has opened up vistas of knowledge. It has helped to understand memory, tolerance, autoimmunity, immunodeficiency as well as inflammatory and immunopathological phenomenon.
- Recent investigations have highlighted the role of increased proinflammatory cytokines, impaired type 1 interferon response and functional exhaustion of antiviral lymphocytes in the elderly.

With input from Dr Monica Vasudev

Nearly One Quarter of Children Hospitalized with COVID-19 Developed Eye Symptoms in China

Among Chinese children hospitalized for COVID-19, about a quarter of them developed ocular symptoms.

Most of them developed eye symptoms later in the disease; however, ocular manifestations were the first sign of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in 9 of them. Ocular symptoms resolved in all the children. The report is published in *JAMA Ophthalmology*.

Out of 216 children hospitalized with COVID-19 in Wuhan, China, 49, i.e., 22.7% had ocular manifestations, including conjunctival discharge, eye rubbing, and conjunctival congestion.

Children with systemic symptoms or cough had a higher likelihood of developing ocular symptoms, which were mild and recovered or improved by minimal eye-drops or self-healing.

Overall, 193 children had an exposure to a family member with confirmed (173) or suspected (20) COVID-19. Among the study children, 93 experienced no systemic or respiratory symptoms before being tested. The most common symptoms among symptomatic children included fever and cough. All the children with mild (101) or moderate (115) symptoms recovered.

The initial symptoms were predominantly fever and cough, while there were other symptoms including diarrhea, fatigue, nasal discharge, nasal congestion, conjunctival discharge and conjunctival congestion.

Forty-nine children had ocular manifestations. Conjunctival discharge was the most common manifestation, followed by eye rubbing and conjunctival congestion.

Children with systemic symptoms were more likely to develop ocular symptoms. It seems possible that cough can lead to ocular infection through hand-eye contact in children. It is also possible that the force of the cough could push nasopharyngeal secretions from the nasolacrimal duct into the conjunctival sac.

Most of the children had other symptoms before the ocular manifestations started.

The new findings are reassuring as all the children recovered from their eye symptoms.

(*Source: Medscape; JAMA Ophthalmology, online August 26, 2020.*)

COVID-19 Often Undiagnosed in Frontline Hospital Workers

Reuters excerpts: A large number of COVID-19 infections among healthcare personnel in the US appear to go undetected, according to a report in the *Morbidity and Mortality Weekly Report* of the US Centers for Disease Control.

From April through June, among over 3,000 frontline workers across 12 states, approximately 1 in 20 had antibody evidence of a previous COVID-19 infection. Of note, 69% of those infections had never been diagnosed.

Among HCWs with antibodies to the novel coronavirus, nearly one-third did not recall having symptoms in the preceding months, about half of them did not suspect that they had been infected, and around two-thirds of them had never had a positive COVID-19 test.

Infections among frontline HCWs appear to be going undetected, as some infections may be minimally symptomatic or asymptomatic. Additionally, personnel with symptoms may not always have access to testing.

COVID-19 antibodies were less common among workers using a face covering for all patient encounters and more common among those who reporting a shortage of personal protective equipment.

With input from Dr Monica Vasudev

Minutes of Virtual Meeting of CMAAO NMAs on "One Year of CMAAO and COVID-19 Update"

5th August, 2020 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Marthanda Pillai, Member-World Medical Council; Dr Yeh Woei Chong, Singapore Chair, CMAAO; Dr Ravi Naidu, Malaysia, Immediate Past President-CMAAO; Dr N Gnanabaskaran, President-Malaysian Medical Association; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Marie Uzawa Urabe, Japan; Dr Prakash Budhathoky, Nepal; Dr Tashi Tenzin; Bhutan'Dr Md Jamaluddin Chowdhury, Bangladesh

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

This meeting was dedicated to the memory of all those who lost their lives in the COVID-19 pandemic.

Key points from the discussion

- **Singapore Update:** The outbreak in the dormitories is reaching its tail end; 40-50 cases; while cases in the community range from 0 to 1-2 cases. The focus is now on the economic damage and how the economy will open up. Singapore has opened its borders to New Zealand and Brunei.
- **Bangladesh Update:** Around 2,000 cases per day; a concern is that people are not going for testing out of fear. A study in Bangladesh conducted by the Institute of Epidemiology, Disease Control and Research and the International Centre for Diarrhoeal Disease Research, Bangladesh in Dhaka has shown that 9% of population in slum areas and 6% in the non-slum areas have the infection. These are asymptomatic infections. The number of deaths is declining but hovering around 35-40 per day.
- **Nepal Update:** The infection rate is increasing, as are severity of infection and deaths. Random samples have tested positive. Russia/China/UK are conducting 3rd phase clinical trials in Nepal. Doctors are conducting awareness programs.
- **Hong Kong Update**: Universal community testing scheme is underway since the past week, although not too many people go for testing; less than 1 million people have joined testing in the last 5 days. Nasal (not nasopharyngeal) and oropharyngeal swabs are collected. Some silent cases have been detected. From 2 weeks of high incidence (140 per day) in end of July, cases have slowly decreased to now single digit in August. In some cases, no source could be traced. Schools have restarted; for now it is online learning; but planning to reopen schooling from end of September.
- **Bhutan Update:** The first case was detected on 5th March in an American tourist aged 76 years. Total 128 cases; 150 have recovered; no deaths have been reported. Some positive cases have been reported in the border town of Phuntsholing (red zone), but no severe cases. The King of Bhutan has actively participated in creating awareness. The quarantine period is 21 days. Cases are discussed with doctors from Singapore and India and other commonwealth countries. All schools have been closed countrywide.
- **Malaysia Update:** There are 9,385 active cases; 9,092 are recovering; less than 20 new cases and total deaths are 128. More than 2.5 million foreign/ migrant workers are a concern; there is no wide testing, like in Singapore. Malaysia has detected a mutated strain of SARS-CoV-2 virus in a cluster of cases, called the "Sivaganga cluster". The index case belongs to Sivaganga in Tamil Nadu. Because of clusters, recovery movement control order (RMCO) has been extended to 31st December. The number of children affected is very small. Young people recover quite well. The Ministry of Health and the Malaysia Medical Association are working close together. People from any country which has 1,50,000 cases are not allowed entry into Malaysia.
- **Japan Update:** About 70,000 have tested positive; 103 deaths; the mortality rate is less than 1%. Treatment of inpatient is being gradually consolidated. Flu will soon begin; preparing to how to deal with both.
- **India Update:** The numbers are rising; India now has the 3rd highest number of cases (at the time of virtual meeting). But, the mortality rate is less than 1.2%. Recovery rate is more than 70%. About 60% of infections are from southern states. Government has been proactive in controlling the disease as and when issues come up. Testing rate is going up. The pandemic in India should plateau within 2 weeks to a month.
- **Australia Update:** Victoria had a second wave due to failure of quarantine measures, but now the number has come down to around 70. Rest of the country has had no cases. The lockdown is going to continue for another week. August 6, the PM is going to give a pathway on how to relax the restrictions. Travel (airports, ships) has been stopped until December. Melbourne, Victoria is

completely closed down. Deaths are mostly in the aged care homes; deaths in Victoria are around 600.

- ***Dr KK Aggarwal introduced his initiatives:*** Health Patrol, International Journal of Pandemic Research and COVID Educator Course. The objective of Health Patrol is to filter out fake news; you can visit the website and ask to check its authenticity. He asked Singapore to join as Knowledge Partner and all NMAs as advisors. The International Journal of Pandemic Research will publish articles related to COVID-19 and any other pandemic, as they are, without any change. Anybody from anywhere can publish data. These would subsequently be peer reviewed. All participating member NMAs were invited to be peer reviewers. Similar COVID Educator Courses can be started in member countries to create COVID Educators in the community.
- There are still some unanswered questions: Why does it cause post-COVID illness after 9 days and causing recurrent inflammations; why children are not spreading infection; which vaccine will work.
- The number of deaths so far in healthcare professionals throughout the world is 8% and the number of infections in them is 10-15% (WMA).
- The vaccine may not be widespread till mid-2021.

IMA-CMAAO Webinar on "Understanding the Molecular Biology of Coronavirus Proteins"

5th September, 2020 (Saturday, 4-5 pm)

Participants: Dr KK Aggarwal, President-CMAAO; Dr RV Asokan, Hony Secretary General-IMA; Dr Ramesh K Datta, Hony Finance Secretary-IMA; Dr Jayakrishnan Alapet; Dr S Sharma

Faculty: Dr Pavithra Venkatagopalan, PhD Coronavirus Studies, Director-Care Health Diagnostic Center, Chennai

Key points from the discussion

- Life has three main domains: Bacteria and Archaea, which are single-celled; everything else - from yeast to humans - comes under Eukarya.
- Viruses have their own domain. A virus is neither living nor dead; it is an obligate intracellular parasite.
- All cells in the domain of life carry DNA (genetic information), which make mRNA (instructions for forming a protein from a gene) via transcription. This information is translated to form proteins.
- DNA viruses can be either double- or single-stranded; double-stranded can be enveloped or unenveloped.
- RNA viruses (coronaviruses) have no DNA in their entire life cycle.
- Coronaviruses are classified under order Nidovirales and family Coronaviridae. The viruses under this order typically infect humans and animals, so they are typically considered zoonotic viruses. Bats are a common reservoir (Nipah, rabies, etc.).
- They mainly cause respiratory and enteric infections. About 30% of all common colds are caused by coronaviruses.
- Coronaviruses are divided into three classes: Alpha, beta (COVID) and gamma. Genetic sequencing has been identified - COVID-19 virus as being very close to bat coronaviruses.
- The virus has four structural proteins (spike, membrane, envelope and nucleocapsid) and one RNA (viral genome).
- The S protein has two domains (N terminal and C terminal); the N terminal is the exposed part and binds to the ACE2 receptors. The C terminal causes change in the viral envelope structure so that it fuses with the cellular envelope, thereby releasing virus RNA into the cell.
- After infection occurs, the S protein downregulates the expression of ACE2 receptors and promotes lung injury, resulting in respiratory distress.
- The virus lifecycle is entirely in the cytoplasm. The viral genome resembles cell mRNA so the cell recognizes it as its own and starts making mRNA. RdRP (RNA-dependent RNA-polymerase) will make more copies of the genome. And, the cellular translation machinery will make all the viral proteins.
- RdRP is the target for antivirals (remdesivir).
- The coronavirus is a single-stranded, positive sense ~30 kb RNA genome virus.
- Functions of coronavirus proteins: The function of ORF 1ab-15 nonstructural protein is virus replication, proofreading and suppression of cellular immunity. The spike protein enables receptor binding and entry into the cell and initiates infection. ORF3 causes virus release, envelope protein is responsible for virus assembly and the membrane protein (most abundant of the viral protein) forms and stabilizes the viral envelope. ORF 6, 7a, 7b, 8a, 8b, 9b suppress

cellular immunity and help virus release. The Nsp 3 protein counteracts host innate immunity, while Nsp 4, 6 and Nsp 7-10 are involved in the replication of the genome. Nsp 16 is involved in proofreading. N proteins increase interferon resistance to cell.

- RT-PCR detects ORF 1ab and E proteins to see if full genome replication is taking place.
- Proteins are synthesized in the endoplasmic reticulum and the assembly takes place in ERGIC (ER-Golgi Intermediate Compartment) and then the virus is released from the cell.
- Testing is relevant as we want to see active virus replication. It checks the entire genome. Whatever gene you test, they should be spaced apart.
- Most labs have cut off value of 40 cycles; New York Public health system says this has to be higher as otherwise asymptomatic cases can be missed.
- Worsening infection does not mean lower cycle threshold (Ct) value.

With input from Dr Monica Vasudev

Anticoagulation or Not

Direct oral anticoagulants widely used among patients requiring both short- and long-term anticoagulation

Direct oral anticoagulants (DOACs) are preferred agents owing to their ease of use, favorable pharmacokinetic profile with fixed dosing, decreased drug-drug interactions and the lack of monitoring requirements. With the increasing use of DOACs, physicians must be able to manage patients on these medications in the perioperative period, while balancing the risk of bleeding with that of thromboembolic events.

COVID-19: Hypercoagulability

Outpatient thromboprophylaxis

Patients discharged from the hospital—Those with documented venous thromboembolism (VTE) need at least 3 months of anticoagulation.

Some individuals who have not had a VTE may also require extended thromboprophylaxis following hospital discharge.

- In individuals with other risk factors for VTE like immobilization, recent surgery or trauma.
- Older age.
- Bleeding risk must be incorporated into decision-making.
- Options for post-discharge prophylaxis include those used in clinical trials, such as rivaroxaban 10 mg daily for 31-39 days.

Patients not admitted to the hospital—Outpatient thromboprophylaxis may be appropriate for some individuals with COVID-19 who are not admitted to the hospital, particularly those with other thrombotic risk factors such as prior VTE or recent surgery, trauma or immobilization. This is based on clinical judgment. If thromboprophylaxis is used in an outpatient, rivaroxaban 10 mg daily for 31-39 days may be given. (*UpToDate*)

Clinical indications for therapeutic anticoagulation

For inpatients, particularly those who are critically ill, LMWH or UFH (unfractionated heparin) for any indication is preferred in place of a DOAC, on account of their shorter half-lives and ability for parenteral administration.

COVID-19 patients tend to have elevated levels of fibrinogen.

The issue of using therapeutic-dose anticoagulation for presumed pulmonary embolism has been encountered in many ICUs across the world owing to the difficulty in moving mechanically ventilated patients to computed tomography (CT) scanners and the desire or the need to limit staff exposure to COVID-19 positive patients. D-dimer is often not helpful, on account of the significant baseline elevations in these patients. Sudden respiratory decompensation, evidence of right-heart strain on echocardiography, or DVT evident on lower-extremity ultrasound performed for these reasons have been used to increase to therapeutic-dose anticoagulation. (*Connors JM, et al. Blood. 2020;135(23):2033-40.*)

Blood thinners may improve survival in hospitalized COVID-19 patients

A study published May 6 in the *Journal of the American College of Cardiology* found that hospitalized COVID-19 patients treated with anticoagulants had improved outcomes both in and out of the ICU setting.

The study revealed that anticoagulants taken orally, subcutaneously or intravenously may play a pivotal role in COVID-19 patients, and may prevent possible fatal events associated with COVID-19, including heart attack, stroke and pulmonary embolism.

Using anticoagulants should be considered when patients get admitted to the ER and have tested positive for COVID-19 in order to improve outcomes. However, each case should be evaluated on an individualized basis to account for potential bleeding risk.

This study follows recent research from the Icahn School of Medicine at Mount Sinai, which showed that a large number of patients hospitalized with COVID-19 developed high levels of life-threatening blood clots, leading to potentially deadly thromboembolic events. (*Source: https://www.eurekalert.org/pub_releases/2020-05/tmsh-btm050420.php*)

The current crisis thus offers several arguments in favor of anticoagulation with DOACs in patients without contraindications.

- For patients in whom oral anticoagulation must be started, it seems appropriate to favor the use of DOACs.
- For patients on long-term vitamin K antagonist (VKA), the current crisis seems to be an opportunity to switch them to a DOAC.
- For patients who should remain on VKAs (mechanical cardiac valve, antiphospholipid syndrome, renal impairment depending on it severity…), the use of point-of-care (POC) devices for measuring INR should be promoted.

(*Impact of the COVID-19 pandemic on therapeutic choices in Thrombosis-Hemostasis. Journal of Thrombosis and Haemostasis. Available at: http://www.sah.org.ar/pdf/covid-19/bibliografia_14845.pdf, First published: 15 April 2020***)**

Dabigatran offers potential advantages over currently available anticoagulants. It excludes the need for parenteral or subcutaneous administration, increasing compliance especially when outpatient antithrombotic treatment is needed following early hospital discharge. (*Wurnig C, et al. Thromb J. 2015;13:37.*)

Rivaroxaban

Rivaroxaban is usually given at a fixed dose without monitoring.

- VTE prophylaxis in surgical patients: 10 mg daily; duration (12 days vs. extended to 35 days) depends on the type of surgery.
- Treatment and secondary prevention of VTE: 15 mg twice a day (with food) for 21 days, followed by 20 mg once a day (with food). If treatment is continued after 6 months, the dose can be reduced to 10 mg once daily for selected individuals. For those with an increased risk for VTE beyond 6 months of anticoagulation (e.g., two or more episodes of VTE), the 20 mg once daily dose should be used.
- Stroke prevention in atrial fibrillation (AF): 20 mg once a day with the evening meal (CrCl >50 mL/min); or 15 mg once a day with the evening meal (CrCl ≤50 mL/min).

Rivaroxaban is not recommended for VTE prophylaxis, treatment or secondary prevention in individuals with a creatinine clearance of <30 mL/min.

Apixaban

Overview (apixaban)—

- VTE prophylaxis in surgical patients: 2.5 mg twice daily; duration (12 days vs. extended to 35 days) depends on the type of surgery.
- Treatment and secondary prevention of VTE: 10 mg twice daily for 7 days, followed by 5 mg twice daily. If therapy continues beyond 6 months, the dose is reduced to 2.5 mg twice daily.Stroke prevention in AF: 5 mg twice daily (CrCl >50 mL/min); or 2.5 mg twice daily for those with any two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL.

Dabigatran

- VTE primary prophylaxis in surgical patients: 110 mg 1-4 hours after surgery, followed by 220 mg once daily for 28-35 days (hip replacement) or 10 days (knee replacement).
- Treatment and secondary prevention of VTE: 150 mg orally twice daily after 5-10 days of parenteral anticoagulation (CrCl >30 mL/min).
- Stroke prevention in atrial fibrillation (AF): 110 mg orally twice a day or 150 mg orally twice a day (CrCl >30 mL/min). European labeling suggests dose reduction in patients >75 years of age (for instance, 150 mg orally once a day or 110 mg orally twice a day).

(*UpToDate*)

Should seriously ill COVID-19 patients be given therapeutic-intensity anticoagulation empirically (in the absence of confirmed or suspected VTE)?

Microvascular thrombosis is believed to be involved in hypoxemic respiratory failure in some patients with COVID-19. Autopsy studies have been limited but they demonstrate large vessel and microvascular thrombosis, pulmonary hemorrhage and high prevalence of VTE.

Should COVID-19 patients receive post-discharge thromboprophylaxis?

Patients hospitalized for acute medical illness have an increased risk for VTE for up to 90 days following discharge. Whether this risk is sufficiently high in patients with COVID-19 to warrant post-discharge

thromboprophylaxis is not clearly known. Non-COVID clinical trials which pointed to a benefit for post-discharge thromboprophylaxis given for up to 42 days enrolled patients with combinations of risk factors, including age, comorbidities such as active cancer, and elevated D-dimer >2 times the upper normal limit.

The decision to use post-discharge thromboprophylaxis should consider the individual patient's VTE risk factors at the time of discharge, which should include reduced mobility and bleeding risk, as well as feasibility.

Aspirin has been evaluated for VTE prophylaxis in low-risk patients following hip or knee arthroplasty but has not been assessed for COVID-19 post-discharge thromboprophylaxis. Patients should be educated on the signs and symptoms of VTE at hospital discharge and advised to seek urgent medical attention if any of these develop.

If a patient with COVID-19 requires therapeutic anticoagulation for VTE or AFIB stroke prevention, do we have any special considerations?

Dexamethasone is an inducer of CYP3A4 and the extent of the drug interaction with DOACs is not well understood. Sarilumab and tocilizumab can heighten CYP450 enzyme activity and should not be used in association with apixaban or rivaroxaban and may also increase the doses of warfarin required.

Atazanavir and lopinavir/ritonavir can increase drug concentrations of apixaban and rivaroxaban and reduce the active metabolite of clopidogrel and prasugrel. The University of Liverpool has assembled a list of drug interactions, which can be accessed at covid19-druginteractions.org. LMWH or UFH in hospitalized critically ill patients is preferred because of the shorter half-life and fewer drug-drug interactions compared with DOACs. Regular warfarin users who cannot get INR monitoring during isolation may be candidates for DOAC therapy; however, patients with mechanical heart valves, ventricular assist devices, valvular AF, antiphospholipid antibody syndrome, or lactation should continue treatment with warfarin therapy. LMWH or UFH are the anticoagulants of choice in pregnancy. *(https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation)*

ChAdOx1 nCoV-19 and Transverse Myelitis

- AstraZeneca had voluntarily halted a randomized clinical trial of its coronavirus vaccine after a volunteer developed transverse myelitis (*NY Times*).
- Phase 1/2, single-blind, randomized controlled trial at five trial sites in the UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control.
- We presume that the team has confirmed that the case was not in the control arm.
- ChAdOx1 nCoV-19 given at a dose of 5×10^{10} viral particles.
- The booster vaccine administered 28 days after the first dose.
- ChAdOx1 nCoV-19 is made from a virus (ChAdOx1), which is a weakened form of a common cold virus (adenovirus) known to cause infections in chimpanzees; it has been genetically changed thus rendering it impossible to grow in humans. Genetic material has been added to the ChAdOx1 construct that is used to make proteins from the COVID-19 virus (SARS-CoV-2) called Spike glycoprotein (S). This protein is usually found on the surface of SARS-CoV-2 and plays a pivotal role in the infection pathway of the SARS-CoV-2 virus. The SARS-CoV-2 virus uses its spike protein to bind to ACE2 receptors on human cells and enters the cells and causes an infection. (*https://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials*)
- The patented Vaccitech adenovirus vectors are chimpanzee adenovirus Oxford 1 and 2 (ChAdOx1 and ChAdOx2), and belong to the group E simian adenovirus family, similar to the chimpanzee adenovirus 63. These viruses have been engineered to make them replication deficient and can be manufactured in well-established HEK293 cell lines containing the adenoviral E1 gene. The viruses have high carrying capacity for the genes encoding cancer or pathogen antigens of interest. (*https://www.vaccitech.co.uk/technology*)
- Chimps can have transverse myelitis (*Miyabe-Nishiwaki T, et al. J Med Primatol. 2010;39(5):336-46.)*
- **Adenoviruses and transverse myelitis:** Species B adenoviruses can be linked with more severe disease, including severe pneumonia, aseptic meningitis, encephalitis and transverse myelitis. Amongst species B adenovirus, type 21 (Ad21) may have caused paralysis. (*Clin Infect Dis. 2003;36(5)550-9.)*
- Acute transverse myelitis is seen in COVID-19 infection. (*https://casereports.bmj.com/content/13/8/e236720*)

Investigators did not detect SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) and postulated that this presentation was likely a result of an immune-mediated inflammatory process rather than direct invasion of SARS-CoV-2 into the central nervous system (CNS).

The incidence of acute myelitis associated with COVID-19 infection is not clearly understood. Three case reports of similar cases have been noted to link COVID-19 to acute myelitis as a neurological complication. The first one is in Wuhan, China by Kang Zhao et al where COVID-19 was first reported. The second is in Boston where the patient presented with symptoms of upper respiratory tract infection and then developed acute myelitis 7 days later by Sarma et al. Whether the myelitis occurs directly from the viral infection or as an autoimmune sequelae is still not known. (*https://www.sciencedirect.com/science/article/pii/S1930043320302478*)

Acute transverse myelitis

It is a neuro-inflammatory spinal cord disorder presenting with rapid onset of weakness, sensory alterations and/or bowel and bladder dysfunction.

Types: Idiopathic transverse myelitis (TM) occurs without a definite etiology. Secondary (disease-associated) TM is related to a systemic inflammatory autoimmune condition. Idiopathic TM is often a post-infectious complication and presumably results from an autoimmune process.

TM can be associated with infectious, systemic inflammatory or multifocal CNS disease. Acquired CNS demyelinating disorders known to cause TM include multiple sclerosis, neuromyelitis optica and acute disseminated encephalomyelitis.

Incidence: 1-8 new cases per million.

Onset: Acute or subacute development of neurologic signs and symptoms consisting of motor, sensory and/or autonomic dysfunction. Motor symptoms include rapidly progressing paraparesis that may involve the upper extremities; initial flaccidity followed by spasticity. In most patients, a sensory level can be identified. Sensory symptoms include pain, dysesthesia and paresthesia. Autonomic symptoms involve heightened urinary urgency, bladder and bowel incontinence, difficulty or inability to void, incomplete evacuation and bowel constipation, and sexual dysfunction.

Diagnosis: No evidence of a compressive cord lesion; exclusion of a compressive cord lesion by magnetic resonance imaging (MRI) and confirmation of inflammation by either gadolinium-enhanced MRI or lumbar puncture.

When inflammation is evident in the absence of cord compression, one must evaluate for the presence of infection, systemic inflammation and the extent and sites CNS inflammation.

Acute idiopathic TM: High-dose intravenous glucocorticoid treatment.

Most patients with idiopathic TM have at least a partial recovery, which usually starts within 1-3 months and continues with exercise and rehabilitation therapy. Some degree of persistent disability is common, and is seen in nearly 40% of the individuals. A very rapid onset with complete paraplegia and spinal shock has been associated with poorer outcomes. Recovery can proceed over years.

Majority of patients with TM have monophasic disease. Recurrence can occur in approximately 25-33% of patients with idiopathic TM. With secondary TM, the recurrence rate may be nearly 70%.

Patients presenting with acute complete TM have a risk of multiple sclerosis of only 5-10%. However, for patients with partial myelitis as the initial presentation and cranial MRI abnormalities showing lesions typical for multiple sclerosis, the transition rate to multiple sclerosis over three to 5 years is 60-90%. Patients with acute partial myelitis with normal brain MRI develop multiple sclerosis at a rate of only 10-30% over a similar time period.

Round Table Expert Zoom Meeting on "Considerations for Wearing Face Masks in Pandemic Era in Different Situations"

12th September, 2020 (Saturday, 11 am-12 pm)

Participants: Dr KK Aggarwal, Dr AK Agarwal, Dr Suneela Garg, Dr Jayakrishnan Alapet, Dr JA Jayalal, Dr KK Kalra, Dr AM Kochhar, Dr Atul Pandya, Dr Anoop Mohta, Dr DR Rai, Dr Anil Kumar, Mrs Upasana Arora, Dr Pragati Sawhney, Ms Ira Gupta, Dr S Sharma

Key points from the discussion

- When virus enters the cell (nasooropharyngeal), different scenarios can result.
- One, it is taken up and is killed by the macrophages. No antibodies are formed, the patient remains asymptomatic.
- In some persons, the virus enters the blood → dendritic cells in thymus → T cells and then to B cells and produces IgG and IgM. The patient is asymptomatic, but antibodies are formed.

- In a third scenario, the cells produce IFN-1 on Day 1, which initiates neutrophils, NK cells and monocytes. The NK cells and monocytes produce IFN-γ, which kills the virus as do the neutrophils. The patient is asymptomatic because of adequate immunity.
- Another scenario, the IFN-γ will produce TNF-α, which causes inflammation. The person will be symptomatic on Day 1 (fever, diarrhea, headache, rash, loss of smell/taste).
- If the immunity is inadequate, the virus is not killed. The cells do not form IFN-1 in such a situation, alternate pathway opens up on Day 3. Macrophages produce NLRP3, which produces IL-1β and IL-18. IL-1β increases ferritin levels, glucuronidase causing tissue damage. IL-18 adds to the inflammation. Cells, through the cellular dendritic cells, produce Th1 cells, which produce IL-6 (formed on Day 3), TNF-α and IL-8. IL-6 causes clot formation, TNF-α (formed on Day 1), IL-8 and IL-1β (formed on Day 3), cause inflammation.
- Masks can be medical masks or fabric masks. Medical masks (surgical and N95) are part of personal protective equipment (PPE) kit, while fabric masks are not.
- Respirators are rated "N," if they are not resistant to oil, "R" if somewhat Resistant to oil, and "P" if they are oil proof, i.e., strongly resistant to oil.
- The number 95 means that these masks have 95% filtration efficiency.
- In areas with known or suspected community transmission, medical masks and not fabric masks in patient care must be used, irrespective of whether patient is confirmed positive or not.
- Medical masks must meet three criteria: High filtration, adequate breathability and fluid penetration resistance.
- Medical masks must filter droplets (3 μm) and particles (0.1 μm).
- The World Health Organization (WHO) recommends that persons with any symptoms suggestive of COVID-19 should wear a medical mask.
- The selection of material is important; higher the filtration efficiency, the more of a barrier provided.
- Breathability is measured in millibars (mbar) or Pascals (Pa). Acceptable breathability of a medical mask should be below 49 Pa/cm^2. For non-medical masks, it should be below 100 Pa.
- Non-medical masks should have a minimum of 3 layers. Nylon or polyester fabric masks may be 2-layered or 4-layered. Cotton handkerchiefs used as masks have only 17% filtration efficiency. Gauze has only 3% filtration efficiency, even if multiple layers are used.
- Users are confused about which mask to use for themselves.
- Guidelines need to be redefined based on whether there is suspected community transmission or not.
- If there is a suspected case in a house, everyone should wear a medical mask.
- All patients coming to a healthcare setting, especially in clinics/OPDs or those who have corona-like illness, should wear a medical mask.
- Even fabric masks should be regulated. It should not be left upon the user to decide the quality of the mask in the event of a pandemic.
- Heart Care Foundation of India (HCFI) may file a question to the ministry or even file a public interest litigation (PIL).
- Masks have to be combined with other prevention measures such as physical distancing, hand washing.
- Correct and consistent use of masks is important if physical distancing is not possible.
- There is a greater need for education of public about masks.
- Fit of the mask is also important.
- Electrostatic charge of the mask is lost by ultraviolet, washing, etc.
- As per the Central Pollution Control Board (CPCB) guidelines, the mask should be stored for 72 hours in a paper bag after use before disposing or kept in sodium hypochlorite solution for 15 minutes.
- Hand hygiene before and after wearing a mask is very important.
- Awareness needs to be created about the correct method of wearing and removing a mask and its disposal.

With input from Dr Monica Vasudev

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News and Views

Coronavirus Vaccine Unlikely in Public Before Fall of 2021, Say Experts

An effective vaccine is unlikely to be available for the general public before the fall of 2021, stated experts working in the field of vaccine development.

Researchers at McGill University in Canada conducted a survey among 28 experts working in vaccinology in late June 2020. The majority of these experts were Canadian or American academics with an average of 25 years of experience working in the field. Jonathan Kimmelman, a professor at McGill University, said that the experts offered forecasts on vaccine development that appeared less optimistic than the timeline of early 2021 given by US public officials. Kimmelman, the senior author on the paper published in the *Journal of General Internal Medicine*, stated, "In general, they seem to believe that a publicly available vaccine next summer is the best-case scenario with the possibility that it may take until 2022." (*Deccan Chronicle – PTI*)

COVID-19 Vaccine Roll-out Expected in Britain in Less Than 3 Months: The Times

A mass roll-out of a coronavirus disease 2019 (COVID-19) vaccine in the UK could be finished within 3 months' time, reported *The Times*, while citing government scientists.

The newspaper stated that scientists working on the Oxford vaccine are hopeful that the regulators will approve it before the beginning of 2021. *The Times* further reported that a full COVID-19 immunization program would exclude children and could be quicker than predicted earlier. Health officials estimate it is possible that every adult could receive a vaccine dose within 6 months. The European Medicines Agency (EMA) has also stated that it is reviewing data on AstraZeneca and Oxford University's potential COVID-19 vaccine, in real time… (*Reuters*)

Drug Combination for Treating Mesothelioma Receives FDA Approval

The US Food and Drug Administration (FDA) has granted approval to nivolumab, in combination with ipilimumab, for the first-line treatment of adults with malignant pleural mesothelioma, which cannot be removed surgically.

This is the first drug regimen that has been granted approval for mesothelioma in 16 years' time and the second FDA-approved systemic therapy for mesothelioma. Both the agents are monoclonal antibodies that, in combination, tend to diminish tumor growth by enhancing T-cell function.

This combination was assessed in a randomized, open-label trial in 605 patients with previously untreated unresectable malignant pleural mesothelioma. Patients receiving the combination therapy survived a median of 18.1 months, while those undergoing chemotherapy survived a median of 14.1 months… (*FDA*)

Reliance Develops RT-PCR Kit That can Give Results in 2 Hours

Reliance Life Sciences has developed a reverse transcription polymerase chain reaction (RT-PCR) kit to test for COVID-19 that may provide results in about 2 hours, stated company sources.

Presently, COVID-19 RT-PCR test, a real-time RT-PCR (rRT-PCR) test, used for the qualitative detection of nucleic acid from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), takes about 24 hours to provide the results.

Computational biologists at Reliance Life Sciences assessed over 100 genomes of SARS-CoV-2 sequenced in India and designed unique RT-PCR primers to develop a quantitative-rRT-PCR kit for the detection of COVID-19. The Indian Council of Medical Research (ICMR) has technically validated the kit for satisfactory performance, stated sources. ICMR's validation process does not approve or disapprove the kit design and it does not confirm user-friendliness. According to ICMR results, the kit has a 98.7% sensitivity and 98.8% specificity… (*ET Healthworld – PTI*)

Unique Patterns in COVID-19 Transmission Identified in India

New Delhi: Researchers, including those from the Government of Tamil Nadu, and Andhra Pradesh, carried out one of the largest analyses of COVID-19 epidemiology till today, and noted that both cases and deaths due to the viral illness have been highly concentrated in the 40- to 69-year age group in India as compared to that seen in high-income countries, among other trends.

The study explored the disease transmission patterns in 5,75,071 individuals exposed to 84,965 confirmed cases of COVID-19 in the two states on the basis of data collected by thousands of contact tracers. The scientists noted that both cases and deaths across the two Indian states were concentrated in younger cohorts than expected from observations in higher-income countries.

Follow-up testing of exposed contacts also suggested that 70% of infected individuals did not infect any of their contacts, while 8% of positive patients accounted for 60% of observed new infections. The study is published in the journal *Science*… (*ET Healthworld – PTI)*

COVID-19: Delirium a Key Symptom in Frail Older People

Confusion or strange behavior in frail older people could be an early warning sign of COVID-19, suggests new research.

The King's College London study assessed data from over 800 people over the age of 65. It included 322 patients in hospital with COVID-19, and 535 people using the COVID Symptom Study app to record their symptoms or log health reports on behalf of friends and family. All had a positive test result. Older adults admitted to hospital, classified as frail, had higher odds of having had delirium as one of their symptoms, compared to people of the same age who weren't frail. For 1 in 5 patients in hospital with COVID-19, delirium was their only symptom. Among the 65 plus people using the app, delirium was more common in frailer people with COVID-19 compared to those of the same age with the infection, who were more robust… (*BBC*)

Oxford to Study Adalimumab as COVID-19 Treatment

London: Oxford University has stated it would study if adalimumab, a type of anti-inflammatory known as an anti-tumor necrosis factor (anti-TNF) drug, was an effective treatment option for COVID-19 patients.

Evidence indicates that COVID-19 patients already taking anti-TNF drugs for inflammatory bowel disease and inflammatory arthritis have a reduced likelihood of being admitted to hospital, said Oxford. The trial, called AVID-CC, will be aimed at treating people in the community, especially in care homes and will enrol up to 750 patients from community care settings throughout Britain. The drug is presently used to treat conditions like rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis… (*NDTV – Reuters*)

Patients with Psychiatric Disorders at Higher Risk of COVID-19 Death

Patients with mental illness have a higher risk for severe COVID-19 outcomes compared to the general population, reported a study from a large hospital system.

Of 1,685 hospitalized COVID-19 patients, those with a prior psychiatric diagnosis had a significantly higher risk of death compared to patients without a diagnosis, after controlling for demographic characteristics, comorbidities and hospital location (hazard ratio [HR] 1.5, 95% confidence interval [CI] 1.1-1.9, p = 0.003), reported researchers in *JAMA Network Open*. The risk was found to be higher among patients with a psychiatric diagnosis at 2 weeks after their index hospitalization (35.7% vs. 14.7%), at 3 weeks (40.9% vs. 22.2%) and 4 weeks (44.8% vs. 31.5%)… (*Medpage Today*)

Stroke may be First Symptom of COVID-19 in Younger Patients

According to a new study, published online in *Neurology*, stroke may be the first presenting symptom of COVID-19 in younger patients.

A meta-analysis was conducted of data from 160 patients with COVID-19 and stroke, and noted that nearly half of patients below the age of 50 were asymptomatic at the time of stroke onset. Although younger patients had the highest risk of stroke, the highest risk of death was seen among patients who were older, had other chronic conditions, and had more severe COVID-19-associated respiratory symptoms. Among patients below 50, many were completely asymptomatic when they had a stroke related to COVID-19, thus suggesting that for these patients, stroke was their first symptom of the disease… (*Medscape*)

Menopausal Symptoms Linked with Cardiovascular Risk

Analysis of data from the Women's Health Initiative CaD (Calcium and Vitamin D) trial has revealed that women with greater menopausal symptoms experienced higher risk of cardiovascular illness.

Women having two or more moderate-to-severe menopausal symptoms were found to have higher rates of stroke (HR 1.40, 95% CI 1.04-1.89) and cardiovascular disease (HR 1.35, 95% CI 1.18-1.54), reported researchers in a presentation at the North American Menopause Society 2020 virtual meeting. The investigators also revealed that calcium and vitamin D supplements did not decrease the risk of adverse health outcomes

in this patient population. More moderate or severe menopausal symptoms were tied to more cardiovascular disease and stroke… (*Medpage Today*)

Orthopedic Problems in Children could be First Indication of Acute Lymphoblastic Leukemia

The diagnosis of acute lymphoblastic leukemia (ALL) can be delayed due to vague presentation and normal hematological results. However, orthopedic manifestations could be the primary presentation of ALL to physicians, and these symptoms in children should raise suspicion, even in the absence of hematological abnormalities, suggests a report published in the *Journal of Orthopaedics*.

The study retrospectively evaluated 250 consecutive ALL patients at a single institution to ascertain the frequency of ALL cases presented to the orthopedic department and to establish the number of these patients presenting with normal hematological results. Around 8.8% of the patients (22/250) presented primarily to the orthopedic department (4 with vertebral compression fractures, 12 with joint pain, and 6 with bone pain), and were later diagnosed with ALL. Six of these 22 patients (27.3%) had a normal peripheral blood smear, reported researchers… (*Medscape*)

New COVID-19 Syndrome in Adults Similar to MIS-C in Kids: CDC

Researchers with the US Centers for Disease Control and Prevention (CDC) have stated that adults can sometimes develop dangerous symptoms that are similar to a coronavirus-linked syndrome in children.

The researchers have termed it multisystem inflammatory syndrome in adults or MIS-A, and suggest that it resembles the multisystem inflammatory syndrome in children or MIS-C. Similar to MIS-C, MIS-A does not show an obvious link to coronavirus and patients may not show any other symptoms that would suggest COVID-19 infection. MIS-A has killed at least 3 patients and disproportionately affects racial and ethnic minorities, stated CDC researchers.

Researchers described the cases of 27 adults, 21-50 years of age, with similar syndromes. Most of them had extreme inflammation in the body and organ malfunction, such as the heart, liver and kidneys, but sparing the lungs. "Although hyperinflammation and extrapulmonary organ dysfunction have been described in hospitalized adults with severe COVID-19, these conditions are generally accompanied by respiratory failure," researchers noted in the CDC's weekly report, the *MMWR*… (*CNN*)

Study Says Nitric Oxide Possible Treatment for COVID-19

Sweden: Researchers at Uppsala University have noted that an effective way of treating the coronavirus that caused the 2003 SARS epidemic also works on the SARS-CoV-2 virus. The substance is nitric oxide (NO), a compound that has antiviral properties and is produced by the body itself.

According to Åke Lundkvist, a professor at Uppsala University, who led the study, NO appears to be the only substance shown to have a direct effect on SARS-CoV-2.

Researchers from Uppsala University and Karolinska Institute investigated how SARS-CoV-2 reacts to the compound. S-Nitroso-N-acetylpenicillamine (SNAP) was shown to exert a clear antiviral effect on this virus and the effect grew stronger as the dose was increased. The study is published in the journal *Redox Biology*. Lundkvist stated that until a vaccine is developed, inhalation of NO might be an effective treatment… (*ET Healthworld*)

Moderna COVID-19 Vaccine Appears Safe in Older Adults

An early safety study of Moderna Inc's COVID-19 vaccine candidate among older adults revealed that virus-neutralizing antibodies were produced at levels similar to those seen in younger adults. The side effects were roughly comparable to high-dose flu shots, stated researchers.

The study, published in the *New England Journal of Medicine*, was an extension of the Phase I safety trial, first conducted in 18- to 55-year olds. Two doses of Moderna's vaccine - 25 μg and 100 μg – were tested in 40 adults aged 56 to 70 and 71 and older.

Among older adults given two injections of the 100 μg dose 28 days apart, the vaccine evoked immune responses that more or less conform to those seen in younger adults… (*Reuters*)

7.1% of Adults Exposed to COVID by August: India's Second National Sero-survey

New Delhi: Nearly 7.1% of India's adults (aged 18 and above) were exposed to the coronavirus by the end of August, suggest the results of the second national sero-survey, conducted by ICMR from August 17 through September 22.

This represents an enormous rise from the 0.73% logged in the first survey, conducted across the same

700 villages and urban wards as the second, from May 11 through June 4. However, the findings of the second sero-survey indicate that a considerable section of the population has still not been exposed to the virus and continues to be at risk of infection. The sero-survey revealed that only 1 in 15 people (aged 10 and above) had likely been exposed to the virus by the end of August. The risk of infection was two-fold in slums in comparison with non-slum areas of urban centers, and four times higher than rural areas… (*NDTV*)

Povidone-iodine Gargle: A Prophylactic Measure to Impede COVID-19 Transmission

Coronavirus disease 2019 or COVID-19, caused by the SARS-CoV-2 virus, has crossed the 33 million case mark across the world, with the death toll surpassing 1 million (as on September 28, 2020).[1]

Human-to-human transmission occurs through close contact with an infected person. Infection can also occur from surfaces contaminated with droplets or secretions. Respiratory pathogens adhere to the oropharyngeal mucosa and colonize and cause upper respiratory tract infection (URTI).[2]

Given the fact that COVID-19 is transmitted through respiratory droplets, it is reasonable to evaluate if the use of a prophylactic mouth rinse with virucidal activity can impede the spread of infection.

Povidone-iodine (PVP-I) products, as mouthwashes and throat sprays, have been shown to have a prophylactic effect on the transmission of SARS-CoV during previous outbreak. PVP-I products were shown to have strong virucidal activity against SARS-CoV.[3]

SARS-CoV-2 virus is closely related to SARS-CoV, and the viral load in the oropharynx in asymptomatic patients with SARS-CoV-2 infection appears to be as high as that in symptomatic patients.[4]

Reducing the viral load in the oropharynx with adequate oral prophylactic measures seems worth exploring.

A study assessed nasal and oral antiseptic formulations of PVP-I for virucidal activity against SARS-CoV-2. PVP-I nasal and oral rinse formulations from 1% to 5% concentrations as well as controls were evaluated for virucidal potential. SARS-CoV-2 was exposed to the test compound for 60 seconds. All the tested concentrations of nasal and oral rinse formulations could completely inactivate the SARS-CoV-2 virus. Nasal and oral PVP-I formulations were thus shown to inactive the SARS-CoV-2 virus at different concentrations. Nasal and oral decontamination with PVP-I formulations thus seem to have potential in limiting the transmission of SARS-CoV-2.[5]

PVP-I mouthwash or gargle thus appears to be a promising approach to inactivate the virus, thus checking the spread of COVID-19.

References

1. Available at: https://www.worldometers.info/coronavirus/
2. Kanagalingam J, Feliciano R, Hah JH, et al. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. Int J Clin Pract. 2015;69(11):1247-56.
3. Kariwa H, Fujii N, Takashima I. Inactivation of SARS coronavirus by means of povidone-iodine, physical conditions and chemical reagents. Dermatology. 2006;212 Suppl 1(Suppl 1):119-23.
4. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020;382(12):1177-9.
5. Pelletier J, Tessema B, Westover J, et al. In vitro efficacy of povidone-iodine nasal and oral antiseptic preparations against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). medRxiv 2020.05.25.20110239 Available at: https://www.medrxiv.org/content/10.1101/2020.05.25.20110239v1.

Regeneron Says Its COVID-19 Treatment Reduces Viral Levels

Regeneron Pharmaceuticals Inc has stated that its experimental two-antibody cocktail reduced viral levels and improved symptoms among non-hospitalized COVID-19 patients, thus improving its odds of becoming a treatment for COVID-19 disease.

Regeneron Chief Scientific Officer, George Yancopoulos, stated that they hope that these data will support an emergency use authorization (EUA) from the US FDA. The treatment, called REGN-CoV2, is also under investigation for use in hospitalized patients, and for prevention of infection in individuals who have been exposed to COVID-19. The treatment could help patients whose own immune system is not strong enough to fight the virus, mentioned Regeneron… (*ET Healthworld – Reuters*)

Chronic PPI Use Linked to Diabetes Risk

According to new research, regular use of proton pump inhibitors (PPIs) is associated with modest duration-dependent risk for developing type 2 diabetes.

In a prospective study of three large US cohorts, and in more than 2,127,471 person-years of follow-up, 10,105 incident cases of diabetes were noted, with regular PPI

users, having a HR of 1.24 (95% CI 1.117-1.31) compared to nonusers, reported researchers. As the duration of PPI use increased, fully adjusted HRs increased to 1.05 (95% CI 0.93-1.19) for >0 to 2 years of use and 1.26 (95% CI 1.18-1.35) for >2 years, in comparison with no PPI use, stated the investigators in *Gut*. The authors stated that caution should be exercised while prescribing PPIs, especially for long-term use… (*Medpage Today*)

COVID-19: ECMO Survival Rate Reasonable

Most of the patients who need extracorporeal membrane oxygenation (ECMO) for severe COVID-19 survive, suggested an international registry.

The estimated 90-day in-hospital mortality was 37.4%, while mortality among those who completed their hospitalization (final disposition of death or discharge) was 39%. The data obtained from 213 hospitals across the world provide a generalized estimate of ECMO mortality in COVID-19, reported researchers in *The Lancet*. The data were also presented at the virtual Extracorporeal Life Support Organization meeting.

The study included 1,035 patients, 16 years and older, with confirmed COVID-19 who had ECMO support initiated from January 16 through May 1, 2020, at 213 hospitals in 36 countries. Independent predictors of mortality in ECMO-supported patients with COVID-19 included age, immunocompromised state, pre-ECMO cardiac arrest, chronic respiratory disease, hypoxemia degree, acute kidney injury and use of ECMO for temporary circulatory support (venoarterial rather than venovenous ECMO support) … (*Medpage Today*)

Introducing Wheat Early may Help Prevent Celiac Disease

Very early introduction of high-dose gluten was shown to be linked with a reduced prevalence of celiac disease at 3 years of age in a pre-specified secondary analysis from the Enquiring About Tolerance (EAT) infant food allergy prevention trial.

None of the infants randomized to the gluten early introduction group of the study developed celiac disease by 3 years of age, compared to 1.4% of children for whom exclusive breastfeeding was recommended for at least the initial 6 months of life (risk difference 1.4% points, 95% CI 0.6-2.6; p = 0.02). The researchers suggest that new randomized clinical trials are required to look into the question of whether early introduction of high-dose gluten is effective for the prevention of celiac disease. The findings were published in *JAMA Pediatrics*… (*Medpage Today*)

In Patients with *H. pylori*, Higher-dose PPIs may Promote Gastric Intestinal Metaplasia

Among patients positive for *Helicobacter pylori* (*H. pylori*), upper quartiles of cumulative PPI doses had a significant association with precancerous gastric intestinal metaplasia (GIM) in a dose-dependent manner, reported a large retrospective study.

Upper quartiles of PPI use were also tied to a 5- to 10-times greater risk for a diagnosis of GIM with low-grade dysplasia, reported researchers in the *United European Journal of Gastroenterology*. The association of cumulative PPI use with the odds of GIM diagnosis depended on *H. pylori* status, ranging from 1.7- to 1.4-fold for patients treated for *H. pylori* infection compared to a nonsignificant association for *H. pylori*-negative patients. The researchers stated that healthcare professionals must consider evaluating the patients' *H. pylori* infection status before starting long-term PPI… (*Medpage Today*)

Metabolic Blood Biomarkers may Help Distinguish Depression from Anxiety

According to a new study presented at the virtual 33rd European College of Neuropsychopharmacology (ECNP) Congress, metabolic alterations linked to inflammation and lipid metabolism can help differentiate depression from anxiety and ascertain disease severity.

A Dutch study included 1,400 individuals with anxiety, depression or both, 800 with remitted mood disorders and more than 630 healthy controls. Those with depression were found to have more inflammation, which was not found in those with anxiety. Individuals with depression had very different amounts and types of lipid in their blood. For instance, the group had high levels of triglycerides but lower levels of omega-3 fatty acids. Furthermore, having more of a lipid associated with depression was tied to a more severe form of depression… (*Medscape*)

A COVID-19 Vaccine won't Eliminate the Need for Masks and Public Health Measures, Says Expert

Dr Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases, said that even an effective COVID-19 vaccine won't be able to replace the need for other public health measures, including wearing a mask, washing hands and practicing social distancing.

According to Fauci, the vaccine will not be 100% effective and taken by 100% of the population, thus leaving room for COVID-19 to spread. He added that

there is good amount of data to suggest that aerosol transmission does occur. This means that the virus can stay in the air for a period of time, instead of falling to the ground in larger droplets. This is another reason for wearing a mask… (*CNN*)

FDA Approves First Drug to Treat Group of Rare Blood Disorders in Close to 14 Years

The US FDA has approved mepolizumab for adults and children, 12 years of age and above, with hypereosinophilic syndrome (HES) for 6 months or longer, without any other identifiable non-blood-related cause of the disease.

The new indication for the drug is the first approval for HES in around 14 years. This is the first time in over a decade that a new FDA-approved treatment option is available for patients with HES, stated Ann Farrell, MD, director of the Division of Nonmalignant Hematology in the FDA's Center for Drug Evaluation and Research.

A randomized, double-blind, multicenter, placebo-controlled trial assessed the drug in 108 patients with HES. Patients received mepolizumab or placebo by injection every 4 weeks and were compared for HES flare during the 32-week treatment period. Fewer patients in the mepolizumab group (28%) had HES flares compared to the placebo group (56%), with a 50% relative reduction… (*FDA*)

Children Half as Likely to Catch COVID-19 as Adults, Reveals Meta-analysis

Children were less likely than adults to contract a COVID-19 infection from an index case, revealed a meta-analysis.

Across 32 contact tracing or population testing studies comparing SARS-CoV-2 prevalence in children and adults, children below 14 years of age had lesser likelihood of being infected from an index case overall (odds ratio [OR] 0.56, 95% CI 0.37-0.85), and particularly in studies evaluating household transmission (OR 0.41, 95% CI 0.22-0.76). Adolescents aged 14 and above were shown not to have a significantly lower risk of infection compared to adults (OR 1.23, 95% CI 0.64-2.36). Additionally, seroprevalence was lower in children than adults, especially for children younger than 14, who had 48% decreased odds of infection compared to young adults aged 20 and above. The findings were published in *JAMA Pediatrics*… (*Medpage Today*)

COVID-19's Mental Health Consequences in Youth

New research suggests that a rise in suicidal thoughts and attempts, anxiety and depression are among the leading mental health consequences of the COVID-19 pandemic in the youth.

A survey of 1,000 high school and college students revealed that nearly 25% reported they knew a peer who developed suicidal thoughts since the beginning of the pandemic. Around 5% reported making a suicide attempt themselves since the COVID outbreak started. Furthermore, more than half reported that they were worried about their own mental health. The findings highlight the toll that the pandemic has had on students' mental health. It was noted that 58% of the college students and 53% of the high school students reported being moderately or very or extremely worried about their mental health… (*Medscape*)

Tobacco Accounts for 20% of Deaths from Coronary Heart Disease

About 1.9 million people die every year from tobacco-induced heart disease, suggests a new report released by the World Health Organization, World Heart Federation and the University of Newcastle Australia.

This amounts to 1 in 5 of all deaths from heart disease. Authors urge all tobacco users to quit and avoid a heart attack, and emphasize that smokers have greater odds of experiencing an acute cardiovascular event at a younger age compared to non-smokers. Only a few cigarettes a day, occasional smoking, or exposure to second-hand smoke tend to heighten the risk of heart disease. However, taking immediate action can help tobacco users decrease their risk of heart disease by 50% following 1 year of smoking cessation… (*WHO)*

Even Moderate Drinking may Increase Hypertension Risk in Diabetes

Even moderate alcohol consumption may heighten the risk of hypertension in adults with type 2 diabetes, suggests new research.

Data from more than 10,000 adults participating in the ACCORD trial was assessed and the investigators noted that moderate alcohol consumption increased the likelihood of elevated blood pressure (BP), stage I hypertension and stage II hypertension by 79%, 66% and 62%, respectively. After accounting for covariates, heavy alcohol consumption was found to be associated with nearly double the risk of elevated BP, a 2.5-fold increase of stage I hypertension and a three-fold risk of stage II hypertension. The findings were published online in the *Journal of the American Heart Association*… (*Medscape*)

Novel Once Weekly Insulin for Type 2 Diabetes

According to a randomized, placebo-controlled phase II trial, a novel insulin formulation administered once weekly appeared to be as safe and effective as a conventional daily insulin product for type 2 diabetes.

When compared with once daily insulin glargine U100, patients administered once weekly insulin icodec experienced similar mean reductions in glycated hemoglobin (HbA1c) levels after 26 weeks (between-group difference -0.18%, 95% CI -0.38 to 0.02, p = 0.08), reported researchers in the study published in the *New England Journal of Medicine* and presented at the virtual European Association for the Study of Diabetes 2020 meeting. Patients on the weekly insulin had an average HbA1c fall of 1.33% compared to 1.15% for those on daily insulin glargine… (*Medpage Today*)

Glomerular Hyperfiltration Tied to Liver Disease Severity in Children with NAFLD

Yodoshi et al conducted a study to establish the prevalence of renal impairment in a cohort of youths with histologically confirmed nonalcoholic fatty liver disease (NAFLD). The investigators also aimed to ascertain its association with liver disease severity.

In a pediatric cohort with biopsy-confirmed NAFLD, investigators collected clinical, laboratory and histology data retrospectively at a tertiary care center from 2010 to 2017. Histological NAFLD severity was scored and glomerular filtration rate (GFR) was calculated and categorized into low (<90 mL/min/1.73 m^2), normal (90-136 mL/min/1.73 m^2) or high (>136 mL/min/1.73 m^2) categories.

There were 179 patients in the study (median age 14 years). About a third of the patients had abnormal renal function, with 36 (20%) having glomerular hyperfiltration and 26 (15%) having low GFR.

Multivariable logistic regression revealed that in comparison with normal GFR, hyperfiltration had an independent association with greater NAFLD activity score, after adjustment for age, sex, ethnicity, obesity severity, presence of type 2 diabetes mellitus, as well as medications.

Renal impairment was found to be highly prevalent in this cohort with histologically confirmed NAFLD, and was associated with liver disease severity, independent of obesity severity. Investigators thus recommend screening patients with confirmed NAFLD for renal complication.

Source: Yodoshi T, Arce-Clachar AC, Sun Q, et al. J Pediatr. 2020;222:127-33.

Bill to Protect Healthcare Workers Against Violence Passed

New Delhi: The Lok Sabha on 21st September passed a legislation providing for up to 7 years in jail for those attacking healthcare workers fighting the coronavirus pandemic or during any situation similar to the current pandemic.

The Epidemic Diseases (Amendment) Bill, 2020, is set to replace an ordinance issued in April by the government. The Rajya Sabha passed the bill on 19th September. As the Lok Sabha gives its nod, it will soon become an act, which will amend a 123-year-old legislation. The Bill aims to ensure that during any situation similar to the current pandemic, there is no tolerance to violence against healthcare professionals and damage to property.

According to the proposed act, commission or abetment of such violence will be punishable with imprisonment for 3 months to 5 years and a fine of ₹ 50,000 to ₹ 2,00,000. In case of grievous hurt, the imprisonment shall be for 6 months to 7 years with a fine of ₹ 1-5 lakh… (*NDTV – PTI*).

Sleep Duration Linked with Cognitive Decline

Global cognitive function was shown to drop faster among individuals with either very short or very long sleep duration compared to people who slept 7 hours a night, suggest combined data from England and China.

Over 1,00,000 person-years of follow-up, cognitive 'z' scores had a pooled β of -0.022 (95% CI -0.035 to -0.009 SD per year) with 4 or fewer hours of sleep a night and a pooled β of -0.033 (95% CI -0.054 to -0.011 SD per year) with 10 or more hours, in adjusted analyses, reported researchers. Extreme sleep duration was shown to be linked with lower cognitive function at baseline. The findings are published in *JAMA Network Open*… (*Medpage Today*)

Study Says Most Homemade Masks Block Large Cough Droplets

Researchers from the University of Illinois at Urbana-Champaign in the US looked into the effectiveness of common household fabrics used to make homemade masks in blocking droplets produced by coughing and sneezing, and noted that they provide appreciable protection even as a single layer.

Investigators assessed the breathability and droplet-blocking potential of 11 common household fabrics, including new and used garments, quilted cloths, bed sheets and dishcloth material, with a medical mask as

a benchmark. All of the fabrics that were tested were found to be considerably effective at blocking the 100 nm particles carried by high-velocity droplets similar to those that may be released on speaking, coughing and sneezing, even as a single layer. The study is published in the journal *Extreme Mechanics Letters*… (*The Indian Express – PTI*)

Antidepressants for Dementia Prevention

Treatment with the selective serotonin reuptake inhibitor (SSRI) escitalopram tends to decrease amyloid-beta-42 (Aβ42) levels in the cerebrospinal fluid (CSF) of cognitively normal older adults, suggest researchers, pointing to a potential role for these drugs in the prevention of Alzheimer's disease (AD).

The researchers; however, acknowledge that it still needs to be seen if the relatively modest reduction in CSF Aβ42 will lead to clinical benefit. Investigators evaluated the effects of escitalopram in 114 cognitively normal adults aged 50 years and older. The patients were given escitalopram 20 mg/day for 2 or 8 weeks or 30 mg/day for 8 weeks while control participants received placebo. Exploring the two dose regimens together, a significant overall 9.4% percentage point greater reduction was seen in CSF Aβ42 in escitalopram-treated patients compared to placebo group. The study is published online in *Neurology*… (*Medscape*)

CDK4/6 Inhibition Improves Progression-free Survival in Endometrial Cancer

Women with advanced, hormone receptor (HR)-positive cervical cancer lived over twice as long without disease progression if they were given the cyclin-dependent kinases (CDK) inhibitor palbociclib in association with hormonal therapy, suggested a small randomized trial.

Median progression-free survival (PFS) was found to increase from 3.0 months with letrozole alone to 8.3 months with letrozole and palbociclib. The disease control rate (DCR, response *plus* stable disease) with the combination was 63.6% compared to 37.8% with letrozole alone. Adding letrozole also added toxicity, as one-fourth of patients in the combination group discontinued treatment due to adverse events (AEs), but the regimen was tolerable in most patients, reported Mansoor R Mirza, MD, of Copenhagen University Hospital, at the 2020 European Society for Medical Oncology (ESMO) virtual congress… (*Medpage Today*)

Dose-Response Relationship Between Exercise and Improvement in Diabetes

The more patients with type 2 diabetes exercise, the greater the decline in A1c, suggests a new post-hoc analysis of data collected over 6 months of supervised exercise.

This dose-response relationship between exercise and fall in A1c was sustained for those who did aerobic training or combined aerobic and resistance exercises, but not for those who only did resistance exercises, suggest researchers in an article published in *Medicine & Science in Sports & Exercise*. According to the findings, an increased volume of aerobic or combined aerobic and resistance exercise is linked with greater improvement in glycemic control. Additionally, individuals who did the most exercise had the greatest improvements in A1c, with a 20% increase in adherence (correlated with an additional two sessions a month) being linked with a 0.15% decrease in A1c… (*Medscape*)

Biologics for Psoriasis may Reduce Coronary Plaque

Biologics used for the treatment of psoriasis may also help reduce lipid-rich necrotic core (LRNC), a high-risk plaque associated with cardiovascular events, suggests new research from a prospective, observational study.

Cardiac CT scans were performed on patients with psoriasis 1 year following the initiation of biologic therapy. A reduction in LRNC was noted among these patients in comparison with patients who were not receiving biologics, reported investigators. The association with reduction in LRNC and biologic therapy remained significant after adjusting for the type of biologic. The findings were published in *Circulation: Cardiovascular Imaging*.

Investigators assessed 289 patients with psoriasis within the Psoriasis Atherosclerosis and Cardiometabolic Disease Initiative cohort. The patients had a mean Psoriasis Area and Severity Index (PASI) score of 6.0. There was a significant decrease in LRNC 1 year after patients started biologic therapy (median, 2.97 mm^2; interquartile range, 1.99-4.66), compared to baseline (median, 3.12 mm^2; IQR, 1.84-4.35) ($p = 0.028$). Patients who did not receive biologic therapy had nonsignificantly higher LRNC after 1 year (median, 3.12 mm^2; IQR, 1.82-4.60), in comparison with baseline (median, 3.34 mm^2; IQR, 2.04-4.74) ($p = 0.06$)… (*Medscape*)

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The Skill of Controlling Anger

KK AGGARWAL

Cynicism is one of the major risk factors for causation of coronary artery disease (blockages in the channels supplying blood to the heart). And anger, jealousy and irritability form the triad responsible for this.

Anger is the enemy of peace, knowledge and devotion. According to Ayurveda, anger is a manifestation of Pitta (metabolism) imbalance and is a predisposing risk factor for causation of heart attack, paralysis, gallbladder stone, kidney stone, acidity, ulcer and cancer.

In Bhagavad Gita, Lord Krishna describes the pathway of anger leading to destruction in Chapter 2 Shloka 62 and 63. According to Lord Krishna, when a man's desires are not fulfilled or expectations are not met, one becomes angry. And when one is under the effect of anger, he does all types of sinful activities. One loses the distinction between good and bad, loses one's memory, the understanding becomes clouded, and the intellect gets perverted. Loss of intellect leads to animal-like behavior, and ultimately to destruction of oneself.

Anger can have several repercussions, which are injustice, rashness, persecution, jealousy, taking possession of others' property, killing, using harsh words and cruelty. The degree of anger may vary from irritation, frowning, resentment, indignation, rage, fury and wrath.

Anger is not always bad. It is only when the anger is an outcome of greed or selfish motives, it is bad.

Righteous or spiritual anger is a type of anger caused with good intentions. This anger passes off the next moment as a wave subsides in the sea. The classical example of righteous anger is when you become angry in a situation where you see a person doing something wrong to check that person. The root cause of anger is ignorance, egoism and passion (strong desires), with passion being the root cause. To control anger, therefore, passion should be controlled first.

Group Editor-in-Chief, IJCP Group

In Vedic language, both anger and passion are Rajo-Vriti disorders and get exaggerated with any Rajas-increasing lifestyle. Living a life with fewer Rajas characteristics will reduce the chances of anger.

Rajas-increasing foods are eggs, fish, onion, garlic, fermented foods, etc. Indulging into modern fashion, night clubs, reading novels with stories of violence, living in the company of bad people, use of tobacco, alcohol and drugs are all Rajas-increasing lifestyles. A typical Rajasik person indulges in eating, drinking and procreating.

Controlling anger and passion involves effort. As a fish swims upstream against the current in a river to breathe, so does a person has to work against the disturbed thoughts. To balance and stabilize the mind, consuming 'satvik' foods like fresh food, vegetables, milk and barley bread will help.

Many exercises can help control anger. A few suggested ones are observing silence for 20-30 minutes in a day, walking regularly, practicing speaking kind words; doing regular meditation, practicing nonviolent communication daily and learning to think differently.

During an episode of anger, one can try left nostril pranayama, a short deep breathing exercise, taking a walk, drinking cold or simple water or chanting AUM or I AM. With inspiration one chants "I" and with expiration "AM" reminding one who I AM. That I am the expression of pure spirit and my purpose of life is not to become angry. Remember, the person who gets angry will have high blood pressure. On whom you are angry may have no change in blood pressure.

One should realize that during anger, one loses the power of discrimination and suffers from intellectual impairment. Therefore, anger has to be controlled much before it becomes full blown. The initial stage of anger is irritability, and therefore, with the onset of irritability, one should try to control it at the earliest.

Never judge an individual with your own level of perception. You should realize that if a servant starts working with your level of expectations, he or she will not be working with you as a servant. Also make sure that you are not hungry at the time of feeling angry or irritable. Regular meals prevent development of anger.

Anger can be expressive or suppressive. Expressive anger presents with aggressive behavior and the outbursts of anger can cause social unhealthiness. It can cause sudden rise in upper blood pressure or cause rupture of a plaque in the artery supplying blood to the heart precipitating a heart attack.

Suppressive anger can lead to acidity, asthma, formation of plaques in the heart arteries, etc. In the long run, suppressed anger, if not expressed may end up with depression, despondency, guilt, etc.

Therefore, anger should neither be passed on to others (expressive) nor taken within (suppressed or repressed). Anger, therefore, should be altered, neutralized or modified. This can be done by temporarily holding it for some time and then taking timely action. Temporary holding can be achieved by using the above exercises. Remember both passion and anger are energies, which should be conserved and not wasted.

The mythological explanation of Shiva, the Neelkanth, is also the same. Neither throw the poison (anger), nor drink it but keep it in the throat for some time and take the right action after the anger manifestations are over.

From Vedic point of view, every thought arises from the silent potential web of energized information or consciousness. This thought from the mind is then analyzed by the intellect and then modified by the ego. At this stage, it leads to an action. An action leads to memory and memory leads to desire for the action again. If this desire is fulfilled, it leads to action again and then desire again. Repeated fulfillment of desires leads to habit formation, addictions and development of a particular personality. An unfulfilled desire leads to irritability and irritability leads to anger, which then can be expressive or suppressive.

The answer, therefore, lies in changing the perception at the level of thought or controlling desires and/or expectations.

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Pesco-Mediterranean Diet, Fasting Promising to Reduce CVD

A Pesco-Mediterranean diet that consists of plants, legumes, nuts, whole grains, extra-virgin olive oil (EVOO), moderate amounts of dairy products and fish and/or seafood, along with intermittent fasting (time-restricted eating), can potentially limit the risk for cardiovascular disease, suggests a new review. The authors propose that following a Pesco-Mediterranean diet in association with time-restricted eating is evidence-based and an ideal approach for reducing cardiovascular risk. The authors stated that under time-restricted eating (a type of intermittent fasting), the daily intake of food is limited to a window of time, usually 6-12 hours a day. The review was published online in the *Journal of the American College of Cardiology*… (*Medscape*)

Parkinson's Disease and COVID-19

There appears to be no robust evidence that having Parkinson's disease heightens the likelihood of COVID-19, or that COVID-19 predisposes to a greater risk of Parkinson's disease. However, there have been reports of worsening Parkinson's symptoms in infected patients, suggested K Ray Chaudhuri, MD, DSc, of King's College London in England.

A community-based case-control study involving 12 cases in Italy pointed to considerable worsening of symptoms in Parkinson's patients with mild-to-moderate COVID-19, independent of age and disease duration. Patient survey data suggested that most individuals with Parkinson's disease and COVID-19 experience new or worsening motor and non-motor symptoms. The survey findings were published in the *Journal of Parkinson's Disease*… (*Medpage Today*)

US Signs Agreement with AstraZeneca for Development and Supply of COVID-19 Antibody Treatment

The US government has signed an agreement with AstraZeneca Plc AZN.L for the development and supply of around 1,00,000 doses of COVID-19 antibody treatment, a similar class of drugs that has been used for the treatment of President Donald Trump. Funding will be provided to AstraZeneca by the US health agency for two Phase 3 clinical trials under operation Warp Speed. The operation aims to expedite treatments and vaccines for COVID-19. One of the trials will assess the safety and efficacy of the experimental treatment to prevent infection for up to 12 months, in nearly 5,000 participants, while the second one will investigate post-exposure preventative and pre-emptive treatment in around 1,100 participants… (Reuters)

The Hotel Clerk

On a stormy night, an elderly man and his wife entered a small hotel in Philadelphia, USA on a stormy night desperately looking for a shelter for the night.

The man asked the front desk clerk if they could get a room. The clerk was a friendly man with a beautiful smile. He looked at the couple and explained that there were three conventions going on in the city and that all the rooms were taken. However, he said that he could not send such a nice couple out into the rain at one o'clock in the morning. He offered them to sleep in his room. He explained that although it's not a suite, but it would make them comfortable for the night.

The couple declined, but the young man persuaded. The couple agreed. As the man paid his bill the next morning, he said to the clerk that he was the kind of manager who should be the boss of the best hotel. "May be someday I'll build one for you," said the old man.

The clerk smiled and the three of them shared a good laugh. The elderly couple thought that the helpful clerk was an exceptional man.

The clerk had almost forgotten the incident when 2 years later, he received a letter from the old man. There was a round-trip ticket to New York with the letter which asked the young man to pay them a visit.

The clerk visited them in New York, and was taken by the old man to the corner of Fifth Avenue and 34th Street. He pointed to a new building there stating that it was the hotel he had built for the young man to manage. The young man was surprised.

The old man was William Waldorf-Astor, and the magnificent building was the original Waldorf-Astoria Hotel. The young clerk who became its first manager was George C Boldt.

Moral - Reach out and touch someone's life; you never know whose heart you may be touching.

■■■■

As Cold Weather Arrives, US Sees Record Rise in COVID-19 Cases

Nine US states have reported record surge in COVID-19 cases over the last 7 days, particularly in the upper Midwest and West.

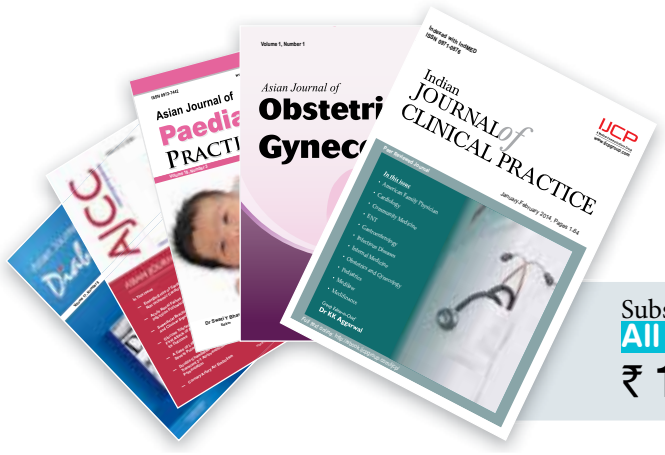
On Saturday (Oct 4), four states - Kentucky, Minnesota, Montana and Wisconsin - noted record surge in new cases and around 49,000 new infections were reported across the nation. This is the highest number for a Saturday (Oct 4) in 7 weeks, as per a Reuters analysis. Kansas, Nebraska, New Hampshire, South Dakota and Wyoming also set new records with regard to cases over the past week.

New York is among the only 18 states where cases have not increased considerably over the past 2 weeks, according to a Reuters analysis. Health experts have been warning that colder temperatures driving people inside could facilitate the spread of the virus… (*Reuters*)

COVID-19 Vaccine Program to Cover More Than 25 cr People by July 2021: Union Health Minister

New Delhi: The government plans to cover nearly 25 crore individuals by July 2021 under the COVID-19 vaccine program, stated Union Health Minister Dr Harsh Vardhan.

The government has set a target of receiving and using 400-500 million doses of the vaccine in this period. The minister said that the government will ensure fair and equitable distribution of vaccines, once they are ready. The government's priority is how to ensure that the vaccine reaches each and everybody in the country. Earlier this week, the minister had said that a COVID-19 vaccine would likely be available by the first quarter of 2021… (*ET Healthworld*)



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Indian Journal of Clinical Practice, Vol. 31, No. 5, October 2020

Lighter Side of Medicine

HUMOR

THE SHIPWRECKED MARINER

The shipwrecked mariner had spent several years on a deserted island. Then one morning he was thrilled to see a ship offshore and a smaller vessel pulling out toward him.

When the boat grounded on the beach, the officer in-charge handed the marooned sailor a bundle of newspapers and told him, "The captain said to read through these and let us know if you still want to be rescued."

INTERVIEW WITH CHRIS GAYLE'S SON

Beta, which standard are you in?

–SIX

And how far is your school?

– At a distance of 10 SIXES from home.

Okay, tell me how much is a dozen?

– 2 SIXES

How many months are in a year?

– 2 SIXES

How many days are in a month?

– 5 SIXES

Umm… ok, I wanna talk to your father, can you give me his no.?

– SIX SIX SIX SIX SIX SIX SIX SIX SIX SIX!

JEALOUSY

A guy approached a beautiful looking woman in a mall and asked, "You know, I've lost my wife here in the mall. Can you talk to me for a couple of minutes?"

"Why?" she asks.

"Because every time I talk to a beautiful woman, my wife appears out of nowhere."

FROM SKIPPING

A blonde woman is terribly overweight, so her doctor puts her on a diet. "I want you to eat regularly for 2 days, then skip a day and repeat this procedure for 2 weeks. The next time I see you, you'll have lost at least 5 pounds."

When the blonde returned, she shocked the doctor by losing nearly 20 pounds.

"Why, that's amazing!" the doctor said. "Did you follow my instructions?"

The blonde nodded. "I'll tell you though, I thought I was going to drop dead that third day."

"From hunger, you mean?" asked the doctor.

"No, from skipping."

I THOUGHT I WAS

A certain little girl, when asked her name, would reply, "I'm Mr Sugarbrown's daughter."

Her mother told her this was wrong, she must say, "I'm Jane Sugarbrown."

The Vicar spoke to her in Sunday school and said, "Aren't you Mr Sugarbrown's daughter?"

She replied, "I thought I was, but mother says I'm not."

Dr. Good and Dr. Bad

SITUATION: The son of a 66-year-old man with type 2 diabetes wanted to know whether the decline in cognitive function of his father was associated with type 2 diabetes.

LESSON: A cross-sectional study showed that in individuals aged ≥65 years, cognitive and physical fragilization is relatively more frequent and is seen at an earlier age in people with type 2 diabetes than in those without diabetes.

Diabetes Res Clin Pract. 2017;135:206-17.

IJCP SUTRA: *"Exercises and stretches can help maintain strength and stop joints becoming stiff in children with spinal muscular atrophy (SMA). Although the amount of exercise will depend on the condition, it's best to try and stay as active as possible."*

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- Method of allocating the subjects into different groups.
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Results

- These should be concise and include only the tables and figures necessary to enhance the understanding of the text.

Discussion

– This should consist of a review of the literature and relate the major findings of the article to other publications on the subject. The particular relevance of the results to healthcare in India should be stressed, e.g., practicality and cost.

References

These should conform to the Vancouver style. References should be numbered in the order in which they appear in the texts and these numbers should be inserted above the lines on each occasion the author is cited (Sinha[12] confirmed other reports[13,14]...). References cited only in tables or in legends to figures should be numbered in the text of the particular table or illustration. Include among the references papers accepted but not yet published; designate the journal and add 'in press' (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as 'unpublished observations' (in parentheses). At the end of the article the full list of references should include the names of all authors if there are fewer than seven or if there are more, the first six followed by et al., the full title of the journal article or book chapters; the title of journals abbreviated according to the style of the Index Medicus and the first and final page numbers of the article or chapter. The authors should check that the references are accurate. If they are not this may result in the rejection of an otherwise adequate contribution.
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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

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

Articles in Books

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

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