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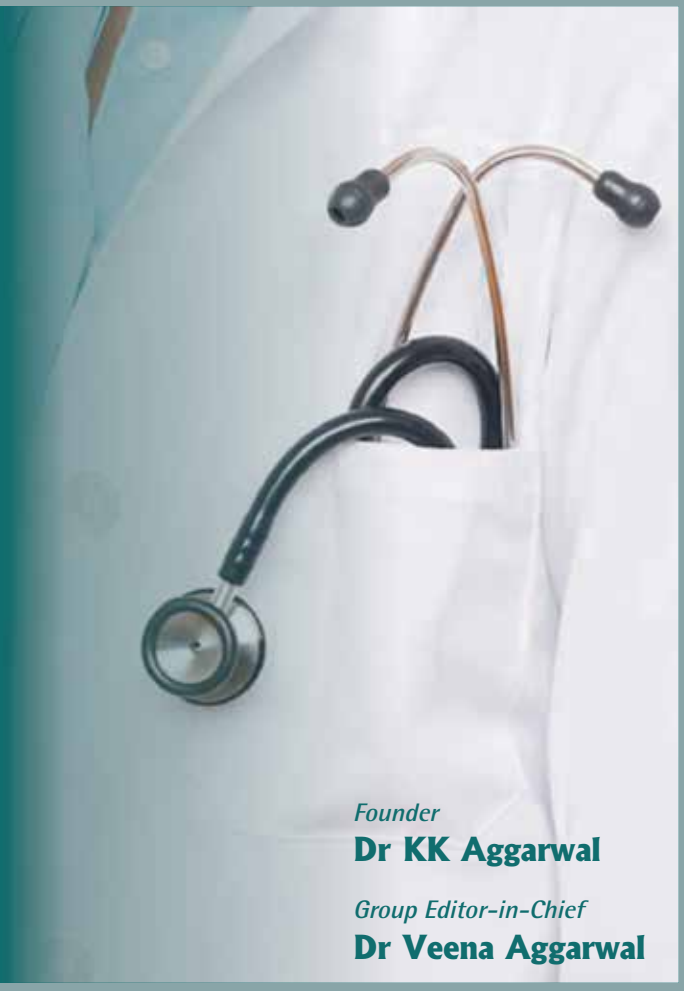

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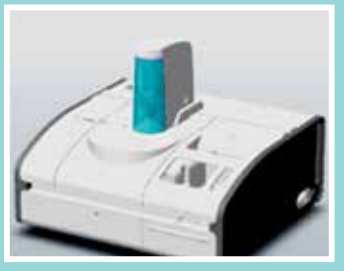

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Coronavirus Updates

Reduced Risk of Hospitalization in Adolescents Following Pfizer COVID Vaccine

The Pfizer BioNTech COVID vaccine decreased hospitalization during the Omicron in children aged 5 to 11 years by 68% in a US study. Among adolescents, the omicron-related hospitalization reduced by nearly 40%. But against the Delta variant, the vaccine effectiveness in preventing hospitalization among adolescents was around 93%. Despite lower protection against Omicron hospitalizations, vaccination prevented critical illness caused by either variant… (*Source: New England Journal of Medicine, March 30, 2022*)

Second Booster Dose for 50+ and Immunocompromised Persons

The US Food and Drug Administration (FDA) has authorized a second booster dose of either the Pfizer-BioNTech or the Moderna COVID-19 vaccines for people aged 50 years and older at least 4 months after taking the first booster dose. Immunocompromised persons such as those with solid organ transplant are also eligible to receive a second booster dose of the vaccines; 12 years and older for Pfizer and 18 years and older for Moderna at least 4 months after the first booster dose… (*Source: US FDA, March 29, 2022*)

WHO Sounds a Note of Caution About the "XE" Omicron Variant

The World Health Organization (WHO) has cautioned about a new variant of Omicron. The XE variant of Omicron is 10% more transmissible than the BA.2 subvariant. It is a recombinant strain and hybrid of the BA.1 and BA.2 sublineages of the Omicron variant. According to the WHO, "The XE recombinant (BA.1-BA.2), was first detected in the UK on January 19 and less than 600 sequences have been reported and confirmed since". There are currently three recombinant or hybrid variants XD, XE and XF. XD is a Delta and BA.1 recombinant detected in France, Denmark and Belgium and XF is the recombinant of Delta and BA.1 detected in Britain… (*Source: Express.co.uk, April 1, 2022*)

Hearing Loss and COVID-19 Vaccines

Cases of hearing loss and other auditory disturbances like tinnitus, though rare, have been reported among COVID-19 vaccinated people. The WHO is reviewing this association. According to a WHO newsletter, globally 164 cases of hearing loss and 367 cases of tinnitus have been reported among COVID-19 vaccinated people. Majority of the tinnitus cases were reported after the Pfizer vaccine… (*Source: Medscape, March 31, 2022*)

With inputs from Dr Monica Vasudev

■■■■

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Semaglutide: Untangling the Gordian Knot of Glucose Control

Diabetes is a complex syndrome, with multiple causative factors, complications and confounding situations. Ever widening spectrum of pharmacological evolution is trying to match the complexities in diabetes management with gradual addition of newer class of drugs one after another.

THE GORDIAN KNOT OF GLUCOSE CONTROL

Many conventional therapies, however, like traditional sulfonylureas, create a Gordian knot which is difficult to disentangle. In a unicentric approach to achieve euglycemia, unwanted side effects like hypoglycemia and weight gain often occur.[1] These results of glucose-lowering therapy, which were hitherto considered inevitable, have been addressed in the concepts of the glycemic pentad and the KgA1c paradox. The glycemic pentad suggests that avoidance of hypoglycemia and glycemic variability is as important a therapeutic goal as achievement of normal glucose values.[2] The KgA1c paradox reminds us of the deleterious rise in body weight that is often seen when HbA1c is lowered with conventional diabetes control strategies.[3]

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

In recent years, injectable glucagon-like peptide-1 receptor agonists (GLP-1RA) have become accepted as first-line injectable therapy in persons with type 2 diabetes, especially those with/at high risk of atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease (CKD).[4-7] GLP-1RA are a multifaceted class of glucose-lowering drugs, which act at various levels of glucose homeostasis to ensure optimization of glucose levels. The glucose-dependent mechanism of action prevents hypoglycemia, while pharmacological actions on the hypothalamus and gastrointestinal (GI) tract ensure avoidance of weight gain, promote weight loss and prevent the KgA1c paradox from setting into motion.

There still remains, however, a slight reluctance to use injections. This avoidance can lead to clinical inertia, and result in suboptimal control.[8] Semaglutide, a novel GLP-1RA, which was earlier available as a once-weekly subcutaneous injectable, has now been formulated as a once daily oral pill.[9]

UNTANGLING THE PHARMACEUTICAL KNOT

Formulating an oral preparation of semaglutide posed multiple challenges to drug developers.

The oral administration of semaglutide or other GLP-1RAs alone led to negligible bioavailability of 0.01%. Protein and peptides like semaglutide get degraded by proteolytic enzymes and low pH. Furthermore, due to high molecular weight, these are not able to permeate through the GI epithelium leading to low absorption. This leads to the lower absorption and very low bioavailability.

This Gordian knot was opened using a absorption enhancer, SNAC {sodium *N*-(8-[2-hydroxybenzoyl] amino)caprylate}. It is a small fatty acid derivative that promotes absorption across gastric epithelium.

SNAC increases the localized pH around the tablet and protects it from degradation by proteolytic enzymes and acidic pH. It helps in absorption of semaglutide through GI epithelium via transcellular route. The action of SNAC is time- and concentration-dependent and is fully reversible. Bioavailability of semaglutide has been increased by 100 times when formulated along with SNAC.[9]

In various pharmacological studies, dose of SNAC has been studied from 150 to 600 mg and it has been found that 300 mg of SNAC is the optimum dose to get the maximum bioavailability. When co-formulated with 300 mg SNAC, 1% of semaglutide usually absorbed in stomach.[10]

CLINICAL TRIALS

A robust phase 3 clinical trial program, based upon results of extensive pre-clinical and early clinical studies, has been published. This supports the easy and effective use of oral semaglutide in diverse patient populations, as monotherapy or in combination with varied concomitant therapy, to achieve a wide-spectrum of desired clinical endpoints (Table 1).

UNTANGLING THE CLINICAL KNOT

The diabetes care physician faces multiple challenges while managing his or her patients. Ensuring patient acceptance, adherence and persistence, while offering an effective and efficient therapy that can be administered with minimal intrusion in the individual's lifestyle, and avoiding adverse events or complications, is a difficult task. Added to these are the needs to ensure vasculo-metabolic and viscera-metabolic safety, and promote cardiovascular health. All these "tasks" are the equivalent of cleaning the Augean stables.

THE PLACE OF ORAL SEMAGLUTIDE

Oral semaglutide, with its unique pharmaco-clinical properties, seems well-poised to be a game changer in glucose control.

Table 1. Summary of Efficacy Outcome in the PIONEER Clinical Trials[11-19]

Trials (N)	Baseline HbA1c	Time Point	Comparator	% mean reduction in HbA1c				Estimated mean change from baseline SBP (mmHg) (on-treatment period)			
				Semaglutide			Comparator	Semaglutide			Comparator
				3 mg	7 mg	14 mg		3 mg	7 mg	14 mg	
PIONEER 2 (822)	8.1	Week 52	Empa 25 mg			−1.3	−0.9			−5	−4
PIONEER 3 (1,864)	8.1	Week 78	Sita 100 mg	−0.6	−1.0	−1.3	−0.8	−2	−3	−3	−0
PIONEER 7 (504)	8.3	Week 52	Sita 100 mg	−1.3	Flex dosing		−0.8	−4	Flex dosing		−2
PIONEER 10 (458)	8.3	Week 52	Dula 0.75 mg	−0.9	−1.4	−1.7	−1.4	−2	−2	−2	−1
PIONEER 9 (243)	8.2	Week 52	Lira 0.9 mg	−0.9	−1.4	−1.5	−1.2	−1	−1	−2	−1
			Placebo				−0.1				−3
PIONEER 4 (711)	8.0	Week 52	Lira 1.8 mg			−1.2	−1.1			−2	−3
			Placebo				−0.2				0
PIONEER 1 (703)	8.0	Week 26	Placebo	−0.9	−1.2	−1.4	−0.3	−4	−4	−5	−2
PIONEER 5 (324)	8.0	Week 26	Placebo			−1.0	−0.2			−7	0
PIONEER 8 (731)	8.2	Week 52	Placebo	−0.6	−0.9	−1.3	−0.1	−1	−2	−5	0

In India, oral semaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus as monotherapy when metformin is considered inappropriate due to intolerance or contraindications or in combination with other medicinal products for the treatment of diabetes. Its use is endorsed by expert guidance from professional bodies across the world (Table 2).

POSOLOGY

Based on various pharmacological studies, dosing conditions have been optimized. Oral semaglutide has to be given after overnight fasting (~6 hours) with up to 120 mL water. As food affects the absorption of semaglutide, post-dose fasting of 30 minutes is recommended before eating, drinking or taking any other medications. Oral semaglutide has to be initiated with the lowest dose of 3 mg and a 4-week dose escalation to 7 mg and then to 14 mg (if needed) is recommended to reduce the risk of GI adverse events.[25]

A GAME CHANGER, A LIFE CHANGER

The availability of GLP-1RA in an oral formulation, a peptide in a pill, opens the possibility of untangling the

Table 2. Recent Guidelines on the Use of GLP-1RAs[6,20-24]

Organization	Year	Indication for GLP-1RA	Mention of Semaglutide
ADA	2022	Among individuals with type 2 diabetes who have established ASCVD or indicators of high CV risk, established kidney disease, or heart failure, a SGLT2 inhibitor and/or GLP-1RA with demonstrated CVD benefit.	Yes (Inj. Semaglutide 2.4 OW for obesity management in patients with type 2 diabetes)
ADA-EASD	2020	GLP-1RA or SGLT2 inhibitor in patients with established or high risk of ASCVD independently of baseline HbA1c levels and glycemic targets, but also independently of baseline metformin use.	NA
ESC	2021	In persons with T2DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcome.	NA
AACE/ACE	2018	GLP-1RA is recommended as monotherapy in individuals with HbA1c <7.5%. In addition, GLP-1RA is recommended in prediabetic patients if glycemia is not normalized with medications such as metformin and acarbose.	No
NICE	2015	If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a GLP-1 mimetic for adults with type 2 diabetes who: • have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or • have a BMI <35 kg/m^2 and: ▸ for whom insulin therapy would have significant occupational implications or ▸ weight loss would benefit other significant obesity-related comorbidities. Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months).	NA
South Asian Task Force	2019	As an adjunct to diet and exercise in adults with T2DM. Recommended as monotherapy in a few countries (e.g., dulaglutide in India). Indicated in adults (liraglutide) with established CVD to reduce the risk of major adverse CV events.	Yes (indicated in adults with T2DM as an adjunct to diet and exercise to improve glycemic control; Lowers fasting and postprandial glucagon concentrations; Delays early postprandial gastric emptying)

ADA = American Diabetes Association; ASCVD = Atherosclerotic cardiovascular disease; CV = Cardiovascular; SGLT2 = Sodium-glucose cotransporter 2; GLP-1RA = Glucagon-like peptide-1 receptor agonists; CVD = Cardiovascular disease; ADA-EASD = American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD); HbA1c =Glycated hemoglobin; ESC = European Society of Cardiology; T2DM = Type 2 diabetes mellitus; AACE-ACE = American Association of Clinical Endocrinology/American College of Endocrinology; NICE = National Institute for Health and Care Excellence; BMI = Body mass index.

glucose Gordian knot, and achieving safe and effective glucose as well as weight control. This baro-glycemic optimization should prove to be a game changer for all stakeholders in diabetes care, and a life changer for those who live with type 2 diabetes.

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South Korea to Remove COVID Restrictions In Spite of Surge in Cases and Deaths

South Korean was preparing for ending COVID restrictions despite reporting 6,21,328 new daily COVID-19 infections and a record high of 429 deaths in a day.

The Korea Disease Control and Prevention Agency (KDCA) said that the current wave has been stronger than expected and the increase in fresh cases was due to the highly infectious Omicron variant which would infect many but severe health issues would be less. The KDCA further stated that 63% of the country's population had received booster shots and 86.6% were fully vaccinated.

Despite the surge, no sign of rethinking plans to lift COVID restrictions was shown by the government. Use of masks is mandatory in all public indoor and outdoor spaces.

A health ministry official said that no deaths were reported among people under 60 who had received a booster shot in the analysis of around 1,41,000 Omicron cases reported in the country over the past year and hence, COVID could be treated like the seasonal flu. (*Reuters, March 17, 2022*)

Immune Status of Older Adults Key Indicator of Severity of a BA.2 Wave in the US

More than 28 million seniors are at risk of severe illness with the new version 'BA.2' of the Omicron coronavirus variant in the United States because of either being partially vaccinated, being unvaccinated or because more than 5 months have passed since their second or third vaccine dose. The CDC data shows that about 15 million older Americans missed their third dose.

An analysis by the UK Health Security Agency revealed that the BA.2 subvariant of Omicron was about 80% more contagious than BA.1, which affected the US last winter. Number of cases and hospitalizations was again surging in the UK and several other European countries due the predominance of the BA.2 strain. The strain could once again adversely affect the healthcare resources in the US if more people are infected by the strain.

Amid all this, the immune status of adults aged above 65 years will be a major indicator of how future variants will impact the US since the risk of severe outcomes is known to increase with age.

Stephen Kissler, who specializes in infectious disease modeling at Harvard's TH Chan School of Public Health, said that the amount of prior immunity that the older adults have, whether from previous infection or vaccination, has been the best indicator of how severe the cases will be, in terms of hospitalizations and deaths.

Experts are of the view that the BA.2 wave in the US may not be as severe as in Hong Kong, but could be similar to the UK. Therefore, vaccinations and boosters for seniors were essential. (*CNN, March 17, 2022*)

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ORIGINAL RESEARCH

Spectrum of Skin Manifestations in CKD: A Tertiary Care Center Experience from North India

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ABSTRACT

Introduction: Dermal manifestations in chronic kidney disease (CKD) patients may range from mild ones, like xerosis, skin pallor, pruritus, coated tongue, superficial infections and hair and nail changes, to severe life-threatening ones, like nephrogenic systemic fibrosis, which is a rare entity in current times. The present study was done to evaluate the spectrum of mucocutaneous manifestations in patients with CKD and to look for an association between them and various biochemical parameters and inflammatory markers. **Material and methods:** This study was a 1 year prospective, observational study conducted on adult patients with CKD who presented to the Nephrology clinic in Pt. BD Sharma PGIMS, Rohtak. Patients between the ages of 17 and 75 years with CKD stages II or more with dermatological conditions were included in this study. Each participant was subjected to detailed clinical, biochemical, radiological and dermatological examination by same consultants in order to avoid interpersonal variations. Various skin, mucosal, nail and hair manifestations along with cutaneous infections were analyzed across the spectrum of CKD. **Results:** Among cutaneous infections, fungal infections predominated, amongst which, onychomycosis was the most common. Xerosis was the most common dermatological disease and the prevalence of xerosis, skin pallor and pruritus was found to increase significantly from Stage II to Stage V and V_D of CKD in a statistically significant manner. An association was found between xerosis and decreasing levels of hemoglobin and while ferritin was not different between patients with and without xerosis, high-sensitivity C-reactive protein (hs-CRP) was significantly higher in patients with xerosis. Similarly, hs-CRP levels were significantly elevated in patients with xerostomia and nail pallor as compared with those who did not have these conditions. Lastly, patients with nail pallor had significantly lower albumin. **Conclusion:** It was observed in our study that in CKD patients on hemodialysis and on conservative management, xerosis, pruritus, pigmentation, nail changes, oral mucosa changes and cutaneous infections were the predominant cutaneous manifestations. In patients with CKD, mucocutaneous manifestations progressively worsened as renal function deteriorated.

Keywords: Chronic kidney disease, xerosis, pruritus, pigmentation, nail changes

Chronic kidney disease (CKD) is characterized by progressive and irreversible loss of renal function over a period of months to years. This decline in renal function, as measured by glomerular filtration rate (GFR), is a function of nephron loss. The true community incidence and prevalence of CKD are difficult to determine as early CKD usually remains asymptomatic. The worldwide prevalence of CKD is estimated to be 13.4%.[1] In the 2015 Global Burden of Disease Study, CKD was the 12th major cause of death, accounting for 1.1 million deaths worldwide. In India, a 2013 study found the prevalence of CKD to be 17.2% with a distribution of 7% in Stage I, 4.3% in Stage II, 4.3% in Stage III, 0.8% in Stage IV and 0.8% in Stage V.[2] Patients with CKD constitute a significant social and economic burden, both in terms of resource utilization and indirectly through loss of productivity and impaired quality of life.

Impaired kidney function leads to disturbances in almost all systems of the body and skin is the most visible of them. Despite that, they are often overlooked by both the patients and the clinicians. Added to this is the fact

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that very little literature is available to describe these skin changes and their effect on the overall outcome for the patient. Dermal manifestations in CKD patients may range from mild ones, like xerosis, skin pallor, pruritus, coated tongue, bacterial and superficial infections, and hair and nail changes, to severe life-threatening ones, like nephrogenic systemic fibrosis, which is a rare entity in current times.

While many of these cutaneous disorders are caused by the underlying renal disease itself, a few are related to the severity and duration of uremia. This increase with increasing duration and severity of renal disease is in parallel with a graded increase in inflammation and oxidative stress. Numerous studies have reported an association between renal impairment and different markers of inflammation, including C-reactive protein (CRP) and serum ferritin. Altered calcium and phosphate homeostasis in CKD patients is also associated with higher prevalence of cutaneous manifestations. Lastly, various socioeconomic factors, such as low socioeconomic status, poor nutrition and poor social and personal hygiene also play an important role, especially in a developing countries like ours.

Skin diseases affect the morbidity, mortality and outcome in CKD patients. Length of hospital stay is significantly greater, and so are the reported treatment costs. Cutaneous findings in CKD patients may also be associated with psychological distress on account of cosmetic concerns. Despite better understanding of the pathophysiologic mechanisms of skin manifestations, optimal treatment still remains elusive for a large number of patients. Hence, it is necessary to search actively for signs of skin manifestation in renal disease because early diagnosis and treatment can improve the prognosis for CKD patients and reduce economic costs connected with treatment. The present study was done to evaluate the spectrum of mucocutaneous manifestations in patients with CKD and to look for an association between them and various biochemical parameters and inflammatory markers.

MATERIAL AND METHODS

This study was a 1 year prospective, observational study conducted on adult patients with CKD who presented to the Nephrology clinic in Pt. BD Sharma PGIMS, Rohtak. Patients between the ages of 17 and 75 years with CKD stages II or more with dermatological conditions were included in this study. A total of 125 patients were hence recruited over a period of 1 year between January and December, 2019.

Patients positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C as well as renal transplant recipients were excluded from the study. Similarly, those with a preceding dermatological disorder, connective tissue disease, comorbid hepatobiliary, pancreatic, thyroid disorder or malignancy were also excluded. After taking written and informed consent and a thorough history, each participant was subjected to detailed clinical, biochemical, radiological and dermatological examination by same consultants in order to avoid interpersonal variations. All patients underwent routine investigations along with high-sensitivity CRP (hs-CRP) measured by particle enhanced immune turbid metric assay and serum ferritin by enzyme immunoassay. hs-CRP >3 mg/L and serum ferritin >200 µg/L were considered significant and suggestive of active inflammatory stage of the patient.

Depending upon the stage of CKD, these 125 patients were classified into 5 groups – Group A through E: **Group A** consisted of 10 patients with eGFR between 60-89 mL/min/1.73 m^2 (CKD Stage II); **Group B** consisted of 15 patients with eGFR between 30-59 mL/min/1.73 m^2 (CKD Stage III); **Group C** consisted of 20 patients with eGFR between 15-29 mL/min/1.73 m^2 (CKD Stage IV); **Group D** consisted of 45 patients with eGFR <15 mL/min/1.73 m^2 not on hemodialysis (CKD Stage V); **Group E** consisted of 35 patients with eGFR <15 mL/min/1.73 m^2 on hemodialysis (CKD Stage V_D).

Statistical Analysis

Data were entered into Microsoft excel workbook 2019 and exported into SPSS. Categorical variables were expressed as frequency and percentage, and compared using Chi-square test. Normally distributed variables were compared between two group using Student *t*-test. One-way analysis of variance followed by Bonferroni post-hoc correction analysis was performed to compare quantitative variables between more than two groups. P value <0.05 was considered significant. Statistical analyses were performed using SPSS version 21.0 (IBM, USA).

RESULTS

Mean age of the patients was 43.1 ± 12.3 years with 5% of patients more than 60 years of age, and 60% of patients being male. The most common etiology of CKD was diabetes mellitus, accounting for 47% of cases, followed by hypertensive nephropathy (39%) and immunoglobulin A (IgA) nephropathy (33%). The least common etiologies of CKD were chronic glomerulonephritis (6%) and renal amyloidosis (5%).

Majority of the patients in our study were obese (67%), followed by normal (19%) and overweight (12%). Only 1.6% patients were underweight.

Various skin, mucosal, nail and hair manifestations along with cutaneous infections were analyzed across the spectrum of CKD. It was noted that xerosis was the most common dermatological disease and the prevalence of xerosis, skin pallor and pruritis was found to increase significantly from Stage II to Stage V and V_D of CKD in a statistically significant manner. Furthermore, xerostomia (the most prevalent mucosal manifestation) and nail pallor (the most common nail manifestation) were also found to have a significant rise in prevalence with increasing stage of CKD. Among hair changes, sparse scalp hair was the most common finding but none of the hair diseases were found to have a statistically significant increase from Group A to E. Among cutaneous infections, fungal infections predominated, amongst which, onychomycosis was the most common. The prevalence of dermatological manifestations and dermatological infections as a function of different stages of CKD is summarized in Table 1 and Table 2, respectively.

Patients were further divided into two groups – those managed conservatively and those on dialysis (Table 3). Perforating folliculitis was found in 4 patients

Table 1. Prevalence of Dermatological Manifestations as a Function of Different Stages of CKD

	Group A	Group B	Group C	Group D	Group E	Total (%)	P value
Skin manifestations							
Early wrinkling	0	1	1	5	3	10 (8%)	0.780
Perforating folliculitis	0	0	0	1	4	5 (4%)	0.122
Skin pallor	0	4	11	18	18	51 (41%)	<0.05
Diffuse hyperpigmentation	2	5	10	13	17	47 (37.6%)	0.199
Xerosis	0	2	7	31	25	65 (52%)	<0.05
Bullous lesions	0	0	1	3	3	7 (5.6%)	0.703
Pruritus	0	8	9	25	13	55 (44%)	<0.05
Mucosal manifestations							
Xerostomia	0	3	3	14	15	35 (28%)	<0.05
Angular cheilitis	1	2	3	7	7	20 (16%)	0.940
Fissured tongue	0	3	3	10	5	21 (17%)	0.512
Coated tongue	1	3	3	10	12	29 (23.2%)	0.372
Hair manifestations							
Lusterless hair	2	6	6	22	12	48 (38.4%)	0.356
Sparse body hair	1	5	5	18	14	43 (34.4%)	0.338
Sparse scalp hair	5	6	8	17	18	54 (43.2%)	0.765
Nail manifestations							
Dystrophic nails	0	1	2	10	5	18 (14.4%)	0.292
Nail discoloration	2	3	7	13	13	38 (30.4%)	0.685
Onycholysis	2	1	2	7	6	18 (14.4%)	0.816
Half and half nail disease	0	4	6	14	9	33 (26.4%)	0.374
Nail pallor	1	2	9	23	17	52 (41.6%)	<0.05

Data expressed in frequency and percentage; compared using Chi-square test.

Table 2. Prevalence of Dermatological Infections as a Function of Different Stages of CKD

	Group A	Group B	Group C	Group D	Group E	Total (%)	P value
Fungal infections (n = 43)							
Onychomycosis	0	4	3	10	9	26 (60.4%)	0.417
Tinea pedis	0	1	1	2	0	4 (9.3%)	0.644
Tinea curis and Tinea corporis	0	1	1	0	1	3 (6.9%)	0.537
Intertrigo	0	0	1	0	1	2 (4.6%)	0.565
Oral candidiasis	0	1	0	2	1	4 (9.3%)	0.770
Pityriasis	0	1	0	2	1	4 (9.3%)	0.747
Bacterial infections (n = 21)							
Folliculitis	0	1	2	4	5	12 (57.1%)	0.713
Furunculosis	0	0	0	2	1	3 (14.2%)	0.713
Ecthyma	0	0	1	1	2	4 (19%)	0.756
Carbuncle	0	0	1	0	1	2 (9.5%)	0.565
Viral infections (n = 8)							
Herpes simplex	0	1	2	2	1	6 (75%)	0.717
Herpes zoster	0	0	1	0	0	1 (12.5%)	0.259
Erythema multiforme	0	0	0	1	0	1 (12.5%)	0.774

All data expressed in frequency and percentage, compared with Chi-square test; total percentage of a specific infection has been calculated as a proportion of total number of infections caused by the particular category of organism.

Table 3. Prevalence of All Dermatological Manifestations in CKD Patients – Nondialysis vs. Dialysis Group

	CKD patients not on dialysis (n = 90)	CKD patients on dialysis (n = 35)	Total (n = 125)	P value
Skin manifestations				
Early wrinkling	7 (7.8%)	3 (8.6%)	10 (8%)	1.000
Perforating folliculitis	1 (1.1%)	4 (11.4%)	5 (4%)	<0.05
Skin pallor	33 (36.7%)	18 (51.4%)	51 (41%)	0.132
Diffuse hyperpigmentation	30 (33.3%)	17 (48.6%)	47 (37.6%)	0.114
Xerosis	40 (44.4%)	25 (71.4%)	65 (52%)	0.335
Bullous lesions	4 (4.4%)	3 (8.6%)	7 (5.6%)	0.640
Pruritus	42 (46.7%)	13 (37.1%)	55 (44%)	<0.05
Mucosal manifestations				
Xerostomia	20 (22.2%)	15 (42.9%)	35 (28%)	<0.05
Angular cheilitis	13 (14.4%)	7 (20.0%)	20 (16%)	0.625
Fissured tongue	16 (17.8%)	5 (14.3%)	21 (17%)	0.840
Coated tongue	17 (18.9%)	12 (34.3%)	29 (23.2%)	0.067

Table 3. Prevalence of All Dermatological Manifestations in CKD Patients – Nondialysis vs. Dialysis Group

	CKD patients not on dialysis (n = 90)	CKD patients on dialysis (n = 35)	Total (n = 125)	P value
Hair manifestations				
Sparse scalp hair	36 (40.0%)	18 (51.4%)	54 (43.2%)	0.247
Lusterless hair	36 (40.0%)	12 (34.3%)	48 (38.4%)	0.555
Sparse body hair	29 (32.2%)	14 (40.0%)	43 (34.4%)	0.411
Nail manifestations				
Nail pallor	35 (38.9%)	17 (48.6%)	52 (41.6%)	0.324
Half and half nail disease	24 (26.7%)	9 (25.7%)	33 (26.4%)	0.914
Dystrophic nails	13 (14.4%)	5 (14.3%)	18 (14.4%)	0.982
Nail discoloration	27 (30.0%)	13 (37.1%)	38 (30.4%)	0.861
Onycholysis	12 (13.3%)	6 (17.1%)	18 (14.4%)	0.794
Infections				
Bacterial infections	12 (13.3%)	9 (25.7%)	21 (16.8%)	0.096
Viral infections	7 (7.8%)	1 (2.9%)	8 (6.4%)	0.313
Fungal infections	30 (33.3%)	13 (37.1%)	43 (34.4%)	0.642

Data expressed in frequency and percentage; compared using Chi-square test.

on dialysis in comparison to 1 patient not on dialysis ($p < 0.05$). Xerostomia was also seen to be more common in patients on dialysis. Pruritus on the other hand, was significantly higher in nondialysis patients. Xerosis, early wrinkling, diffuses hyperpigmentation and bullous lesions were more common amongst conservatively managed patients, but this difference was not statistically significant.

We observed a decrease in serum ferritin levels with increasing CKD stage. Serum ferritin levels in the patients of CKD stage V_D were substantially lower in comparison to other stages ($p < 0.05$). There was no significant difference in serum ferritin levels amongst the other stages. It was also noted that hs-CRP levels increased with increasing CKD stage and patients with Stage V and Stage V_D disease had higher levels of CRP in comparison to other stages ($p < 0.05$); maximum values were noted in Stage V_D. Results of distribution of serum ferritin and hs-CRP among different stages of CKD are shown in Table 4 and Figure 1 a and b.

Table 4. Comparison of Inflammatory Markers among Different CKD Stages

	Serum ferritin	hs-CRP
Group A	202.50 ± 23.36	2.26 ± 0.90
Group B	197.76 ± 20.66	2.60 ± 0.47
Group C	197.65 ± 20.59	3.17 ± 0.51
Group D	193.91 ± 16.49	10.42 ± 6.96
Group E	173.86 ± 18.01	15.55 ± 5.82
P value	<0.05	<0.05
Pair-wise comparison	Group A vs. Group E <0.05 Group B vs. Group E <0.05 Group C vs. Group E <0.05 Group D vs. Group E <0.05 Others = nonsignificant	Group A vs. Group E <0.05 Group B vs. Group E <0.05 Group C vs. Group E <0.05 Group D vs. Group E = 0.05 Group A vs. Group D <0.05 Group B vs. Group D <0.05 Group C vs. Group D <0.05 Others = nonsignificant

Data expressed in mean ± SD; Kruskal-Wallis test used followed by pair-wise comparison.

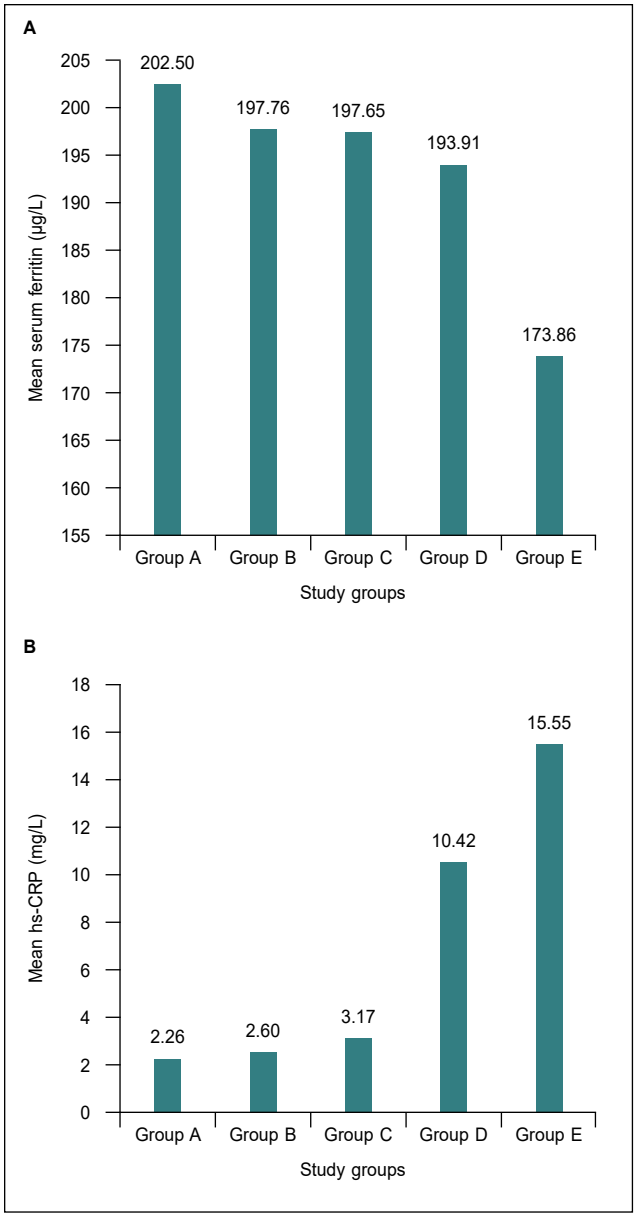

Figure 1 a and b. Association of inflammatory markers with different stages of CKD.

Other notable observations of our study include the fact that patients with skin pallor as well as nail pallor had comparable hemoglobin (9.3 ± 1.4 vs. 9.4 ± 1.3; p = 0.828), in comparison to the patients without these conditions. On the other hand, an association was found between xerosis and decreasing levels of hemoglobin and while ferritin was not different between patients with and without xerosis, hs-CRP was significantly higher in patients with xerosis. Similarly, hs-CRP levels were significantly elevated in patients with xerostomia and nail pallor as compared with those who did not have these conditions. Lastly, patients with nail pallor had a significantly lower albumin.

DISCUSSION

Xerosis was found to be the most common cutaneous manifestation in our study at a high prevalence of 52% with majority belonging to Stage V. The prevalence was reported to be quite high in studies on comparable populations, including Udayakumar et al and Khanna et al, who observed xerosis at a prevalence rate of 79% and 72%, respectively.[3,4] Xerosis was significantly associated with decreasing eGFR and hemoglobin levels and higher hs-CRP levels. Skin pallor was the second most common cutaneous manifestation, observed in 51 (40.8%) patients, out of which 36 patients had advanced CKD. It was significantly more prevalent in patients with lower eGFR ($p < 0.05$). Skin pallor in CKD patients can be explained by decreased renal erythropoietin levels, iron, folic acid or vitamin B12 deficiency, poor erythrocyte survival and blood loss during dialysis. Rashpa et al observed a 50% prevalence of skin pallor in their study of CKD patients, with it being the second most common skin manifestation.[5] Pruritus was recorded in 55 out of 125 patients (44%) in our study, with a majority of patients in CKD Stage V. Hajheydari et al observed that pruritus worsened after dialysis in 46.15% of patients in their study.[6] While it is commonly reported as the most troublesome dermatological symptom of renal disease, Hiroshige et al observed that aggressive dialysis led to significant reductions in pruritus severity.[7]

Xerostomia was the most common mucosal manifestation observed in our study, present in 35 patients (28%). Out of 35 patients, 29 (83%) patients belonged to advanced CKD, out of which 15 patients were on hemodialysis. Hopcraft and Tan reported the association of xerostomia and CKD stages and found that the prevalence of xerostomia in the general population ranged from 10% to 46%.[8] Increase in frequency of xerostomia in patients with worsening renal function can be explained by restricted diets, malnutrition, poor oral hygiene, reduced dental visits, immunosuppression and the effects of medications and uremic toxins on the oral tissues. Xerostomia was also significantly associated with hs-CRP in our study. Patients with xerostomia having higher hs-CRP levels are at increased risk of lesions to the mucosa, gingiva and tongue. Many of these conditions are because of the chronic inflammation that is frequently present in patients on hemodialysis.

Hair changes observed in our study population included sparse scalp and body hair and lusterless hair. The most common finding was sparse scalp hair, seen in 43.2% of patients and its prevalence was higher in

predialysis patients than patients on dialysis. However, none of the hair diseases were associated with CKD stage or biochemical parameters. A study observed that the prevalence of hair findings across all stages of CKD may result from the higher mean age of the patients. Sparse scalp and body hair seen in 35.2% and 13.1% patients, respectively, and lusterless hair seen in 12.3% patients, could be attributed to anemia, stress of end-stage kidney disease/dialysis or neglect of hair care.[5] As for nail changes, nail pallor was found to be the most common nail manifestations seen in 52 out of 125 patients and was found to prevalence rose with increase in CKD stage. Amatya et al reported similar findings with nail pallor (white nail) being the most common nail manifestation in both dialysis and predialysis patients.[9]

The CKD patients have increased susceptibility for skin infections due to reduced immunity. Cutaneous infections including fungal, bacterial and viral were seen in 34.4%, 16.8% and 6.4% of CKD patients, respectively. However, these skin infections were not consistently associated with different CKD stages. Hemodialysis patients get exposed to numerous infections during the course of treatment, and a large proportion of patients need to be hospitalized at least once every year for treatment of the same.[10] The type of vascular access in use plays an important role in the subsequent development of bloodstream infections. Central venous catheters tend to heighten the risk of bacteremia among dialysis patients.[11] Those with temporary catheters have been shown to have a 50% higher risk of septicemia compared to patients with a native fistula. Increasing the use of arteriovenous fistula as hemodialysis access can reduce the risk of infections.

While comparing skin manifestations between patients on dialysis and conservative management, we found a significant difference in terms of perforating folliculitis and xerostomia which were more common in the dialysis group, whereas pruritus had higher prevalence in the predialysis subset. This is in contrast to a study of 150 predialysis and 50 dialysis patients, in which the authors found that the prevalence of xerosis, pruritus and pigmentary changes was higher in dialysis patients, whereas nail changes showed no significant difference between the groups.[4]

We found that serum ferritin level decreased with increasing CKD stage, and was significantly lower in CKD stage V_D. The levels of serum ferritin in a patient of CKD can be extremely variable. In addition to being an index of iron stores within the body, it is also a positive acute phase reactant. Hence, while severe iron deficiency anemia will be associated with low ferritin levels, prominent chronic inflammation associated with CKD would be associated with high levels. Studies have shown that ferritin levels below 200 ng/mL were associated with depleted iron stores, whereas levels in excess of 2,000 ng/mL were associated with iron overload.[12,13] Kalantar-Zadeh conducted a study on 72 hemodialysis patients with serum ferritin levels between 200 and 2,000 ng/mL. They found that increasing ferritin levels within this range was significantly associated with both malnutrition and inflammation as evidenced by SGA (subjective global assessment) and MIS (malnutrition-inflammation score) scores.[14] In our study, most of the patients had serum ferritin levels below 200 ng/mL indicating the high burden of iron deficiency anemia in the study population.

The mean value of serum hs-CRP was found to have an increasing trend from Group A to E and hs-CRP levels were high in 36% of our study population. In addition, most, if not all inflammatory markers, were elevated in CKD Stage V patients on hemodialysis, indicating high prevalence of inflammation in this subset. Chen et al conducted a study on the association of uremic pruritus with inflammation and hepatitis infection on 321 CKD patients on hemodialysis. They concluded that higher hs-CRP levels were associated with more severe pruritus and in turn poorer survival when adjusted for other mortality causing factors.[15] In our analysis; however, we did not find a substantial difference in hs-CRP levels between patients with and without pruritus. Patients with xerosis, on the other hand, had statistically significant hs-CRP levels.

Our study had a few limitations which include the fact that this is a cross-sectional study from which causal relationships cannot be drawn. Furthermore, only clinical examination of the skin lesions was performed and no diagnostic instrumentation or skin biopsy was done. The limited sample size may act as a deterrent to accurate justification of the results in our study.

CONCLUSION

In our study, CKD patients showed at least one cutaneous change. It was observed that in CKD patients on hemodialysis and on conservative management, xerosis, pruritus, pigmentation, nail changes, oral mucosa changes and cutaneous infections were the predominant cutaneous manifestations. Mucocutaneous manifestations progressively worsened as renal function deteriorated. The dermatological manifestations and presence of inflammation in CKD is a complex multifactorial problem which commences early and

progresses with the stage of the disease. Assessment of key components of dermatological manifestations and inflammation early in disease course will help identify high-risk subjects in whom modifying these predictors will assist in providing an active and healthy life to CKD patients.

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Depression Tied to Severity of Dry Eye Disease

A multicenter study published in J*AMA Ophthalmology* stated that patients with dry eyes and concomitant depression experienced more severe eye symptoms and clinical signs.

This was a secondary analysis of data from the Dry Eye Assessment and Management (DREAM) study, a randomized clinical trial which included 535 participants with a mean (SD) age of 58 (13.2) years. Symptoms of dry eye disease (DED) were assessed using Ocular Surface Disease Index (OSDI) and Brief Ocular Discomfort Index (BODI) and signs were assessed by tear film breakup time, Schirmer test, tear osmolarity, corneal and conjunctival staining and meibomian gland dysfunction, at study initiation and at 6 months and 12 months.

Based on Mental Component Summary (MCS) scores, 15.7% of the patients had depression at baseline, 17.3% at 6 months, and 13.2% at 12 months. It was observed that participants suffering from depression had worse DED symptoms by OSDI, BODI and composite DED sign score. Lower MCS scores, which mean worse depression, correlated with higher OSDI scores. The mean corneal staining score was higher in the group with depression. Markers of conjunctival inflammation (cytokines in tears and *HLA-DR* expression) did not differ by depression status.

The study thus concluded that depression was associated with more severe dry eye symptoms and overall signs and support considering depression as a comorbidity when managing patients with DED. (*MedPage Today, March 16; JAMA Ophthalmology, March 10, 2022*)

ORIGINAL ARTICLE

To Study the Clinical Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Moderate-to-Severe COVID-19 Disease in ICU of a Tertiary Center in Bihar

JYOTI PRAKASH*, B DAS†

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) pandemic has adversely affected the human health and wealth across the globe and is still posing a serious challenge to us. In the armamentarium of various drugs approved for COVID-19, remdesivir proved to be a major breakthrough in the treatment of moderate-to-severe cases. Our study is regarding its clinical efficacy and safety in hospitalized reverse transcription polymerase chain reaction (RT-PCR) confirmed adult patients with moderate-to-severe COVID-19 disease. **Material and methods:** A total of 100 patients with moderate-to-severe COVID-19 (RT-PCR positive) admitted in the intensive care unit (ICU) of Sri Krishna Medical College and Hospital (SKMCH), Muzaffarpur, Bihar, were enrolled in the study from 12th August to 11th November, 2020. All patients were given injection remdesivir as 200 mg IV loading dose on Day 1, followed by 100 mg IV daily for next 4 days along with other standard treatment. **Results:** Out of total 100 patients, 88 patients recovered and were discharged, while 12 patients died. Mean age of patients was 54 ± 16 years with male preponderance (4:1). Mean duration of hospital stay was 10.6 ± 5.4 days. C-reactive protein, D-dimer, ferritin and interleukin-6 decreased significantly after treatment with remdesivir, with p value <0.01, as compared to values at the time of admission, without any significant side effects. **Conclusion:** Early administration of remdesivir helps contribute to better clinical outcome in moderate-to-severe COVID-19 disease, without any significant side effects.

Keywords: Remdesivir, COVID-19, RT-PCR, morbidity, mortality, CT severity score, lab markers

Coronavirus disease (COVID-19) is caused by a coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] which originated from Wuhan province of China. It soon spread across the globe and led to considerable damage to the healthcare system, economy and loss of human life. It is transmitted from symptomatic or asymptomatic persons through droplets or aerosols, and less commonly by direct contact of fomites.[2] Despite global efforts and so many lockdowns, over 400 million people have got infected and over 5 million have succumbed to the disease, thus far.[3]

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In view of its contagious nature, virulence, morbidity and mortality, various permutations and combinations of drugs came into the market, but none of them proved to be up to the mark.

In this connection, remdesivir got Food and Drug Administration (FDA) approval for emergency use on May 1, 2020[4] for the treatment of hospitalized patients with severe disease and on October 22, 2020, it was approved by FDA for use in adults and children aged ≥12 years weighing at least 40 kg for COVID-19 treatment requiring hospitalization.[5] Remdesivir is a prodrug of an adenosine analog having broad-spectrum antiviral properties, including against coronaviruses, pneumoviruses, paramyxoviruses and filoviruses.

Previous studies indicate the benefits in terms of morbidity and mortality (11% vs. 15%), when remdesivir was used in hospitalized patients within 10 days of symptoms in moderate-to-severe COVID disease, as compared to placebo.[6,7]

MATERIAL AND METHODS

This study was conducted on 100 symptomatic reverse transcription polymerase chain reaction (RT-PCR)positive COVID patients admitted in intensive care unit (ICU) of Sri Krishna Medical College and Hospital (SKMCH), Muzaffarpur, Bihar from 12th August to 11th November, 2020. This was a prospective, observational, cross-sectional study based on data collected from patients.

- **Inclusion criteria:** RT-PCR positive, symptomatic, adult patients requiring ICU admission (oxygen saturation [SpO_2] <94% on room air, high-resolution computed tomography [HRCT] thorax showing ground-glass opacities, raised inflammatory markers such as C-reactive protein [CRP], lactate dehydrogenase [LDH], ferritin, interleukin [IL]-6, D-dimer, etc.).
- **Exclusion criteria:** Age <18 years and >80 years, pregnant and lactating mothers, acute or chronic liver/kidney failure, malignancy.

Table 1 summarizes the demographic data of patients at admission.

A written informed consent was taken from all patients or their legal guardians. Intravenous remdesivir 200 mg was given as loading dose on Day 1, followed by 100 mg as maintenance dose for next 4 days, along with other standard treatments such as enoxaparin, methylprednisolone/dexamethasone, intravenous broad-spectrum antibiotics, etc., as per the Indian Council of Medical Research (ICMR) guidelines.

Outcome measures, in terms of clinical and biochemical improvement, duration of hospital stay, CT thorax changes, adverse effects, mortality, etc., were analyzed using Python 3 and Jupyter notebook. Continuous variables were expressed as mean ± SD (standard deviation). Statistical analysis was done for laboratory parameters at admission and at discharge using paired *t*-test, significance level being $p < 0.05$.

RESULTS

A total of 100 RT-PCR confirmed moderate-to-severely ill COVID-19 patients received remdesivir. The median age was 54 ± 16 years, with male preponderance (4:1). Fever (92%), breathlessness (90%), dry cough (78%), myalgia (56%), sore throat (46%) and loss of smell/taste (11%) were the most common presenting clinical features (Table 2).

Associated comorbidities were diabetes mellitus (54%), hypertension (24%), coronary artery disease (12%) and chronic obstructive pulmonary disease (COPD)/bronchial asthma (10%) (Table 1).

Table 1. Demographic Data at Admission

Total number of patients (n)	100
Age (years)	54 ± 16
Sex	
Male	80
Female	20
BMI (kg/m^2)	23.8 ± 3.2
Blood pressure (mmHg)	
SBP	118 ± 12
DBP	82 ± 8.0
Pulse rate	
>100	84
60-100	10
<60	6
SpO_2	
>94%	30
<94%	70
Respiratory rate	
<24	34
>24	64
Comorbidities	
Diabetes mellitus	54
Hypertension	24
Coronary artery disease	12
COPD/Bronchial asthma	10

BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; SpO_2 = Oxygen saturation; COPD = Chronic obstructive pulmonary disease.

Table 2. Common Presenting Clinical Features

Clinical presentation	Percentage of patients
Fever	92
Shortness of breath	90
Dry cough	78
Myalgia	56
Sore throat	46
Loss of smell/taste	11

Out of 100 patients, 22 patients did not need oxygen, 78 patients needed supplemental oxygen therapy. Oxygen was delivered through various modes, such as nasal prongs (5), face mask (18), nonrebreather mask (NRBM) (20), high-flow oxygen mask (18), noninvasive

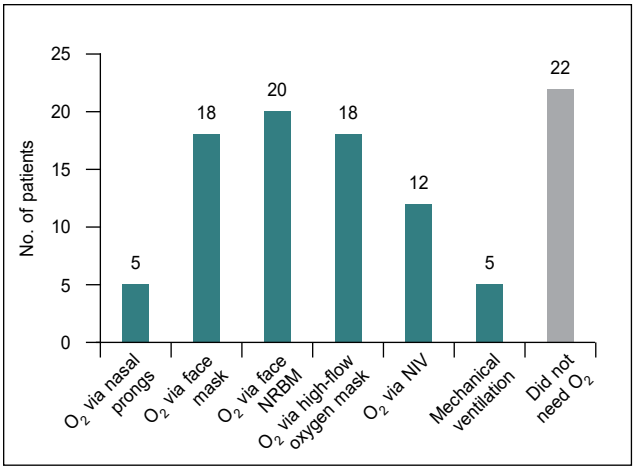

Figure 1. O_2 requirement in patients (n = 100).

Table 3. Lung Involvement (n = 100)

% of lung involvement	No. of patients
<25	15
25-50	25
51-75	55
>75	5

Table 4. HRCT Pattern of Lung Involvement

Ground-glass opacity	100%
Consolidation	55
Bronchiectasis	11
Subpleural bands	13
Nodular opacities	2

ventilation (NIV) (Bi-level positive airway pressure [BiPAP]) (12) and mechanical ventilation (5) (Fig. 1).

HRCT thorax was done on a 16 slice CT machine. Each of the five lobes were scored from 0 to 5. The mean CT severity score was 15 ± 5. The lung involvement pattern is depicted in Tables 3 and 4.

Mean duration of hospital stay after remdesivir administration was 10.6 ± 5.4 days. There were no significant adverse effects. A total of 88 patients recovered and were discharged, while 12 patients died.

Considerable improvement in lab parameters was also noted after remdesivir administration, such as CRP, D-dimer, IL-6, serum ferritin, etc. (Table 5). The mean CT severity score in our study was 14.4 among improved and 18.2 among expired cases (Fig. 2).

Table 5. Inflammatory Markers (n = 100)

	Min	Max
CRP at admission (mg/dL)	8.4	137.6
CRP at discharge (mg/dL)	1.5	45.0
Ferritin at admission (ng/mL)	25.6	2436.0
Ferritin at discharge (ng/mL)	11.8	935.0
D-dimer at admission (µg/mL)	112.4	9582.0
D-dimer at discharge (µg/mL)	110	7225.0
IL-6 at admission (pg/mL)	2.4	1685.0
IL-6 at discharge (pg/mL)	2.0	175.0

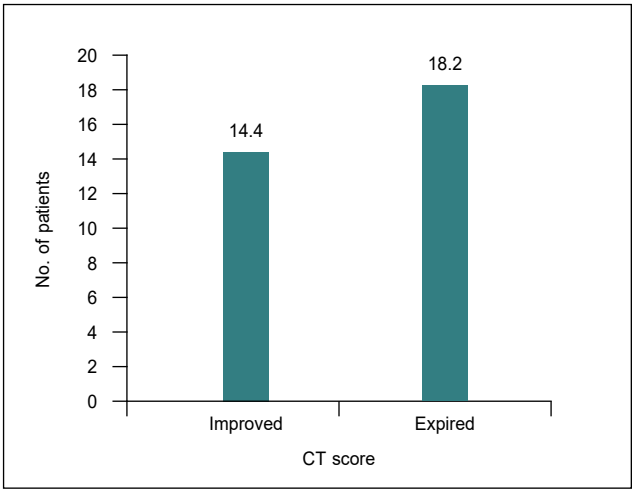

Figure 2. CT severity score.

DISCUSSION

Among the various treatment options available for COVID-19, remdesivir was the first drug to be approved for treatment by the US FDA.[5] The efficacy of remdesivir in terms of hospital stay and associated mortality has been studied by several authors. Early administration of the drug resulted in better outcomes.

ACTT-1 study stated that remdesivir was superior to placebo in terms of hospital stay and better improvement in lower respiratory tract symptoms.[8] Another study by Spinner et al stated clearly that 5 days of remdesivir was associated with higher odds of better clinical status distribution as compared with the standard treatment.[9] Goldman et al demonstrated that there was no difference in clinical outcomes between a 5-day course and a 10-day course of remdesivir given to patients with severe COVID-19 not requiring mechanical ventilation.[10]

In our study, remdesivir was given to RT-PCR positive COVID-19 patients with moderate-to-severe disease, and its effect in terms of hospital stay and mortality (especially in those having comorbidities like diabetes mellitus, hypertension, etc.) was studied. It showed beneficial effects in terms of morbidity and mortality. In our study, mean duration of hospital stay after remdesivir administration was 10.6 ± 5.4 days, as compared to the study by Wang et al where the length of hospital stay in patients treated with remdesivir was 25 days.[7]

Our study has a limitation in the sense that it was not a case-control study.

CONCLUSION

From this study, we conclude that early use of remdesivir (within 5-8 days of symptom onset) in RT-PCR positive moderate-to-severe COVID-19 patients has a beneficial role in morbidity and mortality. It has positive impact on patient's clinical as well as biochemical profile.

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■■■■

COVID-19 Transmission from Mother-to-Baby is Rare

According to a systematic review and meta-analysis published in *The BMJ*, there was a low likelihood of the COVID-19 infection passing from the mothers to their babies. The review included 472 studies with more than 14,000 babies born to mothers with COVID-19 infection and only 1.8% tested positive on an RT-PCR test. Among the 592 COVID-positive babies, only 14 were confirmed cases where the infection was transmitted from the mother. Seven babies acquired the infection *in utero*, two during childbirth and five contracted the infection in the early postnatal period. The overall risk of transmission from mother-to-child was low. The severity of the COVID-19 infection was a key factor determining the transmission. An analysis comprising of 22 studies including nearly 3,000 women, noted that mothers with severe COVID-19 showed more chances of delivering a baby who tested positive (odds ratio [OR] 2.36, 95% confidence interval [CI] 1.28-4.36). Other risk factors associated with COVID-19 infection in the baby included maternal admission to the ICU, maternal death and postnatal maternal diagnosis of COVID-19. The analysis also found that SARS-CoV-2 positivity was not associated with trimester of maternal infection, preterm birth, mode of delivery or separation of mother and baby after birth.

Among 800 COVID-positive babies with data on neonatal outcomes, 20 were stillbirths and 23 died. (*MedPage Today, March 16, 2022*)

REVIEW ARTICLE

The Journey and Excitement Following the Development of the First Peptide in a Pill: A Brief Overview of Pharmacology and Clinical Trials of Oral Semaglutide

BANSHI SABOO*, MANOJ CHAWLA†, SANJAY AGARWAL‡, MITHUN BHARTIA#

ABSTRACT

Oral semaglutide is the newest discovery, the first in class peptide in a pill. Sodium *N*-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC), a small fatty acid, has been co-formulated with semaglutide, which facilitates its absorption from the gastric mucosa. It has 94% homology with human glucagon-like peptide 1 (GLP-1). It comes in three dose forms – 3 mg, 7 mg and 14 mg. It is given as once daily dosing and is recommended in adult type 2 diabetes mellitus patients as monotherapy when metformin is contraindicated or not tolerated and in combination with other oral antidiabetic drugs (OADs). In a phase 3 trial, it has been shown to reduce glycated hemoglobin (HbA1c) up to 1.5%, with weight reduction up to 5 kg with a 14 mg dose. There was nonsignificant risk reduction of 21% in 3-point major adverse cardiovascular events (MACE) and 51% and 49% risk reduction in cardiovascular (CV) deaths and all-cause mortality, respectively. Oral semaglutide was found to be superior to empagliflozin, sitagliptin and liraglutide in both glycemic control and weight reduction. It also exhibits many pleiotropic effects – reduced energy intake, anti-inflammatory and anti-atherosclerotic effect, to name a few. Nausea was the most common side effect which was experienced by only 15% to 20% of patients. It was mild-to-moderate and transient. Overall, oral semaglutide has shown its efficacy both early and late in the management of diabetes, irrespective of renal and hepatic impairment.

Keywords: Oral semaglutide, GLP-RAs, PK-PD, PIONEER Program, safety, PIP

CHALLENGES MANAGING DIABETES IN INDIA

Need of GLP-RA and Peptide in a Pill

India ranks second in the world with over 74 million people with diabetes (PwD). This number is expected to increase to 124.9 million by 2045.[1] We account for 87% of total PwD in Sout-East Asia region.[1] Patients with complications incur expenses three times more than those without complications.[2] Two out of three PwD have diabetes-related complications, and with direct medical cost of INR 50,000 crores.[3] It is also a well-established fact that 7 out of 10 PwD fail to achieve the glycated hemoglobin (HbA1c) target of <7%.[4] Uncontrolled, long-standing diabetes leads to grave complications, ultimately increasing mortality and morbidity and poor quality of life. The most common cause of death among PwD are cardiovascular diseases (CVDs), which results from macrovascular complications. There are more than 6 lakh deaths due to diabetes in India.[5]

Most of the time, diabetes remains a chance diagnosis, when a patient suffers from one or the other complications and visits a healthcare center for the first time. Even though diabetes is a metabolic disease, the patients visit a cardiologist directly with the complication for the first time and it has been observed that a diabetes patient with a complication visits a cardiologist more often than a diabetologist.[6-10]

Traditionally, we only had few options to manage diabetes, for example biguanides, sulfonylureas and

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primitive insulins. But over a period, there have been many developments with numerous modern and newer therapy options – Incretin-based therapy like dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Also, our understanding of natural history of diseases has also evolved. Now diabetes is not merely a disease where we only have imbalance of insulin and glucagon action, but rather a cardio-metabolic syndrome. It is imperative to include the therapies targeting most of the pathophysiological derangements in diabetes.[11]

The CAPTURE study states that 1 in 3 PwD have CVDs and of them, 85.8% are atherosclerotic in origin, and 85% of deaths among PwD with CVDs are due to atherosclerotic cardiovascular disease (ASCVD), again reiterating the importance of cardio-metabolic management approach in PwD.[12] However, in spite of the alarming facts, only 2 out of 10 patients with diabetes and ASCVD are getting a glucose-lowering treatment with a proven cardiovascular (CV) benefit. There are many barriers to the management of diabetes of which nonadherence, self-medication, alternate medicine and fear of injection are few important determinants of poor outcome.[13] Primary nonadherence may be particularly relevant among patients who refuse to initiate injectable hypoglycemic therapy, typically due to injection phobia, inconvenience, poor patient-physician communication and/or negative patient perceptions.[14] It has been established that fear of injection is associated with poor glycemic control, increased incidence of complications and mortality among PwD.

An ideal class of modern noninsulin antidiabetic drugs (MNIADs) for PwD should have the following features: Efficient glycemic control, no to low risk of hypoglycemia, has meaningful weight reduction, established CV safety, tolerable adverse effects, acts on most of the pathophysiological pathways (DeFronzo ominous octet [Fig. 1a][15]), and has a feasible mode of administration.

HOW THE INNOVATION OF ORAL SEMAGLUTIDE HAPPENED (STRUCTURAL CHANGES)

GLP-1 RA is the class of drugs which targets 6 out of 8 components of DeFronzo's octet. They have proven efficacy in reducing HbA1c, body weight reduction, have low risk of hypoglycemia and have proven CV benefits and safety. Among the GLP-1RA class, the most potent molecule is semaglutide (Fig. 1b).[16]

It has 94% homology with human GLP-1. It is a human GLP-based peptide with 30 amino acids (7 to 37) (Fig. 2). The following changes were made to achieve the high potency and longer half-life.

First, at 8th position, alanine was substituted with α-aminobutyric acid to prevent degradation with DPP-4 enzyme. At 26th position, a C-18 long di-fatty acid was attached to lysine with a spacer to increase albumin binding and reduce renal clearance, and lastly at 34th position, lysine has been substituted by arginine to prevent C-18 fatty acid binding at wrong site. These changes have increased the half-life of semaglutide to 160 hours from 1.5 to 2 minutes.[17]

The semaglutide is a multidimensional optimized molecule, it is DPP-4–stable, it has 160 hours half-life, specific affinity towards albumin binding, small molecular weight, and is hydrophilic in nature. These features made it a suitable molecule for oral preparation.

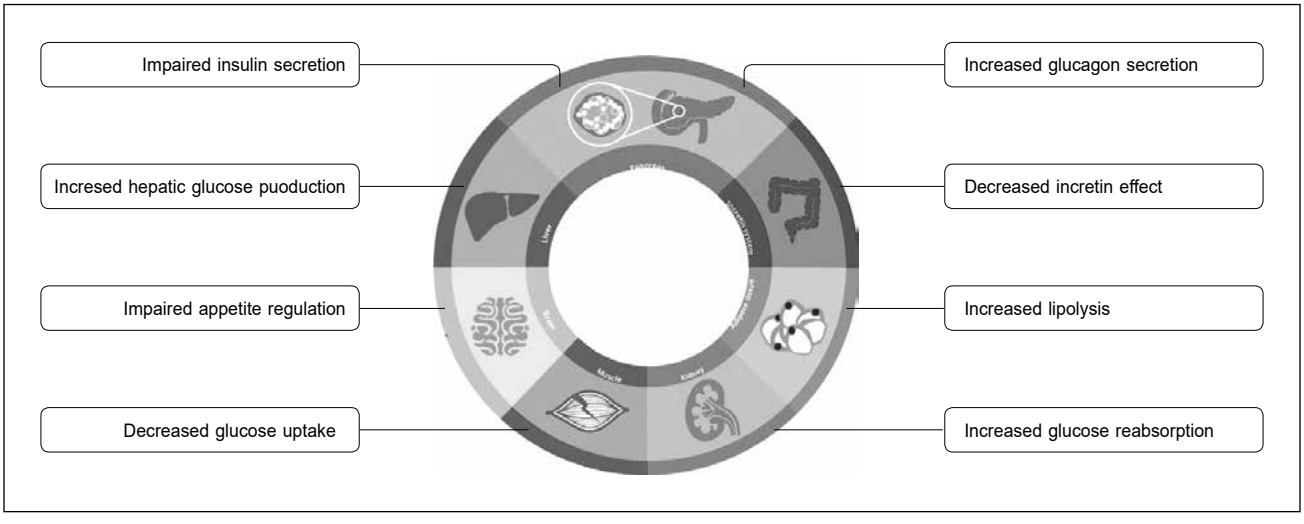

Figure 1a. DeFronzo ominous octet.

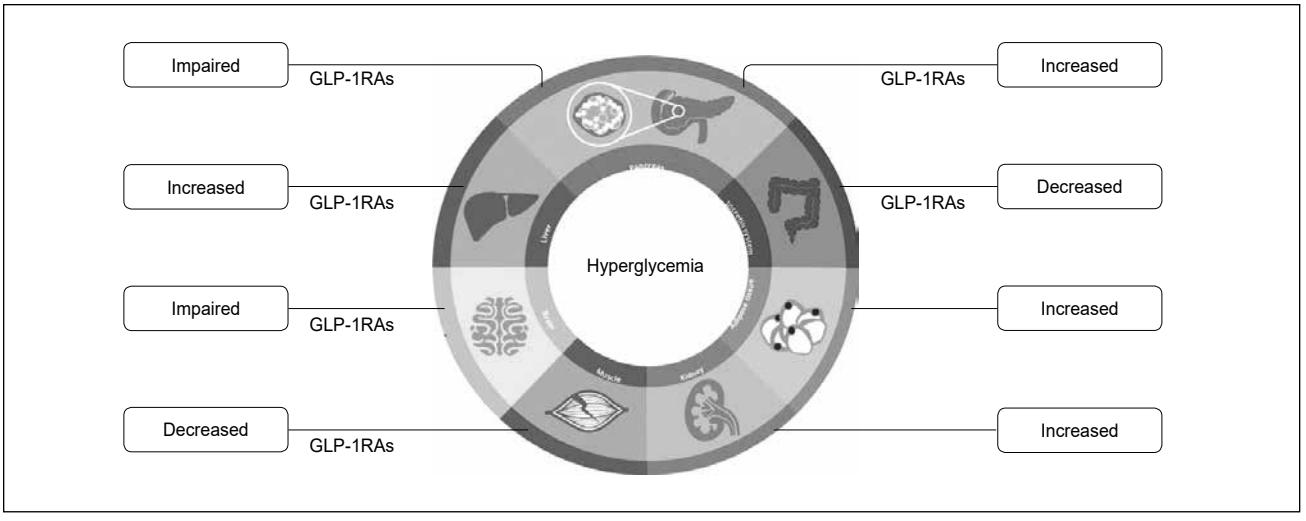

Figure 1b. Role of GLP-1RA in pathophysiology ofT2DM.

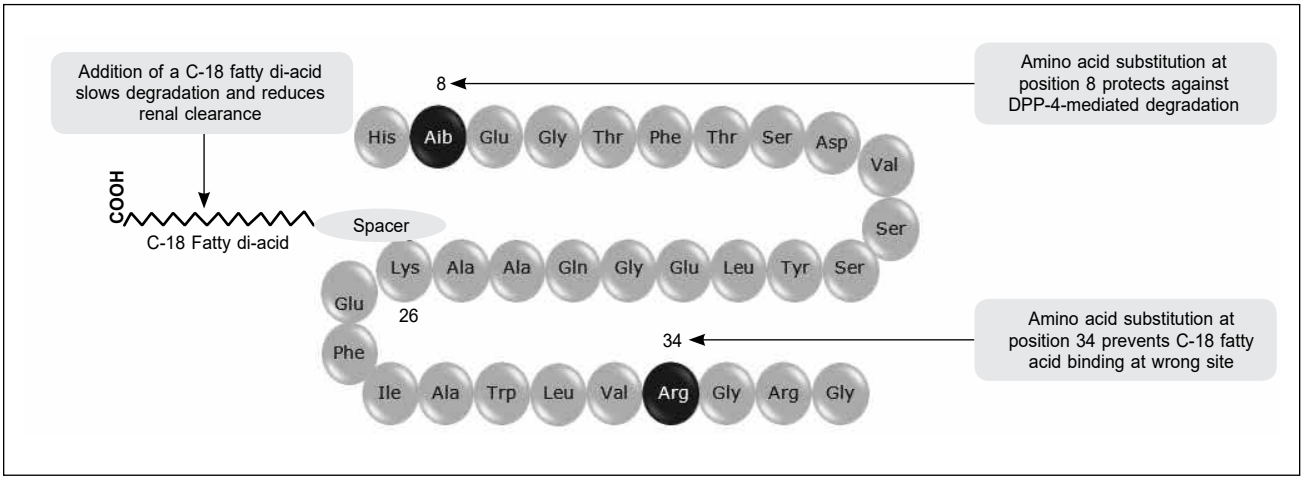

Figure 2. Structure of semaglutide.

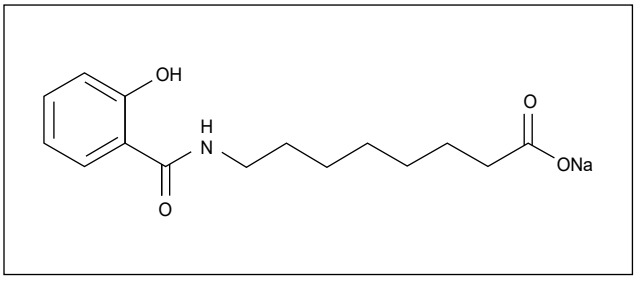

Figure 3. Structure of SNAC.

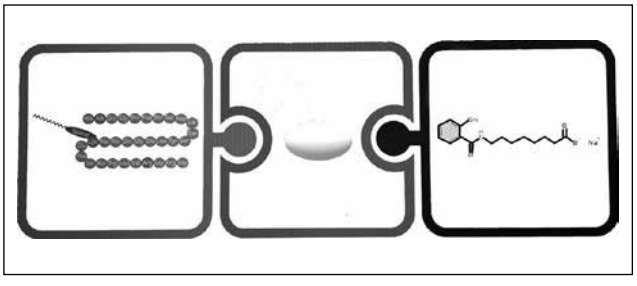

Figure 4. Co-formulation of semaglutide with SNAC.

Sodium *N*-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC) (Fig. 3) is a small fatty acid which was first used in the USA to increase the absorption of vitamin B12. It is a food grade FDA-approved molecule developed by Emisphere Technologies, Inc.

SNAC acts as an absorption enhancer which has been co-formulated with semaglutide for oral formulation. SNAC enhances semaglutide absorption in the gastric epithelium by increasing the local pH, and increasing cell membrane permeability. This facilitates local transcellular absorption of the drug in stomach. This has increased the bioavailability of semaglutide from 0.01% to 1%.[17-20] SNAC is metabolized in the liver by beta glucuronidation and eliminated in kidney. This co-formulation is the world's first peptide in a pill (Fig. 4).

PHARMACOLOGY OF ORAL SEMAGLUTIDE[21-26]

Pharmacodynamics

- GLP-1RAs are incretin-based therapies. Oral semaglutide exerts its action via GLP-1 receptors. It induces glucose-dependant insulin release and glucagon suppression after food intake. It also prevents beta-cell apoptosis, and increases primary and secondary release of insulin. It also delays gastric emptying. Since the release of insulin is glucose-dependent, the risk of hypoglycemia is minimal.
- It regulates blood sugar levels and reduces HbA1c. Oral semaglutide also exhibits many pleiotropic effects – weight reduction, reduced energy intake, reduce hunger and increasing satiety, lipid-lowering action, anti-atherosclerotic action and anti-inflammatory action.

Pharmacokinetics

- Oral semaglutide is absorbed in stomach trans-cellularly with the help of SNAC; it is degraded by DPP-4 enzyme and neutral endopeptidase; it is eliminated in feces and urine. SNAC is metabolized in liver by beta-glucuronidation and eliminated in kidney.

Drug interaction

- Co-administration of placebo with oral semaglutide reduced its area under the curve (AUC) by 34% and maximum concentration (C_{max}) by 32%. There was an increase in AUC by 33% when levothyroxine was co-administered with oral semaglutide at steady state, however, the C_{max} did not change.

Dosing

- Oral semaglutide is available in three dose forms – 3 mg, 7 mg and 14 mg. It should be started with 3 mg once daily dose after overnight fasting with up to 120 mL (half a glass) of water, followed by post administration fasting for 30 minutes.
- The escalation from 3 to 7 mg should be done after 4 weeks and if further HbA1c control is required, the dose can be further escalated to 14 mg after 4 weeks of initiating 7 mg dose.

WHAT TRIALS REFLECT[26-35]

The phase 3 trial for oral semaglutide is called PIONEER Program (Peptide InnOvatioN for Early diabEtes tReatment) (Fig. 5). There were 10 trials in this program wherein semaglutide has been compared with placebo as monotherapy (PIONEER 1), with other oral antidiabetic drugs (OADs) (PIONEER 2, 3, 4 and 7), in special population like CVOT trials (PIONEER 6), renal impairment patients (PIONEER 5), as an add-on therapy to insulin (PIONEER 8) and two trials in Japanese population (PIONEER 9 and 10).

Diet and exercise	OAD	Insulin users	Special populations
PIONEER 1 vs. placebo (Diet and exercise)	**PIONEER 2** vs. SGLT2i (MET) **PIONEER 3** vs. DPP-4i (1-2 OADs: MET ± SU) **PIONEER 4** vs. GLP-1RA/placebo (1-2 OADs: MET ± SGLT2i) **PIONEER 7** Flexible dose adjustment vs. DPP-4i with extension (1-2 OADs: MET, SU, TZD, SGLT2i)	**PIONEER 8** Add-on to insulin (Insulin ± MET)	**PIONEER 5** Renal impairment (± MET, ± SU or ± insulin) **PIONEER 6** CVOT (Standard or care)

Figure 5. Overview of PIONEER Program.

SGLT2i = Sodium-glucose cotransporter-2 inhibitor; MET = Metformin; DPP-4i = Dipeptidyl peptidase 4 inhibitor; OAD = Oral antidiabetic drug; SU = Sulfonylurea; GLP-1RA = Glucagon-like peptide-1 receptor agonist; TZD = Thiazolidinedione; CVOT = Cardiovascular outcome trial.

The population included were people aged ≥18 years, subjects diagnosed with type 2 diabetes at least 90 days prior to screening, HbA1c 7% to 10.5%. Stable treatment with background medication was allowed. Patients with proliferative retinopathy with acute treatment, multiple endocrine neoplastic syndrome, medullary thyroid carcinoma, history of acute and chronic pancreatitis, history of major stomach surgery, major CV event within 180 days, history of malignant neoplasm in last 5 years, were excluded from the study. The primary endpoint was change in HbA1c from baseline (PIONEER 1-5 and 8), time to first 3P major adverse cardiovascular event or MACE (PIONEER 6), and proportion of patients achieving HbA1c <7.0% (PIONEER 7). Secondary confirmatory endpoints were change in body weight from baseline (PIONEER 1-5, 7-8) and time of first expanded composite CV endpoint (PIONEER 6). Summary of PIONEER Program has been mentioned in Table 1.

In the CVOT trial (PIONEER 6), the population included was at least 50 years of age with one CV event in the past or at least 60 years with one established CV risk factor. There were two arms – one placebo and other 14 mg oral semaglutide. There were a total of 3,183 patients, randomized 1:1 into the two arms. Primary endpoint

Table 1. The PIONEER Program

Trial (N randomized)	Background regimen/ trial duration/time of primary endpoint	Mean baseline characteristics	Treatment arms	Reduction in HbA1c (%)
PIONEER 1 (N = 703)	Diet and exercise/26 weeks/week 26	**Age: 55 years** HbA1c: 8.0% Diabetes duration: 3.5 years Body weight: 88.1 kg BMI: 31.8 kg/m^2 eGFR: 98 mL/min/1.73 m^2	Oral semaglutide 3 mg (n = 175) Oral semaglutide 7 mg (n = 175) Oral semaglutide 14 mg (n = 175) Placebo (n = 178)	0.8 1.3 1.5 0.1
PIONEER 2 (N = 822)	MET/52 weeks/week 26	**Age: 58 years** HbA1c: 8.1% Diabetes duration: 7.4 years Body weight: 91.6 kg BMI: 32.8 kg/m^2 eGFR: 95 mL/min/1.73 m^2	Oral semaglutide 14 mg (n = 411) Empagliflozin 25 mg (n = 410)	1.3 0.8
PIONEER 3 (N = 1,864)	MET ± SU/78 weeks/ week 26	**Age: 58 years** HbA1c: 8.3% Diabetes duration: 8.6 years Body weight: 91.2 kg BMI: 32.5 kg/m^2 eGFR: 95-96 mL/min/1.73 m^2	Oral semaglutide 3 mg (n = 466) Oral semaglutide 7 mg (n = 465) Oral semaglutide 14 mg (n = 465) Sitagliptin 100 mg (n = 467)	0.3 0.7 1.1 0.4
PIONEER 4 (N = 711)	Stable dose of metformin ± SGLT2i for ≥90 days	**Age: 56 years** HbA1c: 8.0% Diabetes duration: 7.6 years Body weight: 94 kg BMI: 33 kg/m^2 eGFR: 95-96 mL/min/1.73 m^2	Oral semaglutide 14 mg (n = 285) Liraglutide 1.8 mg s/c (n = 284) Placebo (n = 142)	1.3 1.1 0.1
PIONEER 5 (N = 324)	MET ± SU, SU alone or insulin ± MET ≥90 days	**Age: 70 years** HbA1c: 8.0% Diabetes duration: 14 years Body weight: 91 kg BMI: 33 kg/m^2 eGFR: 30-59 mL/min/1.73 m^2	Oral semaglutide 14 mg (n = 163) Placebo (n = 161)	1.1 0.1
PIONEER 7 (N = 504)	1-2 of: MET, SU, TZD, SGLT2i/52 weeks/ week 52	**Age: 57 years** HbA1c: 8.3% Diabetes duration: 8.8 years Body weight: 88.6 kg BMI: 31.5 kg/m^2 eGFR: 95-97 mL/min/1.73 m^2	Oral semaglutide (flexible 3, 7, or 14 mg) (n = 253) Sitagliptin 100 mg (n = 251)	1.4 0.7
PIONEER 8 (N = 731)	Metformin or no metformin; basal, basal-bolus or premixed insulin/52 weeks/26 weeks	**Age: 61 years** HbA1c: 8.2% Diabetes duration: 15 years Body weight: 85.9 kg BMI: 31 kg/m^2 eGFR: 92 mL/min per 1.73 m^2	Oral semaglutide 3 mg (n = 184) Oral semaglutide 7 mg (n = 182) Oral semaglutide 14 mg (n = 181) Placebo (n = 184)	0.6 1 1.4 0

HbA1c = Glycated hemoglobin; BMI = Body mass index; eGFR: Estimated glomerular filtration rate; MET = Metformin; SU = Sulfonylurea; TZD = Thiazolidinedione; SGLT2i = Sodium-glucose cotransporter-2 inhibitor.

Change in body weight (Kg)	HbA1c <7.0% (%)	Body weight loss ≥5% (%)	Nausea
1.70	59		8
2.50	72		5
4.10	80	42	16
1.50	34	16	6
4.70	72	47	20
3.80	47	42	3
1.90	33		7
2.70	50		13
3.50	52	35	15
1.10	39	14	7
5.00	69	50	20
3.10	63	26	18
1.10	18	12	7
3.70	64	40	19
1.10	21	10	7.5
2.90	63		20.9
0.80	28		2.4
1.30	36	12	11
3.00	47	31	17
4.10	64	41	23
0.6 (gained)	10	2.5	7

was time to first occurrence of 3P MACE. It was an event-based study to prove noninferiority of oral semaglutide. There was 21% relative risk reduction (RRR) in 3P MACE, 51% RRR in CV mortality and 49% RRR in all-cause mortality.

Safety

Across the trial, up to 80% to 85% of subjects tolerated the treatment with the highest dose of oral semaglutide, i.e., 14 mg. The most common system involved was the gastrointestinal tract, and the most common side effect was mild-to-moderate nausea, which was transient in nature.

To tackle nausea, an apt counseling from the healthcare professionals will help. Inform the patients that the nausea can be transient, advise them to have small frequent meals, avoid fried food, take large quantity fibrous food in a single meal, avoid alcohol and cigarettes and drink cold water and to stop eating at first sign of fullness. In case of severe symptoms, they must report to the treating physician.

Patient management strategy for nausea is pause-play-escalate. Stop the drug if a patient in having severe nausea; once it settles, restart the treatment. If the gap is more than 21 days, start with 3 mg dose.

USE OF PEPTIDE IN A PILL – INDIAN PERSPECTIVE

Where can We Place Oral Semaglutide – First-line, Second-line and Third-line

According to the European Society of Cardiology guidelines for diabetes management, GLP-1RA should be started as monotherapy among those drug naïve patients who have established CV risk factor or CV event in the past.[36]

According to the American Diabetes Association (ADA) guideline, in drug naïve patients after lifestyle modification and diet management, GLP-RA should be added to metformin in the presence of CV risk factors or established ASCVD.

GLP-1RAs are also recommended if metformin treatment fails as second-line drug; it can also be added as an add-on therapy to insulin.[11]

Oral semaglutide was found to be superior to empaglifozin, sitagliptin and liraglutide in reducing HbA1c and weight at the end of the trial. It is cardio-safe and well-tolerated. Its efficacy is established early and late in the treatment journey, irrespective of renal and hepatic impairment and no dose adjustment is needed in the elderly.

India is the sixth country to get approval for its commercial use. It is indicated for the management of type 2 diabetes mellitus as monotherapy when metformin is contraindicated or not tolerated, and as a combination therapy with other OADs, in special populations like renal and hepatic impairment patients.

CONCLUSION

Oral semaglutide, the first peptide in a pill is the newest innovation in the managemet of diabetes. GLP-1RA as a class are now recommended to be used as first-line management in drug naïve patients with established CV risk factors, as second-line therapy when metformin fails or is not tolerated and also as third-line when second-line management fails. Oral semaglutide has shown promising data that can help occupy a prominent position in future guidelines.

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Moderna Seeks EUA for a Second COVID Booster for All Above 18 Years

Recently, Moderna announced that it had requested the US FDA for emergency authorization for a second booster shot of its COVID-19 vaccine for all adults above 18 years of age, who had been given an initial booster shot of any of the approved COVID vaccines.

The request was based partly on recent data from the United States and Israel about how effective was the Moderna shot against the Omicron variant.

Previously, Pfizer-BioNTech had also requested emergency approval for a second booster shot, for adults aged 65 and older, which was also based on two Israeli studies which showed enhanced immunogenicity and lower rates of infections and severe illness with an additional booster.

The first study showed that people aged 60 and older who received an additional booster dose had 2 times lower rates of confirmed infections and 4 times lower rates of severe disease.

The second study, which included Israeli healthcare workers aged 18 and above, showed significantly high levels of antibodies among those who received the second booster dose compared to those who did not.

Recent studies showed that while the third dose of an mRNA vaccine increased the antibody levels higher than the initial doses, the second booster dose (or the fourth dose) would return the individuals' levels to that same highly-elevated level. (*ET Healthworld – AFP, March 18, 2022*)

CASE REPORT

Pheochromocytoma: The Great Masquerader

UTSAV SAHU

ABSTRACT

Catecholamine-secreting tumors occur with equal frequency in men and women, primarily in the fourth and fifth decades. The associated hypertension may be sustained or paroxysmal, and patients who are diagnosed in the presymptomatic stage may have normal blood pressure. These tumors can be lethal unless they are diagnosed early and treated appropriately. Numerous disorders can mimic pheochromocytoma, leading to diagnostic dilemma. Described here is a case which was misdiagnosed for 5 years as anxiety, panic attacks, cervical spondylosis, vasomotor symptoms of menopause, arrhythmia and even acute coronary syndrome. Therefore, enhanced adrenal awareness is the need of the hour, to catch this "great masquerade".

Keywords: Pheochromocytoma, diagnostic dilemma, metanephrines

Both pheochromocytomas and paragangliomas are rare tumors of the sympathetic nervous system. Pheochromocytomas originate from the adrenal medulla and secrete epinephrine as well as norepinephrine. Paragangliomas, or extra-adrenal pheochromocytomas, tend to originate from sympathetic paraganglia and usually show metastasis. Tumoral secretion of norepinephrine causes hypertension. Excessive epinephrine causes tachyarrhythmias. These tumors may be seen in one or both adrenals or anywhere along the sympathetic nervous chain. These tumors can be lethal and cause death in at least a third of the patients before even being diagnosed.

Catastrophic hypertensive crisis and fatal cardiac arrhythmias can occur spontaneously or may be triggered by needle biopsy or manipulation of the mass, vaginal delivery, trauma, anesthesia or surgery (both unrelated to the tumor or for its removal). Exercise, bending, lifting, defecation or emotional stress can trigger paroxysms. Certain drugs can precipitate attacks, such as decongestants, amphetamines, cocaine, epinephrine, corticosteroids, fluoxetine, metoclopramide, caffeine, nicotine and ionic intravenous contrast. Described here is a case which was misdiagnosed for 5 years as anxiety, panic attacks, cervical spondylosis, etc.

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CASE REPORT

A 55-year-old normotensive female, with no significant past medical history, presented with recurrent episodes of dizziness, palpitations, paresthesia and chest pain radiating to left arm since last 5 years. The patient reported that she noticed these spells mostly while sitting on the toilet seat and during long distance traveling. The spells used to last for 1 to 2 minutes. She had visited many clinicians and was treated for anxiety, panic attacks, cervical spondylosis, vasomotor symptoms of menopause, arrhythmia and even acute coronary syndrome.

Despite her treatment, the spells persisted and her pulse and blood pressure (BP) were always found normal during and after a spell, except for an isolated home BP reading of 180/90 mmHg. Generally, the patient appeared comfortable. The system examination was benign. Her complete blood count, blood sugar, kidney functions, thyroid profile, Holter and echocardiography were normal.

A 24-hour urinary fractionated metanephrines and normetanephrines of 966 μg and 4371 μg, respectively, clinched the diagnosis. 68-Gallium (^{68}Ga)-DOTATOC-PET (position emission tomography) scan detected a mass lesion of about 5 × 6 cm (Fig. 1), with internal necrosis abutting the right adrenal gland, with no local or distant metastasis. Diagnosis of right adrenal pheochromocytoma was made. She was started on low-dose α-blocker. A β-blocker was later added before surgery. The mass was surgically removed 1 week later.

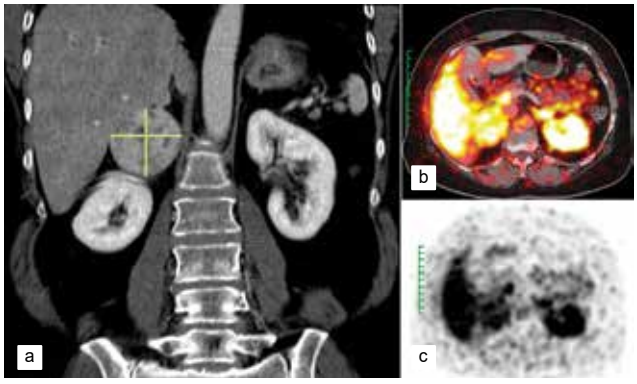

Figure 1. Right adrenal pheochromocytoma (*marked in green*) as seen in **a)** CT image, **b)** PET image and **c)** PET DOTATOC image.

DISCUSSION

Numerous disorders can cause signs and symptoms that may prompt the clinician to test for pheochromocytoma. Around 58% of the patients can have episodic nonspecific spells. Other symptoms may include anxiety, weakness/fatigue, dyspnea, tremors, sweating, dizziness, chest pain, abdominal pain or constipation. Epinephrine secretion by an adrenal pheochromocytoma can cause episodic tachyarrhythmias, orthostatic hypotension or even syncope. Due to its variable clinical presentation, pheochromocytomas have been called "the great masquerader".

Certain conditions mimic pheochromocytoma, such as thyrotoxicosis, labile essential hypertension, myocarditis, acute coronary syndrome, arrhythmia, eclampsia, acute intermittent porphyria, hypogonadal vascular instability (hot flushes), anxiety attacks, cocaine or amphetamine use, and clonidine withdrawal. Patients taking nonselective monoamine oxidase (MAO) inhibitor antidepressants can have hypertensive crisis after eating foods that contain tyramine. Renal artery stenosis can cause severe hypertension and may coexist with pheochromocytoma.

Urinary fractionated metanephrines effectively confirm most pheochromocytomas that were detected by elevated plasma fractionated free metanephrines. Urinary assay for total metanephrines is about 97% sensitive for detecting functioning pheochromocytomas. Plasma fractionated free metanephrines can be elevated in sleep apnea or with stressful illness.

No single imaging modality is 100% sensitive for pheochromocytoma or paraganglioma. PET imaging gives crisper imaging than scintigraphy. ^{68}Ga-DOTATOC-PET scanning is the most sensitive scan, detecting about 90% of pheochromocytomas, paragangliomas and metastases. At the time of symptom-based detection, pheochromocytomas have an average diameter of 4.5 cm.

Patients must receive adequate treatment for hypertension and tachyarrhythmias prior to surgery for pheochromocytoma/paraganglioma. Patients are advised to measure their BP daily and immediately during paroxysms. Alpha-blockers or calcium channel blockers are used, either alone or in combination. BP must be controlled prior to introducing cardioselective β-blockers for control of tachyarrhythmias.

Surgical removal of pheochromocytomas or abdominal paragangliomas is the treatment of choice. For surgery, a team approach—endocrinologist, anesthesiologist and surgeon—is critical. Laparoscopic surgery is preferred, but large and invasive tumors require open laparotomy. Prior to surgery, BP control should be maintained for a minimum of 4 to 7 days or until optimal cardiac status is established. Patients must be very closely monitored during surgery to promptly detect sudden changes in BP or cardiac arrhythmias.

CONCLUSION

Pheochromocytoma is often called "10% tumor" because 10% are bilateral, malignant, extra-adrenal, multiple, familial and occur in children. Pheochromocytoma is one of the causes of hypertension that can be surgically managed. While it is the cause of hypertension in only 0.4% of the hypertensive patients, prompt identification is essential, as it won't just help with the management of hypertension but will also help avert the potentially life-threatening effects of the tumor.

Increasing awareness about disorders of the adrenal gland is vital. It is the first step in creating change and helps people understand the disease, encourages those with symptoms to undergo testing, and makes the emergency medical providers aware of the severity of adrenal crisis.

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70% of Long COVID Patients Suffered from Memory, Concentration Problems

Preliminary data from the COVID and Cognition Study, published in *Frontiers in Aging Neuroscience*, showed that 7 out of 10 long COVID patients experienced concentration and memory problems months after the infection.

The study included 181 long COVID patients, among which 78% complained of having difficulty in concentration, 69% reported brain fog, 68% reported forgetfulness and 60% were unable to find the right word while speaking. These results were compared with similar people who never were infected with SARS-CoV-2.

About 50% of people with long COVID said their symptoms were not being considered seriously and around 75% of those with severe ongoing symptoms complained about their inability to do work for long periods. A cluster of symptoms, including fatigue, chest pain, body pains, headache and limb weakness during the acute illness predicted cognitive symptoms and performance on memory-test up to 6 months later. (*MedPage Today, March 18, 2022*)

CDS Emerges as a New Tool to Reduce CV Risk in Patients with Serious Mental Illness

A study published in *JAMA Network Open* revealed the effectiveness of a clinical decision support (CDS) system that could be implemented in primary care to reduce the cardiovascular (CV) risk factors which are common in patients with serious mental illness (SMI).

It further stressed the fact that early primary care intervention for adults with SMI was highly essential as CV disease was a leading cause for shortening their life spans compared to those without an SMI.

The cluster-randomized clinical trial included 42 intervention clinics and 34 control clinics, which enrolled a total of 8,937 patients with SMI (4,922 women [55.1%]; mean [SD] age, 48.4 [13.5] years). The intervention included a CDS system, which is a technology-based intervention that provided patient-specific information that helped to assess the modifiable CV risk factors and provide personalized treatment recommendations.

A 4% reduction was seen in the rate of increase in total modifiable CV risk over 12 months among intervention patients relative to control patients (relative rate ratio [RR], 0.96; 95% CI, 0.94-0.98). The intervention favored patients aged 18 to 29 years (RR, 0.89; 95% CI, 0.81-0.98) or 50 to 59 years (RR, 0.93; 95% CI, 0.90-0.96), Blacks (RR, 0.93; 95% CI, 0.88-0.98) or Whites (RR, 0.96; 95% CI, 0.94-0.98). Men (RR, 0.96; 95% CI, 0.94-0.99) and women (RR, 0.95; 95% CI, 0.92-0.97) and patients with any SMI subtype (bipolar disorder: RR, 0.96; 95% CI, 0.94-0.99; schizoaffective disorder: RR, 0.94; 95% CI, 0.90-0.98; schizophrenia: RR, 0.92; 95% CI, 0.85-0.99) also attained the benefits of the intervention.

Lead author Rebecca Rossom concluded that such interventions would help clinicians to detect CV risk for patients with serious mental illness early and provide a better treatment option. Differences were observed in the intervention effectiveness by race and ethnicity. (*Medscape Medical News, March 18; JAMA Network Open, March 7, 2022*)

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BRIEF COMMUNICATION

Vacuum Devices for Treating Postpartum Hemorrhage: Indian Innovation, Indian Pride

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ABSTRACT

Postpartum hemorrhage (PPH) is a major cause of maternal morbidity and mortality. We focus on two innovations by Indian gynecologists, the Panicker's vacuum suction cannula and the SR suction cannula. These effective devices are economical and easy-to-use, and help prevent and manage PPH. They can also be used to reduce bleeding in non-PPH indications. These Indian innovations are a matter of pride, and need to be studied extensively in diverse settings. This will help ensure that their benefits can be shared across the world.

Keywords: Atonic PPH, blood loss, India, LSCS, PPH, vaginal delivery

Postpartum hemorrhage (PPH) is a major cause of maternal morbidity and mortality.[1] This is especially true in developing countries, where maternal health resources may be limited. Many of the known risk factors for PPH, such as prolonged labor, anemia and delayed operative intervention, are more common in such settings. The greatest risk is conferred by prior PPH due to any cause, placenta previa, placental abruption, uterine rupture and multiple gestation. Newer risk factors including hypertension, diabetes and ethnicity are also emerging.[2]

Even though there is significant interest in the diagnosis and treatment of PPH, current management strategies leave much to be desired. Uterine massage, oxytocin and methylergonovine are the standard of care, along with hemostatic drugs.[3] In some cases, these do not prove sufficient hemostasis and invasive interventions such as internal iliac artery ligation and hysterectomy may be required. However, there is no concordance between various national guidelines[4] and more effort is required to develop effective means of management.

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IMPACT OF PPH

PPH is associated with a significant impact on maternal health, as well as on the healthcare system and healthcare costs.[1] This impact worsens as the hemorrhage continues. It is rational, therefore, to develop means of preventing, limiting and managing PPH in a time-bound and cost-effective manner. Researchers across the world have proposed novel ways of diagnosing and stratifying PPH, as well as limiting it.[5,6] Many of these methods and devices require technology, which is either inaccessible or unaffordable to persons working in resource-limited healthcare system. In such a situation, Indian innovations, the vacuum suction hemostatic devices, stand out as an efficient and extremely cost-effective method of preventing and managing PPH.

INNOVATION 1

Panicker[7] proposed that creating negative pressure within the uterine cavity, using a cannula made of stainless steel or plastic, results in stoppage of bleeding from the postpartum uterus in women with atonic PPH and abnormal uterine bleeding (AUB). He inserted a 25 cm long cannula, 12 mm in diameter, with multiple holes of 4 mm diameter over the distal 10 cm of the cannula, into the uterus, through the vagina, to reach the fundus (Fig. 1). He connected the cannula to a suction apparatus to produce and maintain negative pressure of 700 mm mercury. This approach was tried in 55 women (40 post-normal vaginal deliveries and 15 post-lower segment cesarean sections [LSCS]) who experienced PPH refractory to uterotonic drugs used as standard of care.[7]

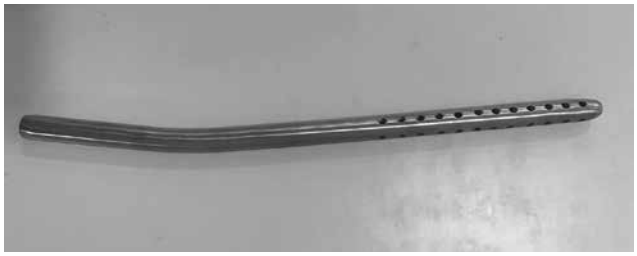

Figure 1.

Panicker reported his findings and highlighted the need to ensure accurate placement and care of the cannula, as well as to manage cervical and vaginal tears and lacerations concomitantly. The author also mentioned the limitations of the cannula, stating that it is effective only in managing uterine sources of bleeding. He suggested an improvisation in case a suction machine is not available, proposing the use of a mechanical suction unit of ventouse or manual vacuum aspiration (MVA) syringe.

INNOVATION 2

The Uterine Vacuum Retraction System, developed by HS Ram[8] uses the SR suction cannula to control PPH after vaginal delivery. Vacuum retraction is created by negative pressure within the uterine cavity, using a cannula made of stainless steel, various lengths of cannulae are available (Fig. 2). The appropriate model, based upon size of uterus and mode of delivery, is inserted in the uterus, through the vagina, to reach the fundus. The cannula is connected to a suction apparatus to produce and maintain negative pressure of 650 mm mercury for 15 minutes.

The SR suction cannula was used to manage atonic PPH in an observational study. The bleeding stopped within 3 minutes in 60 women (50%); in 38 women (31.7%) bleeding cessation occurred between 3 to 4 minutes and in 22 women (18.3%) it took 4 minutes for the bleeding to stop. In 75 (62.5%) women, negative pressure was applied only once, in 20 (16.7%) it was applied twice, while in 25 women (20.8%) the negative pressure had to be applied three times to stop the bleeding. Blood collected in bottle after SR Cannula Application ranged from 100 to 150 mL.[9]

These innovations have been tried in multiple patients at our hospitals, and we attest to the efficacy and efficiency of these economical tools (personal experience).

INTROSPECTION

It is surprising; however, to see minimal research published on Paniker's PPH cannula and SR vacuum suction cannula. Is this because these innovations are from resource-challenged medical care settings, and not from established "research" centers? Is it because these devices display their maximum benefit in peripheral centers, which do not have a "voice" in publications? Is it because the obstetricians who use these cannulae are so busy with their clinical work that they neglect publishing their data?

Figure 2.

INSIGHT

Whatever the reason, we should celebrate Indian innovations with pride, rather than with prejudice.[10] These innovative ideas deserve a fair chance, and must be studied in controlled settings, to assess their efficacy, safety and tolerability. The Indian vacuum devices are supported by experience and by eminence.

We suggest a pragmatic method of placing these devices in clinical practice (Table 1). The cannulae can be used for primary, secondary as well as tertiary prevention of atonic PPH, after both vaginal delivery and LSCS. Application of cannula helps clear the field of vaginal bleeding for better assessment and ease of stitching. As the cervical walls get apposed to the cannula, bleeding from cervical tear reduces and cervical stitching can be done in comfortable and clean environment.

We have used these devices in non-PPH indications as well. Small size cannulae can be used in endometrial

Table 1. Usage of PPH Vacuum Suction Devices

Clinical usage

- Primary prevention: Prophylactic insertion when risk factors are present
- Secondary prevention: Insertion of device when excessive PPH is anticipated, e.g., rise in shock index
- Tertiary prevention: Curative insertion if bleeding is excessive

Caveats

- Check patency of cannula holes
- Check placement of tip of cannula at tip of fundus
- Check degree and duration of negative pressure

Check points

- Hemodynamic monitoring
- Local monitoring of cannula

Concerns

- Does not address cervical/vaginal bleed
- Does not obviate need for good obstetric and nursing care

polyp removal, scar ectopic and post-abortal heavy bleeding. Once backed by robust published evidence, these economical interventions will certainly find utility in maternity centers across the world, and serve to improve maternal health.

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■■■■

Awake Prone Positioning Benefited Select COVID Patients

A meta-analysis reported in *Lancet Respiratory Medicine* stated that the awake prone positioning reduced the need for intubation in selected patients with severe COVID-19. The meta-analysis included data from a 2021 meta-trial with a total of more than 1,000 COVID-19 patients, mostly in ICU, which found awake prone positioning to decrease the need for intubation. It also included data from 7 randomized controlled trials (RCTs) which did not find a difference in intubation risk among almost 700 patients on conventional oxygen therapy. A total of 29 studies were included in the review, with 10 RCTs (1,985 patients) and 19 observational studies (2,669 patients). In 10 RCTs, awake prone positioning significantly reduced the need for intubation in the overall population, compared to supine position, especially among those patients who received advanced respiratory support at enrollment (relative risk [RR] 0.83 [0.71-0.97]) and those in the ICU (RR 0.83 [0.71-0.97]). No reduction was seen in patients receiving conventional oxygen therapy (RR 0.87 [0.45-1.69]) or in non-ICU settings (RR 0.88 [0.44-1.76]).

The study concluded that awake prone positioning should be encouraged among COVID-19 patients with acute hypoxemic respiratory failure, especially when the patients are in ICU and need advanced respiratory support. (*MedPage Today, March 17; Lancet Respiratory Medicine, March 16, 2022*)

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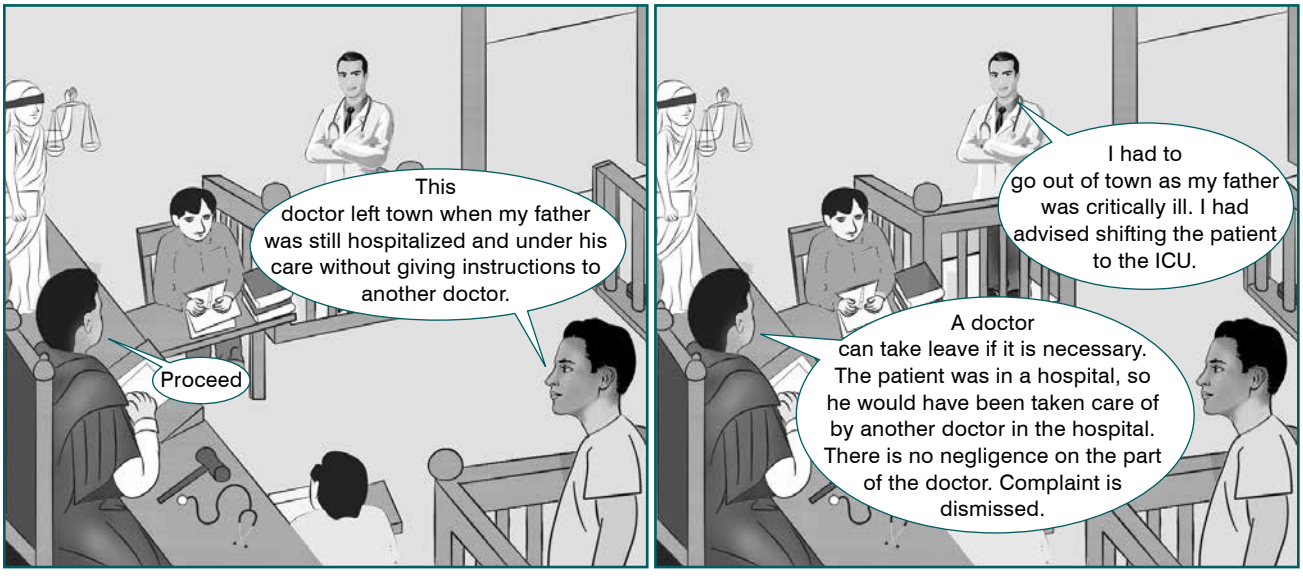
A Doctor, Like Any Other Professional, can Take Leave if Felt Necessary by Him



Lesson: In a judgement, the NCDRC said, "A doctor, like any other professional can take leave if felt necessary by him on account of his personal reasons or otherwise. If that happens it is for the hospital in which the patient is admitted to make alternative arrangement for the treatment of the patient in the hospital… the patient was admitted in a hospital and not in the clinic of Dr…, who could not have been expected to remain with the patient or in the hospital 24 hours of the day. Like other normal human being he also needs to take rest and his meals and then get ready for the duty to be performed on the next day." *Shri Manishbhai Kantilal Joshi vs Sheth P. T. Surat General Hospital, Surat, National Consumer Disputes Redressal Commission, New Delhi, Consumer Case No. 366 of 2014, dated: 09 Feb 2016.*

COURSE OF EVENTS

- 19.11.2012: The patient, an 86-year-old man was hospitalized in Hospital X (*hereby referred to as Opposite Party No. 1*). He was admitted another doctor, but was later put under the treatment of Dr 'A' (*hereby referred to as Opposite Party No. 2*), a chest physician.
- 20.11.2012: The patient was under the care of Dr 'B' (*hereby referred to as Opposite Party No. 3*), after Dr 'A' had retired for the day.
- 21.11.2012: The patient died at about 2.30 am while on ventilator in the ICU.

COMPLAINANT ALLEGATIONS

The son of the patient (*hereby referred to as complainant*) filed a complaint of negligence in the treatment of his father before the National Consumer Disputes Redressal Commission (NCDRC) seeking compensation of Rs. 2 crores along with cost of litigation quantified at Rs. 50,000/-.

- Dr 'A' had left for outstation when the deceased was still admitted in the hospital and was under his treatment.
- Dr 'A' left without giving the instructions to Dr 'B'.
- Dr 'B' was not a qualified specialist in the relevant field.

SOME SALIENT COURT OBSERVATIONS

- Dr 'A' (OP 2) stated that the patient had chronic end-stage respiratory disease, severe chronic obstructive pulmonary disease, fibrotic lung lesion and bronchiectasis. Though the patient had been admitted under another doctor, he had also been treating the patient since last few months as an outpatient.

- The patient had been on nebuliser and home oxygen therapy for 6 months prior to his death. His advanced age ruled him out as a good lung transplant candidate and so steroid treatment was started.
- Dr 'A' (OP 2) planned to leave on 20.11.2012 as his father had taken critically ill in the evening on the same day. He therefore advised that the patient be moved from the ward to the intensive care unit (ICU), where the patient was first put on noninvasive ventilation, and then shifted to invasive ventilatory support on account of the worsening condition after taking the consent from the complainant. The patient's condition was informed to the family members before taking the consent.
- Dr 'A' (OP 2) last saw the patient on 20.11.2012 around 8 pm. "*It is stated in the reply that the patient was duly taken care of treating his treatment in the hospital and there was absolutely no negligence in the said treatment.*" In his reply, Dr 'A' (OP 2) said that the patient succumbed to long existing chronic end-stage respiratory disease.
- In their statement, both Dr 'B' (OP 3) and Hospital X (OP 1) have concurred with Dr 'A' (OP 2) and stated that "*the patient was admitted with past history of Bilateral Centrilobulor Emphysema in the form of Hyperinflated lung with flattening of lobes, Minimal subpleural opacity in the right upper lobe suggest fibrotic/old granulomatous lesion, Atherosclerotic aortic changes and degenerative spinal changes along with Rounding of Trachea and filling defect in upper trachea.*" And that the patient had been treated as per the standard protocol by Dr 'A' (OP 2) "*but the patient succumbed to the chronic disease despite adequate treatment given to him.*" They also said that Dr 'B' (OP 3) is "*a qualified doctor, who was employed on regular basis with the OP 1.*"

COURT OPINION

- The Commission found no merit in the allegation that Dr 'A' (OP 2) had left "*without giving proper instructions*" to Dr 'B' (OP 3) about the treatment of the patient.
- There was no evidence to support the complainant's allegation that Dr 'A' (OP 2) had left town on 20.11.12. The medical records also corroborate the statement by Dr 'A' (OP 2) that he had last seen the patient at 8 pm on 20.11.12. "*Be that as it may, even if we proceed on the assumption that Dr 'A' had taken leave and left for outstation on 20.11.2012 that by itself does not make out any negligence on his part in the treatment of the patient.*"

  "*A doctor, like any other professional can take leave if felt necessary by him on account of his personal reasons or otherwise. If that happens it is for the hospital in which the patient is admitted to make alternative arrangement for the treatment of the patient in the hospital. We have to keep in mind that the patient was admitted in a hospital and not in the clinic of Dr ... Therefore, in the absence of Dr … the patient was to be treated by some other doctor available in the hospital or called by the hospital* from outside. No case of negligence *on the part of the Dr … is therefore made out even if we assume that he had left for outstation on 20.11.2012.*"
- In response to the complainant's allegation that Dr 'A' had left without giving instructions to Dr 'B', the Commission observed that the patient records maintained by the hospital include all relevant information of the patient such as clinical history, treatment administered. Any "*suitably qualified doctor attending the patient*" could manage the patient in the absence of the previous doctor. Hence, "*no such briefing would be necessary*".
- "*So long as the doctor treating the patient in the absence of the previous doctor is a competent doctor he should have no difficulty in treating the patient on the basis of the record prepared in the hospital.*" And Dr 'B' (OP 3) has not stated that "*he was handicapped in any manner in the treatment of the patient on account of having not been adequately briefed*" by Dr 'A' (OP 2). The Commission did not accept the complainant's contention that the leave taken by Dr 'A' (OP 2) was responsible for his father's death.
- Dr 'B' (OP 3) could manage the patient as he had an MD degree and "*it is not as if only a super specialist in chest related disease can treat such a patient.*" The Commission observed: "*A doctor, who has done Post Graduation in Medicine, in our opinion, is fully competent to treat the patient. In fact, in almost all the hospitals, Senior Doctors normally retire for the day in the evening/night and it is only Junior Doctor such as Junior Residents and Senior Residents who remain on duty. The consultant is called if necessary, depending upon the condition of the patient.*" Hence, the commission disregarded the allegation that Dr 'B' (OP 3) was not qualified enough to treat the father of the complainant in the absence of Dr 'A' (OP 2).
- Dr 'A' (OP 2) had last seen the patient on 20.11.2012 at about 8 pm. The patient died at about 2.30 am on 21.11.2012 i.e., "*within a span of 6 ½ hours*" after he had left the hospital.

FINAL JUDGEMENT

The Commission ruled in favour of Dr 'A' (OP 2) and said that "*he could not have been expected to remain with the patient or in the hospital 24 hours of the day. Like other normal human being he also needs to take rest and his meals and then get ready for the duty to be performed on the next day.*" As there was no evidence of any negligence on the part of Dr 'A' (OP 2) in leaving the hospital and the patient being treated by Dr 'B' (OP 3) in his absence, the Commission dismissed the allegations of the complainant with no order as to costs.

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1. Shri Manishbhai Kantilal Joshi vs Sheth P. T. Surat General Hospital, Surat, National Consumer Disputes Redressal Commission, New Delhi, Consumer Case No. 366 of 2014, Hon'ble Mr. Justice V.K. Jain, Presiding Member and Hon'ble Dr. B.C. Gupta, Member, Dated: 09 Feb 2016.

■■■■

Over 25% Rise in Alcohol-related Deaths in the US in First Year of Pandemic

According to research published in the *Journal of the American Medical Association*, there was an increase of 25.5% in the number of deaths related to alcohol in the US between 2019 and 2020. A total of 78,927 alcohol-related deaths were reported in 2019, while 99,017 were reported in 2020, including accidents that happened due to driving after drinking. Alcohol-related deaths accounted for 2.8% of all deaths in 2019 and 3% in 2020.

Researchers state that such behavior was common owing to the increased stress levels due to the adversities of the pandemic. An increase of 16.6% was seen in deaths caused by any reason during this period but alcohol-related deaths surpassed other causes. Data from the CDC showed that January 2021 was the month with the highest number of alcohol-related deaths for the period from January 2019 to June 2021. The jump in alcohol-related deaths was seen across all age groups, with the age group between 35 and 44 years accounting for about 40% increase. Moreover, women exceeded the list.

The scenario was highly concerning and people needed counseling to cope with their stress levels in a healthy way. (*CNN, March 18, 2022*)

Booster Dose of Covishield after two Doses of Covaxin Boosts Antibodies Sixfold: Study

The preliminary scientific evidence submitted by the Christian Medical College (CMC), Vellore, to the Drugs Controller General of India (DCGI) suggested that a booster dose of Covishield after two doses of Covaxin enhanced the immunity 6 times. But, satisfactory data was not available for administering Covaxin as a precaution dose after two doses of Covishield. The study conducted by CMC, Vellore is the first Indian evidence stating the impact of mixing of vaccines on COVID. The study was approved by the DCGI in September 2021. Reports stated that the National Technical Advisory Group on Immunisation (NTAGI) would take the decision on administering a different vaccine as the third dose based on the final data.

Meanwhile, various other studies are being conducted which are studying the effects of mixing Corbevax, Covavax and Biotech's intranasal vaccine. (*ET Healthworld – TOI; March 18, 2022*)

Marinus Pharma's Lead Drug Approved by FDA to Treat Genetic Disorder

Recently Marinus Pharmaceuticals Inc's drug 'Ztalmy' received approval from the US FDA for the treatment of seizures linked with a rare genetic disorder. The drug has been approved for use in patients 2 years of age and older.

The oral drug is indicated for seizures associated with CDKL5 deficiency disorder, a rare form of genetic epilepsy. The regulatory approval was based on a late-stage study that included 101 patients. It showed a mean reduction of 30.7% in 28-day major motor seizure frequency in the drug-treated group compared to the placebo group.

Chief Executive Officer Scott Braunstein said that the drug would cost around $133,000 per patient per year at the wholesale level and the discounted amount would be $105,000 per patient per year, including for Medicaid patients. It was expected to be available in the US commercially in July. (*ET Heathworld – Reuters, March 19, 2022*)

HCFI Dr KK Aggarwal Research Fund

Minutes of an International Weekly Meeting on COVID-19 Held by HCFI Dr KK Aggarwal Research Fund

Topic: Heart surgery – Operating the critically ill, era of COVID

Speaker: Prof Dr Sujay Shad, *Co-Chairman Cardiac Surgery, Sr Consultant Cardiac Surgeon, Director-Heart-Lung Transplant, Sir Ganga Ram Hospital, New Delhi*

- When coronavirus disease 2019 (COVID-19) surfaced 2 years back, it came as a surprise as we did not have a clue as to how to manage the evolving situation. While the harsh lockdown in the initial phase of the pandemic provided an opportunity to sort out masks and personal protective equipments (PPEs), hospitals more or less came to a standstill at that time.
- Papers on myocardial injury in patients who survived COVID were published. There was a panic that even people who did not have apparent cardiac illness are suffering from some myocardial damage due to fibrosis visible on magnetic resonance imaging (MRI).
- Cardiac surgery was also reduced partly because of the lockdown and partly because of the rest and relaxation, stress which precipitated myocardial infarction (MI) also reduced.
- Mechanisms for myocardial injury in COVID-19 include direct angiotensin-converting enzyme (ACE)-mediated viral damage, exaggerated immune response causing hypoxic injury, microthrombosis and systemic inflammatory injury.
- The hyperinflammatory response phase was followed by recovery phase in the majority. Lung damage was important in the initial phase.
- There were multiple issues along the cardio-pulmonary axis. On MRI, there were pulmonary infiltrates/effusion and respiratory failure in suspected acute COVID-19 myocarditis. There was some left ventricle dysfunction, stress-induced cardiomyopathy, which could have contributed to the failing lungs. Diffuse myocardial edema on T2-weighted scans and hyperemia as early gadolinium enhancement was also seen. Overtime, there was lot of fibrosis in the form of necrosis/scar identified with late gadolinium enhancement.
- Emergency cases like aortic dissection, hemo-dynamic instability or patients whose symptoms are worsening underwent surgery, but there were lot of problems in these patients. The most important problem in these patients was persistent hypoxia postoperatively and persistent vasoplegic syndrome after the surgery.
- Elective work like valve repair for asymptomatic valvular disease was stopped completely and postponed if the patient stayed comfortable.
- Semi-elective patients were turned into elective wherever possible. Some patients underwent stenting to bypass the bypass surgery.
- A persistent requirement of vasoconstrictors and inotropes in substantial doses was observed in COVID patients, which lasted for as many as 5 days. This was seen even in patients who had mild COVID-19.
- It is important to understand the reasons for postponing cardiac surgery. The average mortality in patients with an active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ranged from 20% to 41%. The incidence of myocardial injury has been reported to be more than 25% of critically ill COVID patients.
- Nasal swabs or antibody tests for seroconversion were used to determine COVID status. In inconclusive cases, cycle threshold (Ct) value was used. Surgery could reasonably be done in asymptomatic patients with high Ct value. Patients with C-reactive protein (CRP) 5 times above normal could be operated. But surgeries in patients with very high CRP levels were postponed.
- Various postoperative complications included increased ventilator assistance time, length of intensive care unit (ICU) stay, atelectasis, pulmonary edema, gastrointestinal (GI) dysfunction, acute renal injury, coagulation disorders, atrial arrhythmia, etc.
- At 1 year, patients who were not hospitalized tended to do much better than those who were hospitalized. Cerebrovascular disorders, dysrhythmias, and other cardiac disorders such as heart failure, ischemic cardiomyopathy, cardiac arrest, cardiogenic shock, pulmonary embolism (PE), deep vein thrombosis (DVT) and superficial vein thrombosis occurred in these patients.

- The alpha wave could be side stepped because of the lockdown, but the Delta wave hit really hard. Majority of extracorporeal membrane oxygenation (ECMO) that took place in India were during the Delta wave.
- Some centers recommended ECMO early for patients who went from high-flow nasal oxygen (HFNO) to ventilators, while some patients were directly shifted to ECMO without going through the ventilator.
- This was also the time when there was shortage of hospital/ICU beds, oxygen including hospital staff. The mortality with ECMO therapy in the best of centers was 37% to 60%. In India, only 10% to 15% of patients on ECMO could be salvaged.

COVID-19 update

Speaker: Dr Monica Vasudev, *Allergist & Clinical Immunologist, Fellow of American Academy of Asthma, Allergy and Immunology, Advocate-Aurora Health, Wisconsin, USA*

- Global deaths have crossed 6 million. We are seeing a long tail of the pandemic and we cannot let down our guard.
- Surveillance of waste water in the US has shown that there was an increase in the amount of virus shedding in the first 2 weeks of March. More than one-third of places monitoring this showed a rising COVID-19 trend.
- There is still a need to continue to reinforce the benefits of immunization.
- Moderna and Pfizer have requested authorization from the Food and Drug Administration (FDA) for second boosters of their COVID vaccines. These requests were partly based on data from Israel, after the emergence of Omicron variant that showed a second booster dose reduces the infection rates as well as severe illness.
- A study in *JAMA Neurology* has reported that cognitive impairment was more common in older COVID patients aged ≥60 years, especially those with severe illness after discharge from hospitals vs. their uninfected peers.
- Children have low levels of antibodies. They have similar symptoms and levels of virus, but they seem to be able to clear the virus from their bodies much quicker than adults due to a more robust initial immune response. Its to be seen how well children are protected against future infections.
- About 1.6 billion children globally have been affected by the closure of schools due to the pandemic. Children in the low- and middle-income countries have been disproportionately affected as their schools tended to be shut for longer and they were less able to access remote learning.
- According to UN Education expert, Robert Jenkins, "we are running the risk of a lost generation… Without urgent action, many countries could end up without the skilled workers they need for future development."

Hong Kong update

Speaker: Dr Alvin Yee-Shing Chan, *Treasurer-CMAAO*

- The situation is not so good in Hong Kong. The current wave is the fifth wave.
- About 91.5% population is vaccinated with the first dose and nearly 82% are vaccinated with the second dose. So, about 19% of population has not yet received the second dose.
- There is high infection rate and mortality rate right now especially in the elderly above 80 years of age; only half of this population is vaccinated. Even in ≥70 years age group, less than 80% are vaccinated.
- There are around 200 deaths in a day, most of them are in the elderly and immunocompromised. The mortality rate is 0.5%.
- Fifty-six percent of young children (3-11 age group) are vaccinated with the first dose and 8% have been vaccinated with the second dose.
- It is hoped that 95% of the population would be vaccinated by early April.
- There are not enough isolation or hospital facilities. Daily cases were earlier around 30,000 but in the last 2 days have reduced to 2,000 per day.
- There are hidden cases as it is not mandatory to report the results of self-testing.
- Sewage water is being tested. If positive, then the building is put under lockdown and all residents are tested.
- Paxlovid and molnupiravir are now available in public hospitals and designated COVID clinics, but these are not yet available in the private sector.

Participants – Member National Medical Associations: Dr YehWoei Chong, Singapore, Chair of Council-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer-CMAAO; Dr Marthanda Pillai, India Member World Medical Council, Advisor-CMAAO; Dr Heidi Stensmyren, President, World Medical Association; Dr Ravi Naidu, Malaysia; Dr Mvuyisi Mzukwa, South Africa; Dr Angelique Coetzee, South Africa;

Dr Akhtar Hussain, South Africa; Dr Sonam Tshering, Bhutan; Dr Qaiser Sajjad, Pakistan; Dr Ashraf Nizami, Pakistan; Dr Salma Kundi, Pakistan; Dr Md Jamaluddin Chowdhury, Bangladesh

Invitees: Dr Monica Vasudev; Dr Sujay Shad; Dr Patricia La'Brooyi; Dr Lawrence HB Soh; Dr Khoonhui Yeo; Dr Stephen Chang; Dr Ng Hong Yi; Dr Joshua Lim; Dr Sanjeev Aggarwal; Dr Kuenza Wangmo; Dr Colin Goldberg; Dr Kiran Vinayek; Dr Manisha Kukreja; Dr S Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

HCFI Round Table Expert Zoom Meeting on "Challenges in the Life of a Surgeon During the COVID Era"

Speaker: Prof Dr Ashok Gupta, *Reconstructive Plastic Surgeon, Bombay Hospital Institute of Medical Sciences, Mumbai*

March 12, 2022 (11 am-12 noon)

- The COVID pandemic has resulted in feelings of fear, anger and helplessness among surgeons. It has had an extensive effect on surgeons and patients requiring surgical care.
- It is essential to act thoughtfully and support the hospital surgical care system as well as to protect the benefits of the patients and at the same time conserving the hospital resources and protecting the hospital staff.
- Surgical care requires an interaction between the patient and the surgeon, which cannot be replaced by the telehealth system, which can be implemented effectively in many other specialties of medicine.
- The pandemic has posed several challenges. The financial effects of the surgical shutdown have been far-reaching. Many private surgical practices were forced to shut down or relocate as they could not withstand the financial challenges. Some surgeons have retired early or have left the surgical specialty. These problems influence the surgical workforce during a time when there is likely to be a greater need for surgical care.
- To adapt to a new normal, prepare for a rapidly changing situation, postpone elective operations immediately, develop dedicated operating suites, duration of the surgery, need for ICU care after surgery, need for ventilator during or after surgery, blood loss during surgery, number of surgeons and nurses needed in the OR and whether surgery is being performed in the lower risk group or higher risk group.
- The first fundamental for the surgeon is "is it worth the risk?"
- CovidSurg Collaborative, a global study published in October 2020 has shown that for every person who undergoes surgery during the pandemic, there is one in four chance that they will die and a 50/50 chance that they will suffer severe pulmonary complications. CovidSurg has expanded participation doubling the number of hospitals and tripling the number of countries. Seven hundred thirty-three hospitals across 73 countries and more than 24,000 patients were enrolled.
- Surgeons need guidance on how to deliver surgical services safely and effectively during COVID-19 pandemic. The aim was to identify the key domains that should be considered on developing pandemic preparedness for surgical services.
- Surgeons did not have any information about how COVID affects surgical patients.
- The current study tracked more than 1,100 patients who underwent surgery. About 75% had emergency surgeries and 25% had elective surgeries.
- *The Lancet* shows that patients testing positive for the virus 7 days before and up to 30 days after surgery are at high-risk.
- In a study in the publication "Surgeon voices in COVID-19 era", 1 in 4 patients infected with the virus before or after surgery died. One in every 2 patients contracted serious pulmonary complications such as pneumonia, acute respiratory distress syndrome (ARDS) or unexpected postoperative ventilation. The type of anesthesia used (general, regional, sedation or local) did not alter the outcome. This reminds us that COVID is not only a lung disease; it touches almost all other systems of the body. The biggest shock from this study is that the patient may survive the surgery, but still has a higher risk of developing serious complications or even death compared to before the pandemic.
- Impact of SARS-CoV-2 on postoperative pulmonary complications and mortality needs to be established to enable surgeons to make evidence-based decisions.
- The American College of Surgeons (ACS) has developed triage guidelines for COVID-19, which state that the hospitals and outpatient surgery centers should consider their patients' needs and logistics capability to fulfil in real time.
- The need for a procedure should be established by a surgeon with expertise in the relevant surgical

specialty to determine damages to be sustained by delay in undertaking the surgery.

- Feasibility of procedure be determined by administrative personnel accepting the hospital facility, safety and well-being.
- The risk to the patient should include an aggregate assessment of the real risk of proceeding and the real risk of delay.
- COVID-19 is a clear risk for all. Surgical procedures should be considered not based solely on COVID-associated risks but rather on an assimilation of all available medical and logistical information.
- COVID-19 free zones are a very vital recommended criteria to minimize risk of accidental exposure and must be established within the hospitals to protect patients, opting to undergo elective surgery during the pandemic.
- Hospitals should prepare detailed specific pandemic preparedness plans addressing the identified domains. Specific guidance should be updated continuously to reflect emerging evidence during the COVID pandemic.
- A backlog of procedures after the end of the pandemic is inevitable. Hospitals should plan to report effectively to ensure that patients for elective surgery have the best possible outcomes after the pandemic is over.
- The ACS's Elective Surgery Acuity Scale (ESAS) balances the needs of the patient or impact of a surgical procedure with available resources.
- Planning for resuming surgeries should take into account the perspectives of multiple stakeholders, including surgery, anesthesia, nursing and facility administration.
- Elective procedures should be delayed until the patient is no longer infectious and has recovered fully. The impact of SARS-CoV-2 on postoperative recovery must be understood to inform clinical decision making during and after COVID-19.
- An international, multicenter, cohort study at 235 hospitals in 24 countries reported 30-day high mortality and pulmonary complication rates in patients with preoperative/perioperative infection.
- The American Society of Plastic Surgeons reported that most members stopped performing elective surgeries for an average of 28.1 weeks in 2020 due to COVID-19. For more than 2 years, COVID-19 has largely confined people to their homes and has significantly impacted nearly every aspect of lives.
- Now injectable procedures like Botox, fillers continue to be the most sought-after treatments in 2020-21.
- Safety issues in the OR using N95 masks, face shields, eye protection and double layers of PPE are common practices but add to the hazard for performing long duration surgeries.
- Sometimes patients are so sick that the emergency surgery is performed in the ICU, which is not as sterile as the OR.
- Universal use of smoke evacuators to suction away the smoke plumes generated by electrocautery has been encouraged to minimize the risk of exposure to aerosolized tissue.
- Precautions should be taken for surgical cases of minimally invasive procedures that require the creation of pneumoperitoneum must be safely managed or avoided if possible.
- A patient is always informed about the risks before a surgery.
- Preoperative patients could test negative for COVID even though they are infected (incubation period 2-14 days or the test could be false negative).
- Patients may not be infected, but could contract the virus while at the hospital or within the 30 days postoperatively.
- No system is fool proof.
- Transportation to and from the rooms and the elevator, postoperative room can transmit infection.
- Patients should quarantine for 30 days and not have any contact with anyone even for a minor procedure.
- We have to understand the limitations cause by post-COVID recovery. The risk of pulmonary complications almost double if the surgery is for more than 4 hours.
- Interspecialty and multispecialty assessment of patients is required.
- Consent should be well documented before undertaking any procedure, particularly during the COVID era.
- The surgeon must carefully assess the risk-benefit ratio of a surgery.

Participants: Dr KK Kalra; Dr Ashok Gupta; Prof Arun Jamkar; Dr Anita Chakravarti; Ms Ira Gupta; Dr S Sharma

Moderator: Mr Saurabh Aggarwal

eAPICON 2021

NEED FOR WHITE PAPER ON ADULT IMMUNIZATION IN INDIA

Dr NK Ganguly, New Delhi

- Current scenario in India – No coordinated public health infrastructure to support an adult immunization program as there is for children; Little coordination among healthcare providers in terms of vaccine provision; Despite availability of vaccines, many adults remain unvaccinated because they are unaware of the need for adult vaccines or are misinformed about vaccines and the diseases they are designed to prevent; Considerable controversy exists regarding adult immunization especially in developing countries, like India.
- Barriers and challenges of adult immunization – Lack of recognition of the importance of adult immunization; Lack of recommendation from healthcare providers; Lack of healthcare provider knowledge about adult immunization and recommended vaccines; Misrepresentation/misunderstanding of the risks of vaccine and benefits of disease prevention in adults; Lack of understanding of vaccine safety and efficacy; Missed opportunities for vaccination in healthcare providers' offices, hospitals and nursing homes; Lack of publicly-funded vaccine and reimbursement to vaccine providers; Lack of coordinated immunization programs for adults.
- Need for adult immunization – Vaccination recommended: Prevent vaccine-preventable diseases and their sequel; Primary focus of vaccination programs: Historically directed to childhood immunizations; For adults, chronic diseases have been the primary focus of preventive and medical healthcare; Increased emphasis on preventing infectious diseases; Adult vaccination coverage: low for most of the routinely recommended vaccines; Probability of exposure to infectious agents: increased manifold, owing to globalization and increasing travel opportunities both within and across countries; Urgent need to address the problem of adult immunization.
- Mission of white paper – Making adult immunization a public health issue in India to improve patient outcome in adults in India.

ADULT IMMUNIZATION IN INDIA – CHANGING THE IMMUNIZATION PARADIGM

Dr Agam Vora, Mumbai

API Recommendations

- Influenza – An annual dose of quadrivalent vaccine (latest strains recommended) for all adults, especially high risk: for all >65 years, health workers, pregnant women and <65 years with specific chronic medical conditions; 0.5 mL IM injection of inactivated influenza vaccine (IIV); live-attenuated influenza vaccine (LAIV) is not recommended below 2 years; IIV is recommended from 6 months onwards.
- Typhoid – TCV is preferred at all ages because of its improved immunological properties and expected longer duration of protection; TCV 0.5 mL IM single dose; a booster may be given after 3 years; TCV can be given from 6 months onwards, either with IIV at 6 months or with measles, mumps and rubella (MMR) at 9 months; booster dose may be given after 3 years; When Vi-polysaccharide (ViPS) is used, a single dose of the ViPS vaccine should be administered IM or SC from 2 years of age; revaccination is recommended every 3 years for ViPS; Immunocompromised persons, including those with HIV, should receive TCV or ViPS vaccine.
- Hepatitis B – A single dose (20 μg) administered IM in deltoid muscle recommended in adults (chronic kidney disease [CKD] schedule change) in individuals at high risk (especially medical students and students attending allied health courses); Recommended schedule – 0, 1 and 6 months in those who were not immunized in childhood or if anti-HBs <20; Revaccination is recommended every 5 years.
- Human papillomavirus infection – 0.5 mL IM injection of quadrivalent vaccine is recommended in young adults; For 15 to 26 years, three doses of quadrivalent vaccine; Current Government of India recommends vaccination in 9 to 13 years girls in school.
- *Haemophilus influenzae* type b (Hib) infection – 0.5 mL IM injection is recommended in individuals at risk; Single dose of Hib is recommended in individuals at high-risk in those who were not

previously immunized as well as those who were previously immunized; The vaccine recommended is polyribose phosphate, or outer membrane protein and the carrier is tetanus toxoid conjugate or diphtheria CRM protein.

- Pneumococcal infections – Vaccination is recommended for all, especially high-risk individuals; For individuals till 65 years, PCV13 is recommended in series with PPSV23; 0.5 mL IM injection of PCV13-conjugate vaccine or PPSV23-polysaccharide vaccine in those who were previously not immunized; Single dose of PCV13 and 2 doses of PPSV23, duration between two doses is 2 and 6 months and a booster is given after 5 years; PCV13 followed by PPSV23 at an interval of 2-6 months and repeated after 5 years with PPSV23 in individuals >65 years of age; In immunocompromised patients, PCV13 followed by PPSV23 at 6 to 12 months interval, booster dose of PPSV23 for >65 years after 1 year.
- Measles, mumps and rubella – Recommended in adults (26-55 years) but contraindicated in pregnancy, individuals above 65 years, and immuno-compromised states; 0.5 mL of 2 doses (within a gap of 28 days) of the live vaccine administered subcutaneously is recommended in those who were not previously immunized; Recommended in medical students before joining classes (18-24 years), after assessing titer levels of the vaccine.
- Shingles – Recommended in individuals over the age of 60 years; 0.5 mL IM injection administered in deltoid; Two doses 4 to 8 weeks apart.
- Japanese encephalitis – Inactivated vero cell-derived vaccine, 2 doses at a gap of 4 weeks, starting the primary series at ≥6 months of age in endemic settings; Live-attenuated vaccine single dose given at ≥8 months of age; Live recombinant vaccine single dose given at ≥9 months of age; Inactivated JE vaccine can be given to immunocompromised persons including HIV-infected individuals; Healthcare workers at high-risk in endemic regions should be administered vaccines; Migrants to JE endemic area should be vaccinated.
- Cholera – Recommended in regions with endemic cholera, during cholera outbreaks, and in a humanitarian crisis; vaccines should be used along with other cholera prevention and control strategies; whole-cell recombinant B-subunit (WC-rBS) vaccine is recommended in 2 doses to children aged ≥6 years and adults, with an interval of 1 to 6 weeks between the doses; WC vaccines are recommended in 2 doses administered 14 days apart to individuals aged ≥1 year; Oral cholera vaccine should be considered in healthcare workers involved in emergency and relief duties and those who have an increased probability to be directly exposed to cholera patients or contaminated food or water, especially in areas with poor access to healthcare facilities.
- Yellow fever – Single dose of yellow fever vaccine is adequate to offer sustained lifelong protective immunity; Booster dose is not necessary; Preventive mass vaccination campaigns are recommended for individuals living in areas at risk of yellow fever where there is low vaccination coverage; Vaccination should be given to everyone aged ≥9 months in any area with reported cases.
- Chicken pox – Recommended in those who did not have chicken pox; 2 doses of 0.5 mL attenuated live VZV (Oka strain) vaccine in deltoid area administered subcutaneously; In those who did not receive immunization in childhood, two doses are administered 4 to 8 weeks apart.
- Diphtheria, pertussis and tetanus – Tdap (0.5 mL) injection given IM and then Td given once in 10 years; 0.5 mL IM injection of Td given in 3 doses; 2 doses administered 4 weeks apart, 3rd dose 6 to 12 months after second dose. It is recommended between ages 18 and 64 years. Booster dose of Td vaccine is given once every 10 years till the age of 65 years; Earlier Td was used; however, after 2005, Tdap is given for all three diseases.
- Meningococcal infections – 0.5 mL SC injection given in 2 doses 1 month apart; Recommended for high-risk travelers, outbreaks and mass gatherings; In previously immunized people, a single dose is given. In those who were not previously immunized, 2 doses in those aged <16 years and a single dose in those aged >16 years.

■■■■

News and Views

Functional Small Airway Disease in Patients with Long COVID

Functional small airway disease with air trapping may explain the persistence of respiratory symptoms in patients with long COVID, suggests a new study published in the journal *Radiology*.[1]

This prospective single center study recruited 100 COVID-19 adult patients who had symptoms more than a month after their initial diagnosis and were attending the post-acute sequelae of COVID-19 (PASC) between June and December 2020; 100 matched healthy participants, nonsmokers with no past history of cardiac or lung disease, were selected between March and August 2018 to act as controls.

Based on the level of care administered during the acute infection, the patients were categorized as ambulatory (67%), hospitalized (17%) or those requiring intensive care (16%). Compared to the ambulatory group, hospitalized or ICU patients were likely to be older; 44 vs. 64 vs. 60 years, respectively. Seventy-six percent of patients with post-COVID symptoms had at least one comorbid condition; of these 59 were obese, 27 were hypertensive, 26 had asthma, 6 had chronic obstructive pulmonary disease (COPD), while 4 had interstitial lung disease. Hospitalized patients were also more likely to be current or past smokers than the ambulatory patients; 53% vs. 15%, respectively.

Patients underwent quantitative CT analysis using supervised machine-learning to estimate the regional ground-glass opacities (GGOs); air trapping was assessed via inspiratory and expiratory image-matching. The findings on CT were compared with the controls.

Analysis shows air trapping (58%) to be the most common feature on qualitative analysis of chest CT and GGOs were present in 51% of patients. The total lung affected by air trapping was 25.4% among ambulatory patients, 34.6% in hospitalized patients, 27.3% in those requiring intensive care, while it was detected in only 7.2% of controls. Air trapping persisted beyond 200 days in 8 of 9 participants who underwent imaging. Regional GGOs were present in 13.2% of hospitalized patients, 28.7% of those admitted to ICU, 3.7% of ambulatory patients and just 0.06% in healthy controls. A correlation between air trapping and ratio of residual volume to total lung capacity was noted. None of the study participants had obstruction in airways on spirometry.

This study has shown high prevalence of air trapping in patients who had recovered from acute COVID-19 but continued to have symptoms post-COVID. The severity of infection did not affect the percentage of lung affected by air trapping. Since no airflow obstruction was noted in any patient, the authors suggest that air trapping does not involve large airways; instead, small airways, which are noncartilaginous airways with an internal diameter <2 mm, are affected. Any pathology affecting small airways is usually not detected on spirometry until more than 75% of them are involved. Spirometry may often miss air trapping, which can be detected using inspiratory and expiratory CT imaging and plethysmography. Further long-term studies are required to study the course of functional small airway disease in these patients.

***Reference*:** [1]Cho JL, et al. Quantitative chest CT assessment of small airways disease in post-acute SARS-CoV-2 infection. *Radiology.* 2022 March 15:12170.

Pfizer-BioNTech Seek EUA for Second Booster for 65 *plus*

On 15th March, Pfizer Inc and BioNTech SE applied for emergency use authorization (EUA) with US regulators for a second booster dose of their COVID-19 vaccine for people aged 65 years and above. The companies said that a much lower rate of confirmed infections and severe disease was seen in an analysis of data from over a million adults, aged 60 years and older, who received an additional booster dose of the vaccine at least 4 months after the third dose compared to those who were given just one booster shot. The data also suggested that a fourth dose led to a considerable improvement in protection against the Omicron variant compared to the third dose after 3-to-6 months.

The submission to the US Food and Drug Administration (FDA) included data from Israel, where a second booster shot is authorized for many people over age 18 years. In late January, based on health ministry data, Israel said that a fourth dose enhanced the protection against infection 2 times, and 3-5 times against severe disease, compared to people who had received three shots. Pfizer was now designing its study on around 600 people to evaluate the efficacy of the fourth dose. (*Reuters, March 16, 2022*)

Viral Clearance in COVID Patients: Potential Role of Povidone-iodine Gargle

As the third wave of COVID-19, largely fuelled by the Omicron variant of coronavirus, shows a decline in the country, the weekly cases for the week from February 21 to 27 witnessed a drop to below the 1-lakh mark.[1]

Even though the current wave shows signs of ebbing, this is no time to be complacent. Infected people can continue to spread the virus through respiratory droplets via sneezing or coughing, and infect others. People can even get infected through contaminated surfaces.[2]

Therefore, taking adequate precautions and practicing COVID-appropriate behavior still remain key approaches to contain the spread of COVID-19. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load is high in the nasopharynx, saliva and throat.[2] Additionally, angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 cell receptor, has been shown to be expressed on the oral mucosa and the epithelial cells of the tongue.[3]

Considering all this, maintaining optimum oral hygiene and reducing the viral load in the body's reservoirs with high viral load becomes important to limit transmission. Gargling with a virucidal solution appears to be a potential intervention to attain viral clearance. Povidone-iodine (PVP-I) is a broad-spectrum antimicrobial agent which also has virucidal properties.[4]

Reports have shown that PVP-I can block the attachment of SARS-CoV-2 to oral and nasopharyngeal tissues. It can also reduce the viral particles in saliva and respiratory droplets.[4] A randomized, four-arm study by Mohamed et al sought to determine the potential of regular gargling in eliminating SARS-CoV-2 in the oropharynx and nasopharynx.[2] The investigators looked at the effects of gargling 3 times a day for 30 seconds, using PVP-I, essential oils and tap water, on viral clearance among COVID-19 patients. Five Stage 1 COVID-19 patients (asymptomatic state during the first 2 days of infection) were included in each group. Investigators noted that in the PVP-I group, SARS-CoV-2 was not detected in any of the participants on Day 4, Day 6 and Day 12. Among participants in the essential oils group, there were 4 negative samples and 1 either positive or indeterminate result all through Day 4, Day 6 and Day 12. In the tap water group, 2 samples were negative and the other 3 were either positive or indeterminate on Day 4, Day 6 and Day 12. Among participants in the control group, one sample was negative on Day 4 and Day 12; other samples yielded either positive or indeterminate result. Viral clearance was attained in 100%, 80%, 20% and 0% of the patients in PVP-I, essential oils, tap water and control group, respectively. There was high viral clearance rate for PVP-I as early as 4 days following the intervention. The study thus showed that regular gargling with PVP-I could achieve early viral clearance among Stage 1 patients.

Use of PVP-I gargle or mouthrinse could thus play a vital role in limiting transmission of SARS-CoV-2 and help contain the spread of COVID-19.

References: [1]Weekly Covid cases fall below 1 lakh, lower than tally in 1st wk of 3rd wave. Available from: https://health.economictimes.indiatimes.com/news/industry/weekly-covid-cases-fall-below-1-lakh-lower-than-tally-in-1st-wk-of-3rd-wave/89881284. Accessed February 28, 2022. [2]Mohamed NA, Baharom N, Sulaiman WSW, et al. Early viral clearance among COVID-19 patients when gargling with povidone-iodine and essential oils - A clinical trial. Available from: https://www.medrxiv.org/content/10.1101/2020.09.07.20180448v1.full.pdf. Accessed February 28, 2022. [3]Elzein R, Abdel-Sater F, Fakhreddine S, et al. In vivo evaluation of the virucidal efficacy of chlorhexidine and povidone-iodine mouthwashes against salivary SARS-CoV-2. A randomized-controlled clinical trial. *J Evid Based Dent Pract*. 2021;21(3):101584. [4]Chopra A, Sivaraman K, Radhakrishnan R, et al. Can povidone iodine gargle/mouthrinse inactivate SARS-CoV-2 and decrease the risk of nosocomial and community transmission during the COVID-19 pandemic? An evidence-based update. *Jpn Dent Sci Rev.* 2021;57:39-45.

Post-COVID Changes in Cognition, EEG Seen up to 10 Months

A study published in the *Journal of Neurology* stated that interrelated cognitive, electroencephalography (EEG), magnetic resonance imaging (MRI) abnormalities were observed among COVID-19 survivors 2 months after discharge from the hospital. Some disturbances persisted for as long as 10 months. In patients admitted to the emergency department (ED) with COVID-19, who underwent follow-up neuropsychological assessment and an EEG, over half of them had cognitive disturbances affecting memory and attention after 2 months of discharge.

After 10 months of follow-up, a significant improvement was seen in the cognitive impairment, but some cognitive deficits and disturbances in mood persisted in slightly more than one-third of the patients. A partial improvement was seen in the EEG findings, which showed a slowing of cortical activity.

The researchers also stated that more studies were needed to confirm whether these alterations were directly linked with the infection itself or with its related consequences and if these alterations could be completely reversible or were part of a neurodegenerative process.

EEG alterations could be a useful tool to assess early cerebral involvement in COVID-19. (*Medscape, March 15, 2022*)

Government States More Than 656 Tons of Biomedical Waste was Generated Daily During COVID

On 15th March, the Parliament was informed that around 656 tons per day (TPD) of biomedical waste was generated across the country in 2020, of which 590 TPD was collected and treated by common biomedical waste treatment facilities.

Minister of State for Environment, Ashwini Kumar Choubey, further added that there was a generation of about 84.61 TPD of incremental COVID-19 biomedical waste from May 2020 to February 2022 from different healthcare, quarantine, sample collection and home isolation centers and labs, involved in diagnosis, treatment and quarantine of COVID patients. He further added that the Central Pollution Control Board (CPCB) had issued guidelines for proper management of the COVID-waste and had developed an application, COVID19BWM, to track the generation and treatment of the COVID waste in the treatment facilities.

No cases of violation of the CPCB guidelines were reported, but notices had been issued to 33 facilities across the country for not reporting data on COVID19BWM. Currently, the data from State Pollution Control Boards/ Pollution Control Committees (SPCBs/PCCs) for 2020 stated that 208 common biomedical waste treatment facilities were operating in the country. Nine states/Union Territories had no such facility, so captive treatment facilities operated by the healthcare facilities themselves were treating and disposing of the biomedical waste in these areas. (*ET Healthworld – IANS, March 15, 2022*)

Could Genes be Linked with Oral Health?

A study conducted by the American Dental Association has stated that genetic factors were involved in about 60% of cases of tooth decay. Diseases such as oral cancer, gum disease, misaligned teeth or genetic oral abnormalities could all be attributed to genetic factors.

Another study has shown that poor oral hygiene was responsible for the increase in gum-disease bacteria and incidences of oral microbiome aging. A study from the Chinese Academy of Sciences revealed a sharp decline in the good oral bacteria and the beneficial anti-inflammatory chemicals within 24 to 72 hours of disruption in maintenance of adequate oral hygiene. It was also observed that patients with periodontitis showed an increase in the 'bad bacteria', which lead to tooth damage or loss.

The good news is that oral health issues could be easily prevented. Two minutes of daily brushing and maintaining proper hydration were important for healthy teeth and body. Dr Mohender Narula, Dental expert and Co-founder, MyDentalPlan Healthcare, said that diseases like gingivitis can be transferred genetically and call for extra attention if there is positive family history. (*ET Healthworld – IANS, March 15, 2022*)

Preventive Health Checkups Increased Twofold among Women During Pandemic

The life expectancy of Indians has increased from 42.27 years in 1960 to 69.66 years in 2019, with women outliving men. But, it must be noted that around 17.4 and 3.5 per 100 women aged 15 to 49 years suffer from at least one morbidity and multi-morbidity, respectively, with the most common morbidities being hypertension, diabetes and thyroid disorders.

Home diagnostics has become a good option and encouraged women across India to take the preventive health screenings and tests, necessary for the prevention of several chronic ailments, reported *Healthians*.

A report from the Gurugram-based health tech startup stated that there was a rise of 234% between the start and the end of the second pandemic wave in preventive health checkups among women. The trend was maintained at 202% growth between January 2021 and 2022. Several factors, such as sedentary lifestyle, unhealthy eating habits, rise in obesity and stress levels and nuclear families, have increased the risks of chronic ailments like diabetes and thyroid problems in women. This is in line with a 244% increase in diabetes tests and a 213% increase in thyroid profile conducted between January 2021 and 2022. A rise of 189% was observed in tests for vitamin B12 and vitamin D profiles.

Deepak Sahni, CEO and Founder, Healthians, said that the pandemic has taught us the importance of health and wellness in our lives and to take preventive measures as lifestyle disorders could account for around 74% of total deaths by 2030. (*ET HealthWorld, March 16, 2022*)

■■■■

Why Do We Place Our Hands Over the Flame?

Flame is the "flame" of true knowledge. At the end of any aarti, we place our hands over the flame and then touch our eyes and the top of the head. It means "May the light that illuminated the Lord light up my vision; may my vision be divine and my thoughts noble and beautiful."

The metaphysical implication of aarti extends further. The sun, moon, stars, lightning and fire are the natural sources of light. The Lord is the source of these wondrous phenomena of the universe. It is due to Him alone that everything exists.

As we light up the Lord with the flame of the aarti, we turn our attention to the very source of all light which symbolizes knowledge and life. Also, the Sun is the presiding deity of the intellect, the moon, that of the mind, and fire, that of speech. The Lord is the supreme consciousness that illuminates all of them. Without Him, the intellect cannot think, the mind cannot feel and the tongue cannot speak. The Lord is beyond the mind, intellect and speech.

How can these finite entities illuminate the Lord? Therefore, as we perform the aarti we *chant*:

> *Na tatra suryo bhaati na chandra taarakam, Nemaa vidyuto bhaanti kutoyamagnib*
>
> *Tameva bhaantam anubhaati sarvam, Tasya bhasa sarvam idam vibhaati*

"He is there where the sun does not shine, nor the moon, stars and lightning. Then what to talk of this small flame (in my hand), everything (in the universe) shines only after the Lord, and by His light alone are we all illumined."

In our spiritual journey, even as we serve the Guru and Society, we should willingly sacrifice ourselves and all we have, to spread the "perfume" of love to all.

We often wait a long while to see the illuminated Lord. But, when the aarti is actually performed, our eyes close automatically as if to look within. This is to signify that each of us is a temple of the Lord.

■■■■

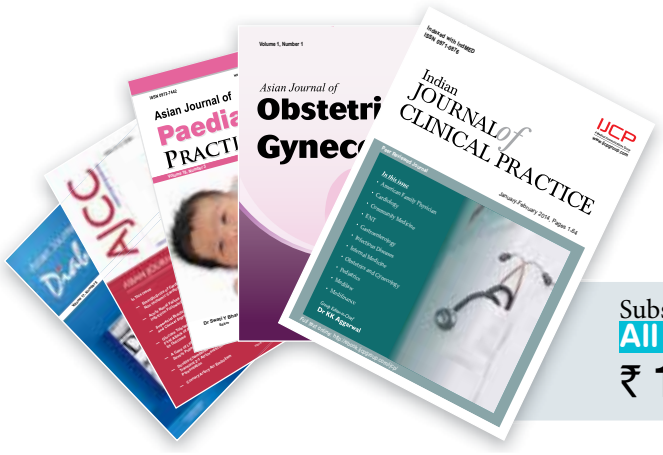
Studies Reveal Omicron Survives Longer on Some Surfaces

Two recent studies report that the Omicron variant of the coronavirus survived at least twice as long on surfaces like plastic, paper and skin compared to the original Wuhan strain. Infections were more likely to occur by inhaling the virus as increased stability helped the Omicron variant survive longer in the air, making it more contagious.

In the first study, researchers in Japan collected and grew all the major coronavirus variants of concern in cells in a lab, concentrating and purifying them and finally spreading them on squares of plastic and skin from human cadavers in warm air at about 77°. It was observed that the Omicron survived on the plastic surface for 193 hours, which was approximately 8 days after it was spread, which was much higher than other variants. While on the skin, the Omicron could be detected even after 21 hours.

In the second study, researchers in Hong Kong spread samples of the original strain and the Omicron variant on squares of stainless steel, plastic, glass and paper. The Omicron variant was detected even after 7 days on those surfaces and longer on tissue and printer papers. This study was done for the BA.1 strain of Omicron and not the newer BA.2.

Hence, experts are of the view that hand hygiene and disinfection of contaminated surfaces are very important. Omicron seems to be stronger than earlier variants and hence proper ventilation, including air filtration, was necessary along with frequent hand washing with soap and water which prevents the virus from entering the body from contaminated surfaces. (*CNN, March 18, 2022*)



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Lighter Side of Medicine

INSPIRATIONAL STORY

EMOTIONAL MANAGEMENT

When someone is doing something or is about to do something, in a way we don't want it to be done and when we are not able to accept it, we become angry.

However, when someone is doing something or is about to do something, in a way we don't want it to be done – and we are able to accept it – we remain tolerant.

When someone has something which we don't have, or someone is able to produce the results which we are not able to produce – and we are not able to accept it – we become jealous. When someone has something which we don't have, or someone is able to produce the results which we are not able to produce and we are able to accept it – we get inspired.

Then emotional equation is quite simple.

Something + Acceptance = Positive Emotion

Something + Nonacceptance = Negative Emotion

So, it is not 'something' or 'someone' who makes us feel positive or negative, but it is our 'acceptance' or 'nonacceptance' of something or someone, which makes us feel positive or negative.

It isn't the world but the quality of our response to the world that determines the quality of our emotions. Next time we feel disturbed with a negative emotion, instead of asking who or what is disturbing us, we should examine who or what we are resisting (not accepting) that is causing this disturbance in us. If we replace resistance (nonacceptance) with acceptance, the negative emotion will turn into a positive one.

Emotional management begins by stopping to blame that 'something' or 'someone' and starting to take the responsibility to respond life with 'acceptance'

HUMOR

I CHARGE YOU FOR OVERLOADING

A man driving home late at night in his Volkswagen beetle car was stopped by policemen on patrol. The police asked the man to produce his car document. When they could not fault the document, the next question to the man was: "My friend, do you realize that you committed a criminal offence by driving alone in this car at late night?"

The man became angry and responded: "How could you say that? God the father, the son and holy spirit, Prophet Elijah and Angels Micheal and Gabriel are all with me in the car."

The policeman replied: "You mean, all these people are in this small car? I charge you for overloading!"

WHAT IT MEANS

Five-years-old Becky answered the door when the Census taker came by.

She told the Census taker that her daddy was a doctor and wasn't home, because he was performing an appendectomy.

"My," said the census taker, "that sure is a big word for such a little girl. Do you know what it means?"

"Sure! Fifteen hundred bucks and that doesn't even include the anesthesiologist!"

Dr. Good and Dr. Bad

SITUATION: An individual who had concomitant T2DM and CVD presented with poor cognitive performance.

LESSON: The researchers have demonstrated a link between insulin resistance and subsequent poor cognitive performance and greater cognitive decline in patients with CVD, both with and without diabetes.

J Alzheimers Dis. 2017;57(2):633-43

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- Statistical methods used for presentation and analysis of data i.e., in terms of mean and standard deviation values or percentages and statistical tests such as Student's 't' test, Chi-square test and analysis of variance or non-parametric tests and multivariate techniques.
- Confidence intervals for the measurements should be provided wherever appropriate.

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

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Examples of common forms of references are:

Articles

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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– Two complete sets of glossy prints of high quality should be submitted. The labelling must be clear and neat.

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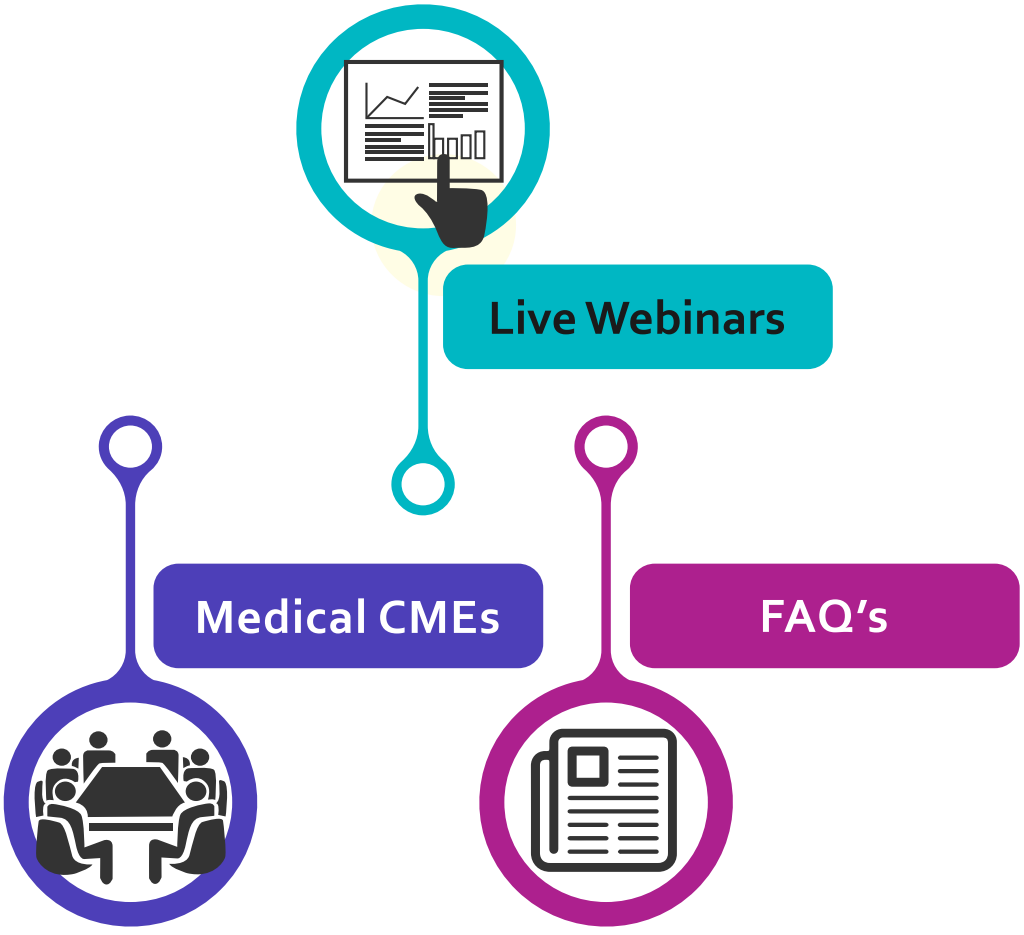

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