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# Contents

## EDITORIAL
1. Drug Revolution in Heart Failure: A Big Step Toward Improving Outcome  
   Prabhash C Manoria ................................................................. 11

## ORIGINAL ARTICLE
2. An Insight into Multisystem Inflammatory Syndrome in Adults Associated with Recent SARS-COV-2 Infection: A Case Series  
   Arun Agarwal, Rekha Jakhar, Ambika Sharma, Aditi Sharma,  
   Aaakanksha Agarwal, Anju Kumari ........................................... 14

3. Swallowing Dysfunction after Acute Stroke: The Incidence, Predictors and Outcome  
   Charulata Londhe, Aashish Agrawal, Sangeeta Pednekar,  
   Dharmendra Pandey, Mohammeddash Neelakanta Khan ........... 21

4. Efficacy and Safety of Directly Acting Antivirals in Patients with Hepatitis C Infection on Hemodialysis  
   Manisha Sahay, Priyashree, Kiranmay Ismal, K Anuradha,  
   Jyoti Lakshmi ................................................................. 25

5. Clinical Profile of Adult Hemophilia Patients with Special Reference to FISH and WFHPE Score: An Observational Cross-sectional Study  
   Minal Shastri, Renuka Vasava, Vaibhavi Pancholi, Vaishnavi M Rathod,  
   Gaurav Mehta, Gayatri Laha, Darshankumar Manubhai Raval .......... 29

6. Knowledge Dissemination for elimination Role of Academic Institutions in Eliminating Viral Hepatitis  
   Tushar Prabhakar, Kanica Kaushal ............................................ 33

7. Nonsmoker COPD represents a clinically Distinct Phenotype: A Prospective Observational Study  
   Richa Rani, Pawan K Singh, Manjunath B Govindagoudar,  
   Tarana Gupta, Parul, Dhruva Chaudhry .................................... 38

8. The Role of Monocyte to High-density Lipoprotein Cholesterol Ratio in Predicting the Severity of Acute Ischemic Stroke and its Association with the NIHSS  
   Deepthi Sharma, Sreedev Aravind, Sony Joseph, Narendra Fagera,  
   Gopikrishnan Rajagopalan .................................................. 43

9. Diabetes in India’s North East Study: Prevailing Insulin Usage and Injection Practices amongst Type 2 Diabetes Mellitus Patients  
   Manash P Baruah, Sonali B Bhuyan, Sanjay Kalra,  
   Mangesh H Tiwaskar ................................................................. 48

## REVIEW ARTICLE
10. ADVANCE to ADVANCE-ON: Unfolding the “Legacy Story” in Diabetes  
    Sanjay Kalra ........................................................................ 58

11. Over 30 Years of Omeprazole  
    Praveen Sharma ...................................................................... 62

12. Expert Recommendations on Optimizing the Diagnosis and Management of Gastroesophageal Reflux Disease Associated with Comorbidities in the Indian Population  
    Harjit Dumra, Rajesh Sainani, Nitesh Pratap, Bhau P Singh,  
    Indranil Halder, Jayesh Shah, Mehal Thakkar, Mohan Kumar V,  
    Nitin Abhyankar, PP Bose, Rutul Gokalani, Vikas Aggarwal,  
    Devashayam J Christopher .................................................. 73

13. A Historical Perspective on Chronic Obstructive Pulmonary Disease: From Past to Present  
    Surya Kant, Ajay Kumar Verma, Anuj Kumar Pandey .............. 79

14. Alternate Biochemical Markers in Organophosphate Poisoning  
    Austin J Mangaly, Chandni Radhakrishnan .............................. 83

## POSITION STATEMENT
15. Simplifying Type 2 DM Care with Linagliptin: A Position Paper  
    Ambrish Mithal, Ambady Ramachandran, Arpande Bhattacharyya,  
    Manoj Chadda, Mala Dharmalingam, Anirban Majumder,  
    Debmalya Sanyal .......................................................... 90

## POINT OF VIEW
16. Show Me the Money: Finance for the Physician  
    Rohit Bansal ................................................................. 97

## CASE REPORT
17. Brucellosis in a Sickle Cell Patient with Hyposplenia  
    Jhasaketan Meher, Nithin MS, Sunil K Behera ...................... 99

## PICTORIAL CME
18. Kidney Biopsy: The Key to Diagnosis of a Systemic Illness  
    Georgi Abraham, Praveen S Raj, Gopinathan Mathiyazhagan,  
    Mily Mathew ................................................................. 101

19. Linezolid-induced Black Discoloration of Tongue  
    Rahul Kumar, Virus Taneja, Pooja Khosla, Manuj Sondhi ............ 102

## MEDICAL PHILATELY
20. Paul Berg and Recombinant DNA  
    JV Pai-Dhunagat ................................................................. 105

## CORRESPONDENCE
    Itta K Chaithanya, Clara Aranka ........................................ 105

22. Remdesivir in the Management of COVID-19! Is there a Way Out of the Predicament?  
    Onkardeep Kaur, Pawan Kumar Singh, Dhruva Chaudhry ............ 105

## ANNOUNCEMENTS
23. Update Mobile Number / Email Id .......................................... 24

24. 1 Year Distance Education Program (Diploma in Allergy & Asthma) 47

25. Going Green ................................................................. 82
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IN21DI00078
Heart failure (HF) is a deadly disease; more people die from it than from acute myocardial infarction (MI). Unlike acute MI, where there is a quick fix in the form of primary angioplasty, no such quick fix exists for the treatment of HF. The human myocyte is not endowed with an endogenous capacity for repair; once dead, it is dead forever. Therefore, HF has a high morbidity and mortality rate; the 5-year mortality rate is to the tune of 50%, a figure higher than most malignant lesions. But with current pharmacotherapy, the mortality rate is likely to decline in the future. HF is akin to malignancy. Once it sets in, it runs a malignant progression and has a high mortality rate, polypharmacy is the rule, and remission and relapses are common. Remission in HF or significant improvement in symptoms should not be taken as freedom from disease because stable HF is a myth. These patients can succumb to sudden cardiac death (SCD) or get admitted with HF without any warning signs because there is always ongoing apoptosis, as evidenced by mild, persistent elevations of serum markers like troponin in the blood. In the context of diabetes, HF is frequent, forgotten, and fatal, and HFpEF is the dominant scenario. But the last couple of years have witnessed a sea change in the management of HF and currently, we have a panoply of drugs to target multiple pathways of HF (Fig. 1).

The four foundational drugs for HF, that is, β-blockers, sodium-glucose cotransporter-2 inhibitor (SGLT2i), sacubitril/valsartan (angiotensin receptor neprilysin inhibitor), and mineralocorticoid receptor antagonists (MRAs), have kicked off a drug revolution in HF that never existed before. All four of these drugs have a class I recommendation, are guideline-directed therapies that produce incremental benefits on top of each other and are poised to improve the outcome of HF with reduced ejection fraction (HFrEF). It is estimated that the projected mean overall survival would increase by 6.3 years if all four foundational drugs were started in patients with HFrEF at the age of 55. Suboptimal guideline-directed medical therapy (GDMT) in India for HF patients is a very important cause of increased all-cause mortality. All four drugs should be initiated early because the 30-day mortality rate for acute decompensated HF is 10% and one out of every four patients hospitalized for HF dies or is rehospitalized within 30 days of discharge. Hospitalization for HF is a serious event in the natural history of the disease because every hospitalization and rehospitalization brings the patient closer to death. Of the four foundational drugs for HFrEF, SGLT2 has the most impressive effect on hospitalization for HF, both in patients with Atherosclerotic cardiovascular disease and in patients with multiple risk factors. In patients with worsening HF, vericiguat is used to decrease hospitalization for HF.

Just as in acute MI to initiate early therapy, we had the dicta of door-to-balloon time, a similar new dictum has emerged for early initiation of therapy in HFrEF, door-to-GDMT time, and door-to-maximum dose GDMT time. So the current trend is to initiate in-hospital quadruple medical therapy on days 1–4 and try to achieve the target dose preferably before discharge but not later than 1–4 weeks.

So powerful is the reverse remodeling effect of the four foundational drugs that the committee members of the third universal definition of HF were forced to create a new subset of improved HFEF that had never existed before. Prior to 2021, HF with preserved EF (HFpEF) was considered an orphan disease, and all trials failed to show a positive outcome. But now we have two positive trials with SGLT2i in HFpEF, that is, the empagliflozin outcome trial in patients with chronic HFpEF Empagliflozin Outcome Trial (Empower) (Fig. 2).

Moreover, sacubitril/valsartan has shown excellent reverse remodeling in the prospective study of biomarkers, symptom improvement, and ventricular remodeling during sacubitril/valsartan therapy for HF (PROVE-HF) trial. It also showed that patients eligible for implantable cardioverter-defibrillator (ICD) with an EF < 35% can be transformed into ICD-ineligible patients by increasing their EF > 35%. In an analysis of 613 patients who had left ventricular (LV) EF < 35% and were eligible for ICD, after 6 months, in 32% of patients, the EF increased >35%, and after 1 year, in 61% of patients, the EF was >35%. Therefore, the new message is to optimize the use of sacubitril/valsartan before...
Drug Revolution in Heart Failure

**Fig. 2:** Showing that SGLT2i can be used across the spectrum of HF irrespective of EF

selecting the patient for ICD implantation for the primary prevention of sudden cardiac death. Some people call sacubitril/valsartan a medical ICD.

What is very exciting is that the use of four foundational drugs is poised to postpone device therapy, that is, ICD, cardiac resynchronization therapy, LV assist device, and even cardiac transplantation. No cardiologist would recommend the implantation of these devices unless all four foundational drugs, in addition to the conventional therapy, have been maximally utilized.

**Sudden Cardiac Death**

Sudden cardiac death (SCD) is more common in mild HF compared to severe HF. In patients with HF, SCD occurs in 64, 59, and 33% of patients with New York Heart Association (NYHA) classes II, III, and IV, respectively. The adverse LV remodeling fibrosis creates a fragile and highly vulnerable subset. Occasionally, there may be an identifiable pathological trigger like ischemia, electrolyte imbalance, catecholamine surges, etc., but usually, there is no acute precipitating mechanism. The drugs for treating HF, like β-blockers, MRAs, and sacubitril/valsartan, have decreased the incidence of SCD.

In an analysis of over 40,000 patients from 12 pivotal HF trials, rates of SCD decreased by 44% over the 20-year period (from mid-1990–2015). This is almost certainly due to advances in HF treatment, as many key guideline-recommended therapies have been developed, including β-blockers, MRAs, and sacubitril/valsartan.

In a meta-analysis of 30 trials that randomized 24,779 patients with HF, β-blockers reduced the risk of SCD by 31%, CV death by 29%, and all-cause mortality by 33%.

Sacubitril/valsartan showed a reduction in SCD by 20% in patients with chronic HF and a 50% decrease in the risk of death in patients with baseline ICD. In a meta-analysis of 11,032 patients recruited in three placebo-controlled randomized trials, MRAs reduced the risk of SCD in 23% of patients with HF and LV systolic dysfunction.

Sodium-glucose cotransporter-2 inhibitors (SGLT2) have no good data on their effect on SCD, although a subgroup analysis from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial has shown a reduction in ventricular arrhythmias.

The guidelines for primary prevention of SCD in HF recommend an ICD to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischemic etiology (unless they have had a MI in the prior 40 days) and an LVEF < 35% despite >3 months of optimal medical therapy, provided their expected survival is >1 year with good functional status (class I). The recommendation of an ICD for the primary prevention of SCD in nonischemic HF is less strong (class IIa).

**New Drugs for Heart Failure**

Besides the four foundational drugs and the other drugs, we have two other new drugs that act on entirely new pathways in HF that have never been targeted. Vericiguat directly stimulates intracellular soluble guanylate cyclase, which stimulates the production of cyclic guanosine monophosphate, which has a protective action on the cardiac myocytes and vasculature. It was tested in the vericiguat global study in subjects with HFrEF (VICTORIA) trial in patients with worsening HF and has shown positive results. The primary composite endpoint of CV death and first HF hospitalization showed a statistically significant reduction of 10%, driven by a decrease in HF hospitalization. The CV death was not affected. The absolute primary event reduction was 4.2/100 patient-years on top of guideline-based care, and the number needed to treat for 1 year is only 24. The drug is administered once daily, does not require monitoring of estimated glomerular filtration rate or potassium levels, and hardly has any side effects. The initial dose is 2.5 mg, and it can be titrated to a maximum dose of 10 mg. The drug is approved for clinical use in India and is commercially available.

Omecamtiv mecarbil, which is a myosin activator, has also shown positive results in the Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in HF trial. There was a statistically significant reduction in the primary endpoints of HF events and CV deaths by 8%, driven mainly by the decrease in HF events. The CV death was not affected. The benefit was generally consistent across most prespecified subgroup analyses; however, there was heterogeneity seen for baseline EF, with a greater treatment effect with LVEF < 28%. The drug is not yet approved by the guidelines and is not available for clinical use. Therefore, we are currently equipped with a panoply of wonderful new drugs that are poised to improve the outcome of HF in the years to come.

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An Insight into Multisystem Inflammatory Syndrome in Adults Associated with Recent SARS-COV-2 Infection: A Case Series

Arun Agarwal1*, Rekha Jakhar2, Ambika Sharma3, Aditi Sharma4, Aakanksha Agarwal5, Anju Kumari6

Received: 31 January 2023; Accepted: 01 April 2023

ABSTRACT


Objective: To report seven cases of MIS-A with evidence of recent COVID-19 infection. This is a case series-based study and presents bona fide experiences in terms of main findings and treatment options.

Materials and methods: It is a retrospective observational study. We retrospectively collected data on all patients who were diagnosed and treated for MIS-A during the period after the second wave of COVID-19 in India, that is, from June 2021 to November 2021 and who were hospitalized in the author’s unit. All patients fulfilled the morbidity and mortality weekly report (MMWR) criteria for multisystem inflammatory syndrome in adults. The presenting symptoms, clinical and laboratory parameters, management, and outcome of these seen cases are discussed in this case series-based review.

Results: Data from seven patients were analyzed. Six of them were male, and one patient was female. The median age was 65 years. Four patients had a history of vaccination for COVID-19; three had a history of COVID-19 symptomatic infection in the past, and one patient had contact with COVID-19 in the previous 12 weeks. None of them tested positive for COVID-19 real-time reverse transcription polymerase chain reaction (RT-PCR) test, and all had positive COVID-19 serology. The commonest extrapulmonary organ involved were the cardiovascular and renal systems, followed by the gastrointestinal and central nervous systems (CNS). All had evidence of hyperinflammation. Intravenous immunoglobulin (IVIg) was used in four patients, and steroids were used in all seven patients. The median length of stay (LOS) was 11 days. One patient succumbed to multiorgan failure.

Conclusions: Multisystem inflammatory syndrome (MIS) can affect children (MIS-C) as well as adults (MIS-A). MIS-A is a serious, life-threatening, hyperinflammatory febrile syndrome associated with recent COVID-19 infection and involves multiple organs like the heart, lungs, kidneys, brain, gastrointestinal organs, skin, eyes etc. Clinical suspicion and testing for evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are needed to identify and treat adults suspected to have MIS-A. This case series demonstrates that even the elderly population can be affected and that administration of IVIg and steroids are effective options in management in addition to the usual “standard of care” treatment. Early recognition and prompt treatment of MIS-A could improve clinical outcomes and reduce the mortality rate.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) disease is predictably unpredictable. Since the identification of the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 7th January 2020, it continues to haunt us even after 3 years. However, by early-April 2021, a major second wave of infection seized India with ruinous effects, and it placed a major burden on the healthcare system. Our tertiary care hospital in North India handled >2,100 cases of COVID-19 during that period. In fact, after the second wave, we all started seeing post-COVID-19 manifestations in varied forms, including organ involvement, febrile inflammatory syndromes, long COVID and other atypical symptoms, etc. Nevertheless, our knowledge also has been constantly evolving, and we need to constantly look into its varied forms and presentations and need to develop targeted treatments.

Kawasaki-like multisystem inflammatory syndrome (MIS), after viral clearance, has been described in children (MIS-C), and since June 2020, similar cases of MIS have been described in adults (MIS-adults (A)) after viral clearance of SARS-CoV-2.1-7 In October 2020, the Centers for Disease Control and Prevention (CDC) introduced MIS-A as a similar illness to MIS-C, seen in adults, but affecting a different age group. The CDC also concluded that inflammatory cytokine storms after SARS-CoV-2 infection can affect all ages. The pathophysiology of both MIS-C and MIS-A is unknown, but it appears to be a hyperinflammatory immune phenomenon similar to Kawasaki syndrome.8

In this case series-based review, we present seven cases of MIS-A and discuss its various features, including demographics, clinical presentation, laboratory parameters, diagnostic criteria, and treatment considerations. Besides reporting these cases, we also feel that there were a large number of such cases that were unrecognized and unreported. The incidence, therefore, remains unknown.

MATERIALS AND METHODS

The present study has been approved by the Institutional Ethics Committee vide letter No. FEHU/IEC/21/016 dated 16th November 2021. It is an observational retrospective study. The aim of this study was to see the incidence, severity, complications and outcomes of patients with MIS-A due to recent COVID-19 infection. In early April 2021, a major second wave of infection took hold in the country with destructive consequences and straining the health care systems. Our tertiary care hospital in North India handled >2,100 cases of COVID-19 during the second wave. However, we started looking at this entity only after it was reported in the literature and were able to identify seven such cases of MIS-A from June 2021 to November 2021.

All patients with clinical suspicion of MIS-A admitted to our medical unit in Fortis Escorts Hospital, Jaipur, were evaluated. Medical records of such patients admitted between 1st June 2021 and 30th November 2021 were reviewed.
dimensional (2D) echocardiography on day 1 of admission. On day 2, he had acute chest pain with electrocardiogram (ECG) changes (Fig. 1) and global hypokinesia with left ventricular ejection fraction (LVEF) 30% on 2D echocardiography. Coronary angiography was done, which was unremarkable. He recovered, and at discharge, his echocardiography showed an LVEF of 50%. P2 had pancreatitis and pericarditis (Figs 2 and 3), P3 had multiple splenic infarcts (Fig. 4), P4 had subacute intestinal obstruction, P5 had spontaneous pneumothorax requiring placement of intercostal drain (Fig. 5), P6 deteriorated 2021 were extracted from the medical records department of our institute. A total of 12 such cases with features of MIS-A were identified. Since the working case definition excludes patients with severe respiratory dysfunction to distinguish MIS-A from severe COVID-19, 5 cases were excluded. Various laboratory parameters, including age, gender, presenting complaints, history of COVID infection or contact with a positive case of COVID-19 in the preceding 12 weeks, COVID-19 vaccination, results of COVID-19 serology and reverse transcription polymerase chain reaction (RT-PCR) test, comorbidities, complications, extrapulmonary organs involved, hematology and biochemistry, imaging features, treatment details, length of stay (LOS), and outcomes were recorded and tabulated.

The detailed profile of these seven cases (P1–P7) is presented in Table 1.

**Results and Findings**

Seven patients of MIS-A were discussed. Six patients were male, and one was female. The median age was 65 years. All of them tested negative for COVID-19 RT-PCR test. Four of them had received at least one dose of COVID-19 vaccination, and three were not vaccinated. P2 had symptomatic COVID-19 disease in November 2020, P3 in October 2020, P4 in May 2021, and P7 in April 2021. P5 had a history of contact with a confirmed COVID-19 case within the preceding 12 weeks. All seven patients tested positive for COVID-19 serology.

As regards other findings, the following patterns were observed:

- **Comorbidities:** Type 2 diabetes mellitus (T2DM), hypertension (HTN), and benign prostate hyperplasia (BPH) were present in two patients. P1 had psoriasiform dermatitis, P2 had chronic kidney disease (CKD) and was on maintenance hemodialysis (MHD), and P4 had a history of traumatic spinal cord injury with paraplegia. Other associated comorbidities are mentioned in Tables 1 and 2.

- **Complication and extrapulmonary organ systems affected were as follows:** Coagulopathy in all seven patients, cardiovascular system (CVS) in six patients, renal in four, gastrointestinal system (GIT) in two, central nervous system (CNS) in two, hematology (blood) in two and spleen, liver, and pancreas in one patient, respectively. The details of these complications are mentioned in Tables 1 and 2.

All these patients were critically ill and required medical intensive care unit admission. P1 had severe myocarditis with normal two-dimensional (2D) echocardiography on day 1 of admission. On day 2, he had acute chest pain with electrocardiogram (ECG) changes (Fig. 1) and global hypokinesia with left ventricular ejection fraction (LVEF) 30% on 2D echocardiography. Coronary angiography was done, which was unremarkable. He recovered, and at discharge, his echocardiography showed an LVEF of 50%. P2 had pancreatitis and pericarditis (Figs 2 and 3), P3 had multiple splenic infarcts (Fig. 4), P4 had subacute intestinal obstruction, P5 had spontaneous pneumothorax requiring placement of intercostal drain (Fig. 5), P6 deteriorated...
Table 1: Clinical, laboratory, imaging, treatment, and other salient features of patients P1–P7

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P1</th>
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<td>65</td>
<td>62</td>
<td>46</td>
<td>88</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>Day of discharge/death</td>
<td>23rd September 2021</td>
<td>30th June 2021</td>
<td>24th August 2021</td>
<td>7th July 2021</td>
<td>14th July 2021</td>
<td>8th September 2021</td>
<td>8th September 2021</td>
</tr>
<tr>
<td>Chief complaints</td>
<td>Fever with chills, copious watery loose stools, decreased urine output, and hypotension of 2 days</td>
<td>Fever, aches, and weakness for 15 days</td>
<td>Extreme weakness, fatigue, mild cough, fever, and breathlessness for 2 weeks</td>
<td>Fever, weakness, abdominal pain, vomiting, and abdomen distention for 6 days</td>
<td>Decreased appetite, fever for 5 days, H/O fall, bowel bladder incontinence, and inability to swallow</td>
<td>Weakness, polyuria, breathing difficulty, and drowsiness for 1 week? Fever</td>
<td>Fever with chills, decreased appetite, dullness, and drowsiness for 14 days</td>
</tr>
<tr>
<td>COVID vaccination</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Symptomatic COVID-19 infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Contact with COVID-19 cases in the last 12 weeks</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>COVID-19 RT-PCR</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>COVID serology IgG AB value (&lt;1.5 c/o)</td>
<td>0.23</td>
<td>7.32</td>
<td>&gt;250 µ/mL</td>
<td>5.04</td>
<td>2.16</td>
<td>1.25</td>
<td>2.51</td>
</tr>
<tr>
<td>Total AB value (&lt;1.0 c/o)</td>
<td>5.63</td>
<td>8.72</td>
<td>6.75</td>
<td>26.0</td>
<td>6.03</td>
<td>5.86</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Psoriasiform dermatitis with onycholysis</td>
<td>CKD, HTN</td>
<td>Esophageal candidiasis, BPH, COPD, hepatitis B surface antigen positive status</td>
<td>Traumatic spinal cord injury with paraplegia. D10/11 laminectomy done 17th May 2021</td>
<td>ILD/UIP, PH</td>
<td>T2DM</td>
<td>DM, HTN, and BPH, Depression</td>
</tr>
<tr>
<td>Complications</td>
<td>Transient VT, myocarditis, LVEF 30%, AKI, mild Pneumonitis; shock, coagulopathy</td>
<td>Myocarditis, pancreatitis, pericarditis, coagulopathy</td>
<td>Multiple splenic infarcts/coagulopathy/severe anemia</td>
<td>SAIO, coagulopathy, and hypotension</td>
<td>Spontaneous right pneumothorax/atrial tachycardia with variable AV conduction, hypotension, coagulopathy, thrombocytopenia</td>
<td>Myocarditis, shock, coagulopathy, AKI, mental obtundation</td>
<td>Myocarditis, AF, LVEF 25%, AKI, coagulopathy</td>
</tr>
<tr>
<td>Extrapolmonary organ system involved</td>
<td>CVS, renal, GIT, Pancreas, CVS.</td>
<td>Blood and Reticuloendothelial system</td>
<td>GIT</td>
<td>CNS, CV, renal, blood</td>
<td>CNS, CV, renal, blood</td>
<td>B/L multiple small nodular lesions and GGOs</td>
<td>Bilateral moderate pleural effusion (cardiogenic), cardiomegaly and interlob lar septal thickening</td>
</tr>
<tr>
<td>NCCT chest</td>
<td>Bilateral GGO; with left lower lobe consolidation with B/L pleural effusion</td>
<td>Bilateral pleural effusion, moderate pleural effusion, mediastinal I lymphadenopathy</td>
<td>Minimal pleural effusion bilaterally</td>
<td>ILD? UIP, emphsematous lungs with bullae? Gastric volvulus</td>
<td>B/L multiple small nodular lesions and GGOs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCCT abdomen</td>
<td>?Pancreatitis with peripancreatic fat stranding with fluid collection, mild pelvic ascites</td>
<td>Moderate hepatosplenomegaly, multiple splenic infarcts</td>
<td></td>
<td></td>
<td></td>
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Contd…
An Insight into Multisystem Inflammatory Syndrome

Contd…

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<tr>
<th>Parameter</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
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<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
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<tr>
<td>MRI brain</td>
<td>Age-related cerebral atrophy</td>
<td>Subacute/chronic occipital lobe infarct. Age-related cerebral atrophy</td>
<td>Infarcts, embolic and restricted diffusion in bilateral thalamus, hippocampus and parahippocampal gyrus</td>
<td>Diffuse cerebral atrophy</td>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
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<tbody>
<tr>
<td>ESR (&lt;20 mm/1st hour)</td>
<td>13</td>
<td>120</td>
<td>35</td>
<td>45</td>
<td>25</td>
<td>95</td>
<td>115</td>
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<tr>
<td>CRP (&lt;6 mg/L)</td>
<td>282.4</td>
<td>233</td>
<td>137.7</td>
<td>201</td>
<td>54.7</td>
<td>271.2</td>
<td>301.9</td>
</tr>
<tr>
<td>LDH</td>
<td>539</td>
<td>182</td>
<td>341</td>
<td>310</td>
<td>294</td>
<td>268</td>
<td>267</td>
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<tr>
<td>D-Dimer (&lt;500 ng/mL)</td>
<td>1001</td>
<td>3350</td>
<td>3630</td>
<td>1015</td>
<td>15900</td>
<td>8040</td>
<td>2460</td>
</tr>
<tr>
<td>Ferritin (13–150 ng/mL)</td>
<td>578.4</td>
<td>1308</td>
<td>&gt;2000</td>
<td>518</td>
<td>1576</td>
<td>532.5</td>
<td>584.1</td>
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<tr>
<td>Procalcitonin (&lt;0.046 ng/mL)</td>
<td>10.5</td>
<td>4.7</td>
<td>0.540</td>
<td>1.54</td>
<td>8.71</td>
<td>NA</td>
<td>1.090</td>
</tr>
<tr>
<td>IL-6 (&lt;7 pg/mL)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>97.02</td>
<td>NA</td>
<td>32.11</td>
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<tr>
<td>SGOT/SGPT (up to 32 U/L)</td>
<td>155/67</td>
<td>14/7</td>
<td>158/64</td>
<td>40/81</td>
<td>2593.5/1348</td>
<td>77/135</td>
<td>22/33</td>
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<tr>
<td>Serum Albumin</td>
<td>3.3</td>
<td>3.1</td>
<td>2.2</td>
<td>3.3</td>
<td>2.9</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>TLC (4–5 × 10^3/mm³)</td>
<td>12.3</td>
<td>18</td>
<td>16.65</td>
<td>12</td>
<td>31.1</td>
<td>14.1</td>
<td>22.94</td>
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<tr>
<td>Absolute lymphocyte count/cumm</td>
<td>861</td>
<td>1547</td>
<td>1380</td>
<td>2760</td>
<td>1320</td>
<td>576</td>
<td>917</td>
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<tr>
<td>N/L (&lt;3.5)</td>
<td>13.28</td>
<td>6.69</td>
<td>4.0</td>
<td>3.34</td>
<td>7.33</td>
<td>15.0</td>
<td>23.5</td>
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<tr>
<td>NT-ProBNP (&lt;125 pg/mL)</td>
<td>5924</td>
<td>8880</td>
<td>387</td>
<td>808.9</td>
<td>&gt;35000</td>
<td>&gt;35000</td>
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<td>Troponin T</td>
<td>438</td>
<td>63</td>
<td>36</td>
<td>25</td>
<td>42</td>
<td>357</td>
<td>1228</td>
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<tr>
<td>Blood culture</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>Urine culture</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Enterococcus faecium</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Enterococcus faecium and Candida species</td>
<td>Sterile</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
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<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>IVg</td>
<td>Given</td>
<td>Given</td>
<td>Not given</td>
<td>Not given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
</tr>
<tr>
<td>Steroids</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
</tr>
<tr>
<td>LMWH</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Not given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Given</td>
<td>Not Given</td>
<td>Not Given</td>
<td>Not given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
</tr>
<tr>
<td>Supportive Treatment</td>
<td>Oxygen by mask</td>
<td>MHD</td>
<td>Oxygen by mask</td>
<td>Blood transfusion</td>
<td>HD/NIV</td>
<td>Later mechanically ventilated</td>
<td></td>
</tr>
<tr>
<td>LOS</td>
<td>11 days</td>
<td>25 days</td>
<td>8 days</td>
<td>15 days</td>
<td>8 days</td>
<td>11 days</td>
<td>9 days</td>
</tr>
<tr>
<td>Outcome</td>
<td>Discharge</td>
<td>Discharge</td>
<td>Discharge</td>
<td>Discharge</td>
<td>Discharge</td>
<td>Discharge (LAMA)</td>
<td>Discharge</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AKI, acute kidney injury; BPH, benign prostate hyperplasia; CNS, central nervous system; CRP, C reactive protein; CKD, chronic kidney disease; COPD, chronic obstructive airway disease; CVS, cardio vascular system; ESR, erythrocyte sedimentation rate; GIT, gastrointestinal system; HD, hemodialysis; HTN, hypertension; IgG ab, immunoglobulin G antibody; IL-6, interleukin 6; ILD, interstitial lung disease; IVig, intravenous immunoglobulin; LDH, lactate dehydrogenase; LAMA, left against medical advice; LOS, length of stay; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; mg/dL, milligram per deciliter; MHD, maintenance hemodialysis; mm³, cubic millimeter; MRI, magnetic resonance imaging; NCCT, noncontrast computed tomography; ng/mL, nanogram per milliliter; N/L, neutrophil lymphocyte ratio; pg/mL, picogram per milliliter; PH, pulmonary hypertension; ProBNP, pro-B-type natriuretic peptide; SAIO: subacute intestinal obstruction; SGOT: serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; T2DM, type 2 diabetes mellitus; Total AB, total antibody; TLC, total leucocyte count; UIP, usual interstitial pneumonia; U/L, units per liter; VT, ventilricular tachycardia; NA, not available

clinically and required multorgan support, and P7 had severe myocarditis.

- Radiological imaging: All patients were evaluated by imaging as required. None of them had severe lung involvement. P3 had features of chronic obstructive airway disease (COPD), and P5% had underlying interstitial lung disease (ILD). P5 and P6 had evidence of cortical infarcts in the brain. P5 had gastric volvulus, and a feeding jejunostomy was done. Other findings are in Table 1.
- Laboratory findings: All seven patients had markedly elevated inflammatory markers, as depicted in Figs 6 and 7. Four of them had markedly raised N-terminal pro–brain natriuretic peptide (NT-ProBNP) due to myocarditis with reduced LVEF–heart failure with reduced ejection fraction, and/or acute kidney injury. They also had features suggestive of pleural effusion. All patients had sterile blood and sputum cultures except for P6, who grew non-Candida albicans on sputum culture (likely colonization).
An Insight into Multisystem Inflammatory Syndrome

Patients, mostly below 50 years of age. However, our case series had only two patients below 50 years, and five were >50 years of age. CDC has already commented that all ages can suffer from the ramifications of an inflammatory cytokine storm following a SARS-CoV-2 infection, and obviously elderly cannot be an exception. This is the first case series that reports MIS-A in the elderly population.

Morbidity and mortality weekly report (MMWR) MIS-A criteria and CDC working case definition for MIS-A have been developed for early identification of MIS-A. It is to be noted that the CDC working definition includes subjective or documented fever as a requisite criterion, whereas MMWR criteria do not mention the presence of fever. All patients in the case series had a fever and fulfilled MIS-A criteria. The diagnosis of MIS-A needs to be contemplated in any patient who presents with features of hyperinflammatory illness along with severe extrapulmonary multiorgan dysfunction, particularly cardiovascular, and arising within 2–5 weeks of preceding COVID-19 illness or exposure to a person with diagnosed COVID-19. As many patients can have a negative COVID-19 RT-PCR testing due to various reasons and many persons can have an asymptomatic infection or contact with an asymptomatic COVID-19 case, a history of antecedent COVID-19 may not be available.

**Table 2:** Morbidity and mortality weekly report (MMWR) criteria for multisystem inflammatory syndrome in adults

All five criteria have to be met for the diagnosis of MIS-A.

- A severe illness requiring hospitalization in a person aged ≥21 years.
- A positive test for current or previous SARS-CoV-2 infection (nucleic acid, antigen or antibody) during admission or in the previous 12 weeks.
- Severe dysfunction of one or more extrapulmonary organ systems (e.g., hypotension, shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism or acute liver injury).
- Laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer, or interleukin-6).
- Absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia). Patients with mild respiratory symptoms who met these criteria were included. Patients were excluded if alternative diagnoses, such as bacterial sepsis, were identified.
An Insight into Multisystem Inflammatory Syndrome

Table 3: Case definition for MIS-A

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical criteria:</strong></td>
</tr>
<tr>
<td>- Subjective fever or documented fever (≥38.0°C) for ≥24 hours prior to hospitalization or within the first 3 days of hospitalization PLUS</td>
</tr>
<tr>
<td>- At least three of the following clinical criteria occur prior to a hospitalization or within the first 3 days of hospitalization. At least one must be a primary clinical criterion.</td>
</tr>
<tr>
<td><strong>Primary clinical criteria:</strong></td>
</tr>
<tr>
<td>- Severe cardiac illness (includes myocarditis, pericarditis, coronary artery dilatation/anerysm, or new-onset right or left ventricular dysfunction (LVEF of &lt;50%), second/third degree AV block, or ventricular tachycardia).</td>
</tr>
<tr>
<td>- Rash and nonpurulent conjunctivitis.</td>
</tr>
<tr>
<td><strong>Secondary clinical criteria:</strong></td>
</tr>
<tr>
<td>- New-onset neurologic signs and symptoms.</td>
</tr>
<tr>
<td>- Shock or hypotension not attributable to medical therapy.</td>
</tr>
<tr>
<td>- Abdominal pain, vomiting or diarrhea.</td>
</tr>
<tr>
<td>- Thrombocytopenia (platelet count of &lt;150,000/μL).</td>
</tr>
<tr>
<td><strong>Laboratory criteria:</strong></td>
</tr>
<tr>
<td>- The presence of laboratory evidence of inflammation and SARS-CoV-2 infection.</td>
</tr>
</tbody>
</table>

A patient aged 21 years or older; hospitalized with a severe illness ≥24 hours or with an illness resulting in death, which meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis or exacerbation of a chronic medical condition).

Clinical criteria:
- Subjective fever or documented fever (≥38.0°C) for ≥24 hours prior to hospitalization or within the first 3 days of hospitalization PLUS
- At least three of the following clinical criteria occur prior to a hospitalization or within the first 3 days of hospitalization. At least one must be a primary clinical criterion.

Primary clinical criteria:
- Severe cardiac illness (includes myocarditis, pericarditis, coronary artery dilatation/anerysm, or new-onset right or left ventricular dysfunction (LVEF of <50%), second/third degree AV block, or ventricular tachycardia).
- Rash and nonpurulent conjunctivitis.

Secondary clinical criteria:
- New-onset neurologic signs and symptoms.
- Shock or hypotension not attributable to medical therapy.
- Abdominal pain, vomiting or diarrhea.
- Thrombocytopenia (platelet count of <150,000/μL).

Laboratory criteria:
- The presence of laboratory evidence of inflammation and SARS-CoV-2 infection.

As more data about MIS-A emerge, this working case definition may be revised.

This necessitates antibody testing to identify such cases. In our case series, all patients had a negative COVID-19 RT-PCR test. P1, P3, P5, and P7 had received at least one dose of vaccination for COVID-19 much before illness and P2, P3, P4, and P7 had a history of symptomatic COVID-19 illness at least 7 months, 10 months, 4 weeks, and 4 months earlier to present admission. P4 also had a history of contact with symptomatic COVID-19 cases in the preceding 12 weeks. All these patients presented with severe illness, febrile syndrome, multiple organ involvement, and evidence of hyperinflammation. Clinical suspicion and positive COVID-19 serology helped in the early diagnosis and timely management of MIS-A in these patients.

All patients discussed had coagulopathy (100%, 7/7). Cardiovascular abnormalities such as hypotension, global hypokinesia, reduced LVEF, high troponin T values, pericarditis, and cardiac arrhythmias were the most frequently reported findings (85.7%, 6/7). In the case of P1, coronary angiography was done to rule out acute coronary syndrome in view of acute severe chest pain and ECG changes. However, it was normal. The other prominent symptoms were as follows: fever (7/7, 100%), acute kidney injury (4/7, 57.1%), CNS–cortical infarcts (2/7, 28.6%), hemolologic–anemia and thrombocytopenia (2/7, 28.6%), gastrointestinal symptoms suggestive of subacute intestinal obstruction (1/7, 14.3%), hepatitis, pancreatitis, and splenic infarcts in 1/7 (14.3%) each, respectively. None of the patients presented respiratory complaints. All these cases with MIS-A had higher levels of inflammatory biomarkers such as C-reactive protein (CRP), D-dimer, and ferritin. The mean level for CRP was 211.7 ± 82.26 mg/L, the mean level for the neutrophil-lymphocyte ratio (N/L) was 10.448 ± 6.708%, and the mean level for lymphocyte count was 1337.285 ± 660.438 cells/mm³. The median level for ferritin was 578.4 ng/mL, and the median level for D-dimer was 3350 ng/mL.

Multisystem inflammatory syndrome–adults (MIS-A) is a hyperinflammatory syndrome that can worsen rapidly; patients need prompt and emergent treatment to mitigate morbidity and mortality. Diagnosis and treatment guidelines for MIS-C related to SARS-CoV-2 infection have been published by the American College of Rheumatology. It recommends pulse steroid treatment with methylprednisolone (MPS) in moderate severe cases, and it was reported that a combination of IVIg and steroid therapy might be more effective for symptom relief than IVIg alone in Kawasaki disease (KD), having similar pathophysiology characteristic to MIS-C.13,14 For these patients, supportive care in addition to therapy for underlying inflammatory process with IVIg, steroids, aspirin, and anticoagulation is recommended.14 However, there are no guidelines for the management of MIS-A. A case of Kawasaki-like disease in an adult showing rapid resolution of clinical and laboratory features after the use of MPS pulse therapy, IVIg and aspirin had been reported. Another case of adult MIS post-COVID-19 was reported who met the American Heart Association criteria for KD and showed complete resolution with LMWH, IVIg, and tocilizumab. As previously discussed, the only difference between MIS-C and MIS-A is age criteria and both the syndromes being similar, treatment strategies have been universalized from suggested therapies for MIS-C. Each center implements its own protocol based on the available medical literature. In the present case series-based review, 7/7 (100%) patients were treated with steroids (MPS), four (57%) were given IVIg, six (86%) were given LMWH, and four (57%) were given aspirin. All patients received ICU and supportive care. One patient–P2, received MHD; P1 and P3 received oxygen support as per the disease severity; P3 received packed red blood cell transfusion, and P5 received hemodialysis, NIV and later mechanical ventilation. P5 died during the course of treatment on day 8. P6 was also critically ill and was discharged against medical advice. Five (71.4%) patients were discharged to home. Nevertheless, it is important to have a multidisciplinary approach for optimum outcomes in these patients.

**Conclusion**

- Multisystem inflammatory syndrome–adults (MIS-A), a febrile syndrome with hyperinflammation and multiorgan dysfunction, can rapidly worsen and needs early recognition, rapid diagnosis, careful monitoring and prompt treatment.
- Intravenous immunoglobulin (IVIg) and pulse steroid treatment are effective options for managing this syndrome and mitigating morbidity and mortality.
- It is possible that several cases of MIS-A, as reported here, may have gone unnoticed due to unrecognized, false negative test results and/or asymptomatic SARS CoV-2 infection.
- It looks like the cases reported just represent the tip of an iceberg with a large pool of unrecognized cases.

**What is Added by the Study**

- Multisystem inflammatory syndrome–adults (MIS-A) has been reported by several authors. These case series show that besides affecting children and young adults, as reported by other authors, MIS-A affects the elderly population also and that they are not an exception.
- The case series also have implications for public health. Clinical suspicion and SARS-CoV-2 antibody testing are needed to recognize these cases. However, further research is needed to look into its pathogenesis, long-term effects of this syndrome and management strategies. No one knows how long COVID-19 is going to stay or return.

**Authors Contribution**

- Conception and design of the work: AA.
- Data acquisition: AmS, RJ and AK.
- Drafting the work and writing: AA.
- Tabulation work: AdS and AaA.
An Insight into Multisystem Inflammatory Syndrome

- Revision: AA.
- Final approval of the version to be published: All authors.

**REFERENCES**

Swallowing Dysfunction after Acute Stroke: The Incidence, Predictors and Outcome

Charulata Londhe1*, Aashish Agrawal2, Sangeeta Pednekar3, Dharmendra Pandey4, Mohammed Fasahatulla Khan5

Received: 06 April 2023; Accepted: 25 April 2023

ABSTRACT
Introduction: Swallowing dysfunction is common after acute stroke. It increases the risk of aspiration pneumonia and affects nutrition. In this study, we aimed to determine the incidence of dysphagia after a single episode of acute stroke in conscious patients and the factors predisposing the patient to dysphagia. We also assessed the course of dysphagia over a period of 8 weeks after stroke.

Materials and methods: It was a prospective observational study. We included patients of acute stroke (ischemic, hemorrhagic, lacunar, anterior, as well as posterior circulation) with Glasgow Coma Scale (GCS) of ≥12; within 48 hours of onset. Patients were screened for dysphagia by the Gugging Swallowing Screen (GUSS) screening tool; then assessed in detail using by Mann Assessment of Swallowing Ability (MASA) scoring scale. Patients with dysphagia were reassessed at 7 days and at 8 weeks after stroke for the presence and severity of dysphagia.

Results: We included 150 patients. The incidence of dysphagia at day 1, day 7, and 8 weeks was 42, 24, and 9%, respectively. The proportion of patients with moderate and severe dysphagia also decreased during a follow-up period of 8 weeks from 18 to 3% and from 20 to 6%, respectively. The incidence of dysphagia was significantly greater in moderately severe stroke (National Institutes of Health Stroke Scale (NIHSS 5–14)) than in mild stroke (NIHSS <1). It was also more common in total anterior circulation infarct (TACI) than partial anterior circulation or lacunar infarct (LacI) and in posterior circulation strokes than the strokes involving anterior circulation. Patients with dysphagia had longer hospital stays (7.29 ± 3.4 days vs 3.62 ± 1.5 days, *p* = 0.001) and higher mean modified Rankin scale at discharge (3.45 vs 2.17, *p* = 0.001).

Conclusion: Swallowing dysfunction should be checked in all cases of strokes, including unilateral hemispheric strokes and in fully conscious patients. Swallowing improves with time, but the patient may require feeding assistance in an acute setting. Dysphagia is more common in strokes with higher NIHSS, involving more brain parenchyma and posterior circulation strokes.

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INTRODUCTION
Swallowing dysfunction after acute stroke is a common phenomenon. Various studies have reported the incidence of poststroke dysphagia from 20–80%.1-6 The wide variation in incidence is because of the differences in patient selection, methods of assessment of swallowing, and the duration after stroke. Dysphagia after stroke carries a threefold increased mortality risk and a sevenfold increased risk of aspiration pneumonia.7 It also affects nutrition and reduces the quality of life.

It is widely known that dysphagia is common if the lesion is in the brainstem or the bilateral supra-tentorial lesions. However, a unilateral hemispheric lesion may also produce dysphagia. There is an asymmetric representation of the muscles of swallowing in the motor cortices. A stroke involving the hemisphere with dominant swallowing projection leads to dysphagia. Recovery of swallowing function may occur in a few months after the neuroplastic compensatory changes take place in the unaffected hemisphere.8 Appropriate functioning of the brainstem, basal ganglia, thalamus, limbic system, cerebellum, motor and sensory cortices, and cortico-bulbar tracts is required for normal control of swallowing.3 Process of swallowing has two phases—the oropharyngeal phase, which is voluntary, and the esophageal phase, which is involuntary. In the majority of patients, the oropharyngeal phase is affected after a stroke.

In this study, we aimed to determine the incidence of dysphagia after a single acute stroke and factors predisposing the patient to dysphagia. We also assessed the course of dysphagia over a period of 8 weeks after stroke.

MATERIALS AND METHODS
The study was a prospective, observational study; performed at the Medicine wards of tertiary care, urban, teaching, and public hospital. After approval from the Institutional Ethics Committee, 150 patients of acute ischemic or hemorrhagic stroke with Glasgow Coma Scale (GCS) of ≥12 on day 1 were included in the study. Patients having a previous history of swallowing dysfunction due to any other cause were excluded. Patients with impaired consciousness (GCS of <12) were also excluded because of the difficulty in assessing swallowing in them. They need tube feeding as consciousness is necessary to initiate the swallowing process. Patients presenting after 48 hours of the onset of stroke symptoms were also excluded.

All patients were screened on day 1 for swallowing dysfunction by Gugging Swallowing Screen (GUSS) test.10 It is a simple and step-wise, bedside screening test to assess the swallowing of solid, semi-solid, and liquid. Patients who had swallowing dysfunction by GUSS screening test were evaluated in detail by the Mann Assessment of Swallowing Ability (MASA) clinical swallowing tool.11 It consists of 24 clinical items comprising four main components—general patient examination, oral preparation phase, oral phase, and pharyngeal phase. It classifies dysphagia into mild, moderate, and severe grades according to score.

The patients who had dysphagia on day 1 were reassessed on day 7 or on the day of discharge, whichever was earlier. The patients who had dysphagia on day 7 or at discharge were reassessed at 8 weeks after the onset of stroke for the swallowing function.

The following parameters were also noted in each patient: demographic details, risk factors for stroke, type of stroke [ischemic/hemorrhagic, large vessel infarct/lacunar infarct (LacI)], location (anterior circulation/posterior circulation), the severity of stroke on day 1 [by National Institutes of Health Stroke Scale (NIHSS)],12 patient disability by the modified Rankin scale13 at discharge and at 8 weeks, presence of aspiration pneumonia, duration of hospital stay, the requirement

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of the nasogastric tube at discharge, and mortality. Data were tabulated and analyzed.

**Results**

We included 150 patients. The age of patients ranged from 27 to 85 years, with a mean age of 55 years. There were 68% males and 32% females. Approximately 57% had hypertension, and 22% had diabetes. A total of 78% of patients had GCS 15 on day 1; others had it between 12 to 14. LacI was present in 72 patients (48%); large vessel infarct was seen in 50 patients (33%), while 28 (18%) had a hemorrhagic stroke. About 15 patients (10%) had posterior circulation stroke. Approximately 57% had a left-sided stroke, and 43% had a right-sided stroke. About 75 patients had mild stroke (NIHSS 1–5), 75 had mild to moderately severe stroke (NIHSS 5–14). Patients with severe and very severe strokes were excluded due to low GCS.

The incidence of dysphagia on day 1 and its progression at day 7 and at 8 weeks is shown in Table 1. It shows that of the 64 patients with dysphagia on day 1, 44% could swallow normally on day 7. Of the remaining patients with persistent swallowing dysfunction, a further 34% had normal swallowing at 8 weeks. Only 22% had persistent dysphagia at 8 weeks (9.3% of all patients). A total of 48 patients required tube feeding on day 1; 26 needed it on day 7, and 14 needed it at 8 weeks after the stroke.

The proportion of patients with severe dysphagia also reduced over the period of 8 weeks, as shown in Table 2. The statistical analysis did not show any correlation between the patient’s age, gender, or presence of hypertension or diabetes with poststroke dysphagia.

The incidence of dysphagia was significantly higher in moderately severe stroke (66.6%) than in mild stroke (18.6%); p < 0.001, as shown in Table 3. There was no significant difference between the incidence of dysphagia in ischemic stroke (41.8%) and hemorrhagic stroke (46.4%), p = 0.19.

Dysphagia was more frequent among posterior circulation strokes (10/15, i.e., 66%) than among anterior circulation (54/135, i.e., 40%) strokes. p = 0.047.

Dysphagia was significantly more common in total anterior circulation infarct (TACI) than in partial anterior circulation infarct and LacI in anterior circulation (Table 4).

We did not find any significant difference in the incidence of dysphagia among the anterior circulation ischemic strokes involving the left vs right hemispheres (Table 5). Left hemispheric ischemic strokes (57%) were slightly more common than right ones (43%).

In our study population, 15 patients (10%) had lower respiratory infections during the hospital stay. All had severe dysphagia on admission. Patients with dysphagia had longer hospital stays than patients without dysphagia. (7.29 ± 3.4 days vs. 3.62 ± 1.5 days, p = 0.001). Patients with dysphagia also had higher mean modified Rankin’s score at the time of discharge than patients without dysphagia (3.45 vs 2.17, p = 0.001).

**Table 1:** Number of patients with acute stroke having dysphagia at the acute stage and on follow-up

<table>
<thead>
<tr>
<th>Day</th>
<th>No. of patients with dysphagia (n = 150)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>42.7</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>9.3</td>
</tr>
</tbody>
</table>

**Table 2:** Number of patients as per the severity of dysphagia (measured by MASA score) over 8 weeks period after stroke

<table>
<thead>
<tr>
<th>Dysphagia severity</th>
<th>No dysphagia</th>
<th>Mild dysphagia</th>
<th>Moderate dysphagia</th>
<th>Severe dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>86 (57.3%)</td>
<td>5 (3.3%)</td>
<td>28 (18.7%)</td>
<td>31 (20.7%)</td>
</tr>
<tr>
<td>Day 7 or at discharge</td>
<td>112 (74.7%)</td>
<td>11 (7.3%)</td>
<td>7 (4.7%)</td>
<td>18 (12%)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>134 (89.4%)</td>
<td>0</td>
<td>5 (3.3%)</td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>

**Table 3:** Correlation of severity of stroke by NIHSS with dysphagia

<table>
<thead>
<tr>
<th>Mild stroke NIHSS 1–5</th>
<th>Moderate stroke NIHSS 5–14</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>14 (18.6%)</td>
<td>64</td>
</tr>
<tr>
<td>No dysphagia</td>
<td>61</td>
<td>86</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>150</td>
</tr>
</tbody>
</table>

p < 0.001

**Table 4:** Correlation of dysphagia with location and extent of ischemic stroke (n = 124)

<table>
<thead>
<tr>
<th>Type of ischemic stroke</th>
<th>Dysphagia</th>
<th>No dysphagia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACI</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>PACI</td>
<td>12</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>PoCI</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>LacI</td>
<td>25</td>
<td>47</td>
<td>72</td>
</tr>
</tbody>
</table>

LacI, lacunar infarct; PACI, partial anterior circulation infarct; PoCI, posterior circulation infarct; TACI, total anterior circulation infarct; p = 0.0035

**Table 5:** Correlation of dysphagia with dominant and nondominant hemispheric lesions in patients with anterior circulation stroke (n = 135)

<table>
<thead>
<tr>
<th>Right side stroke</th>
<th>Left side stroke</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>No dysphagia</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>77</td>
</tr>
</tbody>
</table>

p = 0.256

**Table 6:** Correlation of modified Rankin scale at the time of discharge with dysphagia

<table>
<thead>
<tr>
<th>Moderate ranking score</th>
<th>No disability (0–1)</th>
<th>Slight disability (2)</th>
<th>Moderate disability (3)</th>
<th>Moderately severe and severe disability (4–5)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>2</td>
<td>5</td>
<td>18</td>
<td>37</td>
<td>62</td>
</tr>
<tr>
<td>No dysphagia</td>
<td>29</td>
<td>23</td>
<td>24</td>
<td>10</td>
<td>86</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>28</td>
<td>42</td>
<td>47</td>
<td>148</td>
</tr>
</tbody>
</table>

Two deaths; p = 0.001
Rankin’s scale score at discharge. There were two deaths in the study population. Both had severe dysphagia and aspiration pneumonia.

**Discussion**

In this study, we intended to determine the incidence of dysphagia in an acute stroke of mild to moderate severity, its progression in the poststroke period, the risk factors or factors predicting the occurrence of dysphagia after stroke, and clinical outcomes of patients with poststroke dysphagia.

The incidence of dysphagia on day 1 of stroke is 42.7% in our study. The swallowing function improves with time; the incidence at day 7 is 24%, and at 8 weeks is 9.3%. The risk of dysphagia is higher in more severe strokes, posterior circulation strokes, and total anterior circulation ischemic strokes. Patients with dysphagia have higher mean modified Rankin score at the time of discharge, longer hospital stays, and more risk of aspiration pneumonia.

The mean age of our study population is 55 years, which is younger compared to many studies in the Western population. Atherosclerotic cardiovascular diseases strike Indians a decade earlier than the Western population. Our study population also shows male preponderance. At premenopausal age, females have a lesser incidence of atherosclerotic cardiovascular diseases than males. The lacunar infarcts are seen more commonly than large vessel infarcts in our study. We have excluded patients with impaired consciousness who are likely to have a severe stroke due to large vessel infarction or a major intracerebral hemorrhage.

The incidence of poststroke dysphagia ranges from 25 to 81% in various studies, depending on inclusion criteria and the methods used to assess swallowing dysfunction. This is elaborated in Table 7.

Dysphagia improved with time in the majority of patients. The recovery is more likely in mild or moderate dysphagia. Table 8 gives the proportion of patients with persistent dysphagia in the follow-up period after acute stroke in various studies.

Association between the presence of dysphagia and higher NIHSS scores, as seen in our study, is also reported by Paciaroni et al.,16 and Okubo et al.17 We found dysphagia is more common in total anterior circulation ischemic stroke, partly due to more severity and a larger area of brain parenchyma affected. The incidence of dysphagia is least in lacunar strokes due to small infarct volumes, affecting deep gray matter. The incidence of dysphagia among hemorrhagic strokes is 46% in our study, which is lower than the study by Sundar et al. (67%).

The differences may be attributable to patient selection criteria, differences in definitions, and tools of swallowing examinations. The incidence of dysphagia among ischemic stroke is comparable to other published studies. Barer et al.,20 reported poststroke dysphagia in 32% of dominant hemispheric strokes vs 27% of nondominant strokes. In our study, also, left hemispheric strokes have slightly more incidence of dysphagia than right hemispheric strokes, though the difference is not statistically significant.

The incidence of aspiration pneumonia and death in our study is less than in other studies, as our study population included only mild or moderately severe strokes, and the proportion of severe dysphagia is also lesser (20%).

We assessed swallowing with clinical tools. Instrumental assessment may diagnose more cases of dysphagia. Mann et al.,5 reported dysphagia in 64% and aspiration in 22% at a median of 10 days after the onset of stroke by the video-fluoroscopic method. At the 6-month follow-up, repeat videofluoroscopy of swallowing identified swallowing abnormality in 80% of cases, and 25% were aspirating; but the majority had returned to the previous diet. Logemann21 suggested that swallowing may recover functionally; but may remain abnormal at a more intricate level. This may account for an increased incidence of dysphagia after recurrent strokes.

Our study underlines the importance of examination for swallowing dysfunction in

### Table 7: Incidence of poststroke dysphagia in various studies

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Study by</th>
<th>Sample size</th>
<th>Inclusion criteria</th>
<th>Methods used to assess dysphagia</th>
<th>Incidence of dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gottlieb et al.</td>
<td>180</td>
<td>Consecutive; Rehab stroke</td>
<td>Drink 50 mL of water without coughing</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>Gordon et al.</td>
<td>91</td>
<td>Consecutive acute stroke</td>
<td>Drink 50 mL of water without choking</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>Meng et al.</td>
<td>36</td>
<td>Consecutive; Rehab, brainstem stroke</td>
<td>Clinical and Video-fluoroscopy to a subgroup</td>
<td>81%</td>
</tr>
<tr>
<td>4</td>
<td>Smithard et al.</td>
<td>121</td>
<td>Consecutive; conscious; acute stroke</td>
<td>Clinical and Video-fluoroscopy to a subgroup</td>
<td>51%</td>
</tr>
<tr>
<td>5</td>
<td>Mann et al.</td>
<td>128</td>
<td>Consecutive; conscious; acute stroke</td>
<td>Clinical and Video-fluoroscopy</td>
<td>Clinical; 51% Instrumental: 64%</td>
</tr>
<tr>
<td>6</td>
<td>Sundar et al.</td>
<td>50</td>
<td>Consecutive; GCS &gt; 9, acute stroke</td>
<td>Clinical</td>
<td>41%</td>
</tr>
<tr>
<td>7</td>
<td>Present study</td>
<td>150</td>
<td>Consecutive; conscious; acute stroke</td>
<td>Clinical</td>
<td>42%</td>
</tr>
</tbody>
</table>

### Table 8: Incidence of poststroke dysphagia after a follow-up period in various studies

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Study by</th>
<th>Sample size</th>
<th>Incidence at baseline</th>
<th>Follow-up period</th>
<th>Incidence of persistent dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidd et al.</td>
<td>60</td>
<td>42%</td>
<td>3 months</td>
<td>8%</td>
</tr>
<tr>
<td>2</td>
<td>Smithard et al.</td>
<td>121</td>
<td>51%</td>
<td>6 months</td>
<td>8%</td>
</tr>
<tr>
<td>3</td>
<td>Arnold et al.</td>
<td>570</td>
<td>20.7%</td>
<td>Discharge (mean 4.4 days)</td>
<td>10.5%</td>
</tr>
<tr>
<td>4</td>
<td>Sala et al.</td>
<td>187</td>
<td>36.4%</td>
<td>6 months</td>
<td>4.4%</td>
</tr>
<tr>
<td>5</td>
<td>Mann et al.</td>
<td>127</td>
<td>64%</td>
<td>6 months</td>
<td>26.6%</td>
</tr>
<tr>
<td>6</td>
<td>Present study</td>
<td>150</td>
<td>42.7%</td>
<td>2 months</td>
<td>9.3%</td>
</tr>
</tbody>
</table>
all cases of stroke, including unilateral and anterior circulation strokes.

REFERENCES

Efficacy and Safety of Directly Acting Antivirals in Patients with Hepatitis C Infection on Hemodialysis

Manisha Sahay1*, Priyashree2*, Kiranmai Ismal3, K Anuradha4, Jyoti Lakshmi5

Received: 17 March 2023; Accepted: 25 April 2023

Abstract

Introduction: The high prevalence of hepatitis C virus (HCV) infection among patients on maintenance hemodialysis (MHD) has been reported in India. Due to the strong association of HCV infection with death and cardiovascular disease, it is important to treat the infection. However, treatment poses a challenge since only a few directly acting antivirals recommended in the guidelines for HCV treatment in the dialysis population are available in India. Pangenotypic sofosbuvir has concerns about its safety due to its renal elimination.

Materials and methods: This prospective study was undertaken between 2019 and 2020 among patients on hemodialysis with HCV infection. Clinical details, biochemical parameters, viral load, and genotyping were recorded and the outcome of treatment with sofosbuvir in combination with velpatasvir/daclatasvir for 12 weeks was noted. Descriptive and inferential statistical analysis was carried out. The Chi-squared/Fisher exact test was used.

Results: In the present study, 54 hemodialysis patients with HCV were treated with full doses of sofosbuvir and velpatasvir/daclatasvir. Genotype 1 was the most common, seen in 75.9% (n = 41). Around 96.29% (n = 52) of patients achieved sustained virological response (SVR) at the end of the study. None of the patients experienced serious side effects requiring dose reduction or discontinuation of the treatment.

Conclusion: Sofosbuvir combination therapy offers an excellent response in dialysis patients irrespective of the genotype and presence of cirrhosis with minimal monitoring as in non-chronic kidney disease (CKD) patients.

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Introduction

The prevalence of hepatitis C virus (HCV) is high among patients on maintenance hemodialysis (MHD) due to nosocomial transmission of infection and multiple blood transfusions during HD.1–3 The prevalence of HCV in patients with MHD varies between 6 and 60% in various parts of the world.4

Apart from the increased liver-related morbidity and higher cardiovascular risk in dialysis, the persistence of infection after kidney transplantation is associated with increased mortality and graft dysfunction.5 Also, mortality rates are higher in HCV-infected hemodialysis patients than in noninfected hemodialysis patients.6 Chronic HCV infection has a significant impact on renal function and also has a negative psychological impact in patients undergoing MHD due to the requirement of separate dialysis machines.

Clearing HCV in this population may improve their quality of life and decrease the risk of nosocomial transmission in dialysis units.5–7 With the advent of newer direct-acting antivirals (DAA), the treatment of HCV infection has become simple, finite, and impressively effective with sustained virological response (SVR) rates of >95%.

However, treatment in patients with [end-stage renal disease (ESRD)] is associated with a few problems. Firstly, the recommended regimes of elbasvir/grazoprevir, dasabuvir/ombitasvir/paritaprevir/ritonavir, and glecaprevir/pibrentasvir are not available in developing countries including India.8,9 Secondly, the commonly used pangenotypic drug sofosbuvir was thought to have toxic metabolite GS331007 and fixed drug combinations of sofosbuvir/velpatasvir were not used in these patients.10,11 So the commonly used regime in this scenario was to use half a dose of sofosbuvir and a full dose of daclatasvir.12 The potential toxicity of using a full dose of sofosbuvir on one hand and usage of subtherapeutic dosage leading to concerns of treatment failure/resistance was the major drawback of HCV treatment in patients with MHD in previous studies.

There is scant data on the safety and efficacy of full-dose sofosbuvir in ESRD patients on MHD.12–14 This study was undertaken to determine the safety and efficacy of full-dose sofosbuvir with daclatasvir or velpatasvir in patients with ESRD on MHD and to study the factors determining treatment response.

Materials and Methods

This prospective study was conducted in a tertiary care hospital between January 2019 and December 2020 after obtaining Institutional Ethics Committee approval.

Inclusion and Exclusion Criteria

All patients above 15 years of age with HCV infection with ESRD who were undergoing MHD were included in the study after obtaining informed consent. Patients coinfected with HBV, human immunodeficiency virus were excluded. Patients on antiepileptic drugs, immunosuppressants, chemotherapeutic drugs, and antiarrhythmic drugs were excluded due to drug interactions with DAA. Patients with a previous history of treatment with interferon or DAA, children, and pregnant patients were also excluded from the study. Patients with the presence of antibodies to HCV with no documented HCV RNA were considered as spontaneous clearance and excluded from the study.

Quantitative HCV RNA viral load using commercially available Quantiplus reverse transcription polymerase chain reaction (RT-PCR) kits, and HCV genotype by molecular diagnostics were done for all patients. A cutoff of 15 IU/μL was utilized for detecting the minimal quantity of RNA in the blood.

Baseline data including demographic profile, dialysis vintage, duration of HCV, symptomatology, history of blood transfusions, co-morbidities, details of treatment received, and drugs used was noted. All patients underwent an ultrasound abdomen to assess the presence of fibrosis or cirrhosis.

Conclusion: Sofosbuvir combination therapy offers an excellent response in dialysis patients irrespective of the genotype and presence of cirrhosis with minimal monitoring as in non-chronic kidney disease (CKD) patients.

Liver fibrosis was measured noninvasively by transient elastography (FibroScan) and the liver stiffness measurement was expressed in kilopascals (kPa). A kPa of >11 was considered to be cirrhosis and 7–11 kPa was labeled as fibrosis. Also, fibrosis-4 (FIB-4) and AST to platelet ratio index (APRI) scores were used for assessing fibrosis. APRI score >2 and FIB-4 > 3.25 were considered suggestive of cirrhosis. Assessment for portal hypertension with upper gastrointestinal (GI) endoscopy was performed in indicated cases.

Sofosbuvir 400 mg + velpatasvir 100 mg (fixed drug combination) daily for 12 weeks was administered in patients with fibrosis/ cirrhosis and sofosbuvir 400 mg + daclatasvir 60 mg daily for 12 weeks in patients without fibrosis according to assessment by APRI score, FIB-4 score, and FibroScan according to National Viral Hepatitis Control Program by Ministry of Health and Family Welfare, India. Drugs were administered after the dialysis session on the day of MHD.

Postinitiation of DAA, patients on MHD were dialyzed using bridge machines. HCV RNA was performed after 12 weeks after the stoppage of treatment to assess SVR-12.

FibroScan was repeated at 6 months posttreatment to assess the change in liver stiffness. All patients were monitored monthly with complete blood counts, liver function tests and assessed for adherence and side effect profiles.

**Statistically Analysis**

The data were analyzed descriptively using percentages, means, and standard deviations. Tests of significance were performed using independent student t-tests and χ² analyses as appropriate for the variables used in the comparisons. The level of significance was set at 0.05. All analyses were done with the Statistical Package for the Social Sciences for Windows (version 16; SPSS, Chicago, Illinois).

**Results**

A total of 54 patients with chronic kidney disease (CKD) on MHD with HCV were studied in this period of 2 years. The mean age of the study population was 45.1 ± 10.7 years with males contributing up to 75.9%. The etiological profile for CKD was 35.2% (n = 9) of patients had chronic interstitial nephritis (CIN), 42.6% (n = 23) had chronic glomerulonephritis (CGN), 22.2% (n = 12) had diabetic kidney disease with a mean duration of diabetes being 10.8 ± 2.2 years.

The mean duration of MHD was 3.4 ± 1.6 years with a range of 6 months to 9 years. A total of 37 patients of 54 (68.5%) had a past history of blood transfusion either before or after the initiation of Hemodialysis. None of the patients had a history of intravascular drug abuse or high risk behavior.

Hypertension was present in 83.3% (n = 45) patients and a history of coronary artery disease was present in 7.4% (n = 4). The duration between diagnosis and treatment initiation was 4 ± 2 months.

The baseline biochemical parameters are depicted in Table 1.

Hepatitis C virus (HCV) genotyping was studied in all patients. HCV genotype 1 was the most common, seen in 75.9% (n = 41) followed by genotype 3–24.07% (n = 13) of the patients.

The median HCV RNA load (performed by Quantiplex HCV RT-PCR kit) was 2,83,894.5 IU/mL with a range of 18.7–7834124 IU/mL. Ultrasound abdomen showed fatty liver in 13% (n = 07) patients and altered echotexture in 18.5% (n = 10) patients.

Fibrosis of liver assessment with FibroScan showed 55.5% (n = 30) had fibrosis and 16.6% (n = 09) patients had cirrhosis. The mean value on FibroScan was 8.5 ± 1.4 kPa. Upper GI endoscopy was done in patients with FibroScan values of >11 kPa and none of the patients had features suggestive of portal hypertension (varices or portal hypertensive gastropathy).

The mean APRI score was 0.71 ± 0.55 with 9.2% (n = 5) patients having scores >2 (cirrhosis).

The mean FIB-4 score was 1.5 ± 0.89; 7.4% (n = 4) of patients had a score >3.25 (cirrhosis).

The presence of diabetes was associated with higher fibrosis as assessed with FibroScan as shown in Table 2. Duration of HCV did not show a similar influence on fibrosis.

Patients with the presence of fibrosis or cirrhosis 72.2% (n = 39) were treated with FDC of sofosbuvir and velpatasvir. The remaining 27.7% (n = 15) of patients received sofosbuvir and daclatasvir.

Among this, all patients who received sofosbuvir + velpatasvir achieved SVR-12. Two patients (4.1%) in the sofosbuvir + daclatasvir group did not achieve SVR-12. Six patients succumbed in the study period before the measurement of SVR-12. All deaths were related to severe COVID-19 infection with multiorgan dysfunction.

Among patients who did not achieve SVR-12, both were males and had CIN as their native kidney disease. Both the patients had HCV genotype 1 infection with a mean MHD duration of 3.5 ± 0.7 years.

Fibrosis was assessed with noninvasive methods before treatment and after achieving SVR-12 as shown in Table 3. A significant reduction in fibrosis values was noted posttreatment when measured with FibroScan. However, a similar significant reduction was not recognized when assessed with APRI or FIB-4 score. Biochemical parameters did not show significant change with the completion of treatment as shown in Table 4. Clinical and biochemical parameters between patients who achieved SVR-12 and who did not are shown in Table 5.
None of the patients experienced serious side effects requiring dose reduction or discontinuation of the DAAs. Minor side effects include—vomiting in 11.1% (n = 6), headache in 5.5% (n = 3), and myalgia in 1.8% (n = 1) patients.

**Table 3:** Changes in fibrosis before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Before DAA (in kPa)</th>
<th>After DAA (in kPa)</th>
<th>Significance (student t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroscan</td>
<td>10.5 ± 6.3</td>
<td>7.4 ± 2.6</td>
<td>0.008</td>
</tr>
<tr>
<td>APRI score</td>
<td>0.71 ± 0.55</td>
<td>0.5 ± 0.62</td>
<td>0.329</td>
</tr>
<tr>
<td>Fib-4 score</td>
<td>1.5 ± 0.89</td>
<td>1.4 ± 0.72</td>
<td>0.423</td>
</tr>
</tbody>
</table>

**Table 4:** Changes in biochemical parameters with treatment

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.6 ± 1.2</td>
<td>8.8 ± 1.2</td>
<td>0.054</td>
</tr>
<tr>
<td>Platelet count (lakh cells/mm³)</td>
<td>2.02 ± 0.66</td>
<td>2.11 ± 0.59</td>
<td>0.421</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.82 ± 0.35</td>
<td>0.75 ± 0.23</td>
<td>0.268</td>
</tr>
<tr>
<td>Serum albumin (gm/dL)</td>
<td>3.08 ± 0.5</td>
<td>3.05 ± 0.5</td>
<td>0.892</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>36.7 ± 20.1</td>
<td>31.9 ± 14.3</td>
<td>0.610</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>35.5 ± 23.2</td>
<td>31.3 ± 16.7</td>
<td>0.521</td>
</tr>
</tbody>
</table>

**Table 5:** Comparison of clinical and biochemical parameters between patients who achieved and failed SVR-12

<table>
<thead>
<tr>
<th></th>
<th>SVR attained (n = 46)</th>
<th>SVR not attained (n = 2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.3 ± 10.6</td>
<td>33.5 ± 16.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Disease CKD/CGN/DKD</td>
<td>19/17/10</td>
<td>0/2/0</td>
<td>0.23</td>
</tr>
<tr>
<td>Genotype: 1/3</td>
<td>28/9</td>
<td>2/0</td>
<td>0.57</td>
</tr>
<tr>
<td>HCV duration</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.39</td>
</tr>
<tr>
<td>MHD duration</td>
<td>3.4 ± 0.7</td>
<td>3.5 ± 0.7</td>
<td>0.96</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8.7 ± 1.2</td>
<td>7.6 ± 0.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Platelet</td>
<td>2.0 ± 0.6</td>
<td>1.7 ± 0.4</td>
<td>0.55</td>
</tr>
<tr>
<td>Serum creat</td>
<td>6.7 ± 1.8</td>
<td>6.1 ± 0.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.5 ± 0.4</td>
<td>3.07 ± 0.5</td>
<td>0.27</td>
</tr>
<tr>
<td>APRI</td>
<td>0.6 ± 0.4</td>
<td>0.2 ± 0.07</td>
<td>0.24</td>
</tr>
<tr>
<td>Fib-4</td>
<td>1.5 ± 0.8</td>
<td>0.8 ± 0.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Fibroscan</td>
<td>8.5 ± 2.9</td>
<td>5.4 ± 0.2</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**Table 6:** Comparison of various studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients(N)</td>
<td>62</td>
<td>59</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>Genotype</td>
<td>64.9%</td>
<td>46%</td>
<td>79%</td>
<td>77%</td>
</tr>
<tr>
<td>1</td>
<td>29%</td>
<td>32%</td>
<td>15%</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median HCV RNA (IU/MI)</td>
<td>10^6</td>
<td>5.8 Log₁₀</td>
<td>2 × 10⁶</td>
<td>283894.5</td>
</tr>
<tr>
<td>Treatment regime</td>
<td>Sofosbuvir (daily) +</td>
<td>Sofosbuvir (400 mg) +</td>
<td>Sofosbuvir (400 mg) +</td>
<td>Sofosbuvir (400 mg) +</td>
</tr>
<tr>
<td></td>
<td>ribavirin/daclatasvir</td>
<td>velpatasvir (100 mg) +</td>
<td>velpatasvir (100 mg) +</td>
<td>velpatasvir (100 mg) +</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir (Alt day) +</td>
<td>daily</td>
<td>daily</td>
<td>daily</td>
</tr>
<tr>
<td>Ribavirin/daclatasvir</td>
<td>daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR₁²</td>
<td>95.2%</td>
<td>95%</td>
<td>96%</td>
<td>95.6%</td>
</tr>
<tr>
<td>Side effects</td>
<td>Dyspepsia</td>
<td>Headache</td>
<td>Nausea</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td></td>
<td>Headache</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Myalgia</td>
</tr>
</tbody>
</table>

**Discussion**

Despite the lack of dosing recommendations for sofosbuvir-containing regimens for HCV in ESRD patients, it is commonly used as an off-label in clinical practice. Moreover, some of the real-world case series have shown negligible safety concerns with full-dose sofosbuvir-based regimes. Although HCV infection is curable in the general population, there is still hesitancy in treating patients with MHD in this part of the world due to the nonavailability of recommended drugs and the fear of renal adverse events.

In this study, we followed National hepatitis C guidelines in the management of HCV infection in ESRD patients on MHD. Patients were treated with pangenotypic regimes of full-dose sofosbuvir with velpatasvir or daclatasvir based on the presence of fibrosis/cirrhosis.

A recent meta-analysis in patients with CKD on MHD had shown a pooled SVR of 93.2% with a minor difference in terms of genotype. Our study showed an SVR of 95.6% with only two patients not attaining SVR. Both patients had genotype 1 with no fibrosis and were treated with daclatasvir. In a similar study from India, SVR with daclatasvir was achieved at 95.2% (Table 5).

Desnoyer et al. had shown that sofosbuvir or its inactive metabolite did not accumulate with both full or half-dose sofosbuvir between hemodialysis sessions or throughout the treatment course. Importantly, SVR rates were similar in both doses of sofosbuvir. Also, pharmacokinetic properties with different dosing regimens of sofosbuvir were determined, suggesting that the low sofosbuvir dose might be suboptimal in these patients. The adverse events were not related to an elevated toxic metabolite which was
Efficacy and Safety of directly acting Antivirals in Patients with HCV exceeded only in the full-dose sofosbuvir group. The available limited studies with full-dose sofosbuvir-based regimens show similar efficacy across all genotypes and regions.20

Another important concern after efficacy is the safety of different doses of these regimens. Initial studies have shown the worsening of renal function with sofosbuvir-based regimens in patients with moderate renal insufficiency.21 However, it is difficult to attribute it to drug per se and may be related to the natural dynamic course of CKD itself. There are more recent data suggesting excellent safety with full-dose sofosbuvir regimens. Meta-analysis of 11 studies has shown a pooled adverse events rate of 8–11%, with negligible serious events in most of the studies.22 It is important to note that the adverse events were more common in patients with advanced liver disease and patients with prior treatment failure who may require a longer duration of treatment or the addition of ribavirin. Ribavirin is known to cause anemia and increase the need for erythropoetin in CKD patients.21 Our study showed minor adverse events in 10 (18.5%) patients, which were self-limiting and did not require modification or discontinuation of dose. There was no difference in hemoglobin, creatinine, or liver biochemistry posttherapy. These results are comparable to two papers from North India, where rates of adverse effects were 10% with no difference between the predialysis and dialysis groups.22,23

With the newer available DAA, the major determinants of poor response are fibrosis/cirrhosis, prior failure with interferon or earlier DAA therapy, and genotype 3. This population requires 6 months of DAA therapy and resistance testing before initiation of DAA.24,25

In our study, cirrhosis was present in nine (16.6%) patients. None of them had compensated liver disease. Fortunately, all of them achieved SVR with no major adverse effects. A study by Taneya et al.9 in patients with ESRD, found 19.6% of patients with cirrhosis (FibroScan values of >12.5 kPa) among which one patient had decompensated cirrhosis, and another study by Manoj et al. had 23.9% patients with compensated cirrhosis.22,24 FibroScan-based assessment of fibrosis needs costly equipment which may not be available in all centers. We assessed fibrosis with novel biomarkers like APRI, and Fib-4 scoring which showed only four-five patients with cirrhosis. This shows a lower prevalence of patients with significant fibrosis in our cohort. Fibrosis was also assessed pre and posttreatment and showed a significant reduction in fibrosis. This determines the reduction in ongoing inflammation with treatment. A similar reduction has been shown in other studies also.22,23 Also, diabetes was determined as an important confounding factor for the presence of fibrosis. In a study by Hajiani et al., mean liver stiffness scores in the diabetic group were significantly higher than in nondiabetics.23 Diabetes is one of the common causes of nonalcoholic fatty liver disease and may have an additive effect on overall fibrosis.25

Due to the lower number of patients in DAA failed cases (n = 2), a multivariate analysis could not be performed to find predictors for nonattainment of SVR. On univariate analysis, none of the parameters were predictive. Hence, DAAAs were effective in achieving SVR regardless of age, sex, genotype, duration of disease, or degree of fibrosis.

The small sample size, single-center study, and nonestimation of sofosbuvir and its metabolites to correlate side effects were a few of the limitations of the study. Also, comparison with ESRD patients, not on MHD would have given more insight on the adverse effects profile in this difficult-to-treat population. The 6 months courses of full-dose sofosbuvir in patients with concomitant CKD and decompensated liver disease or prior DAA failure cases would further validate the safety profile in these cases. Nevertheless, we had a comparatively larger cohort from a single center with different CKD profiles and a sufficient follow-up period. Also, fibrosis assessment and correlation were done in all patients.

To conclude, data from this study support the use of full-dose sofosbuvir with velpatavir or daclatasvir with excellent efficacy and safety in patients with ESRD on MHD.

References
Clinical Profile of Adult Hemophilia Patients with Special Reference to FISH and WFHPE Score: An Observational Cross-sectional Study

Minal Shastri¹, Renuka Vasava², Vaibhavi Pancholi³, Vaishnavi M Rathod⁴, Gaurav Mehta⁵, Gayatri Laha⁶, Darshankumar Manubhai Raval⁷

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ABSTRACT
Background and objectives: Hemophilia is an X-linked recessive inherited disease affecting the coagulation pathway due to congenital deficiencies in either factor VIII (hemophilia A) or factor IX (hemophilia B). The clinical assessment of a patient’s functional ability and the state of joint conditions is carried out by the clinicians by administering questionnaires namely the Gilbert or the World Federation of Hemophilia Physical Examination (WFH-PE) score for joint condition and Functional Independence Score in Hemophilia (FISH) for joint function.

Here, we have studied the clinical profile of adult hemophilia patients with the short- and long-term complications of the disease. Additionally, the FISH score and the Gilbert score are calculated to assess functional independence and joint condition, respectively. The scores were also compared according to the severity of the disease.

Materials and methods: An observational cross-sectional study of 40 adult hemophilia patients was carried out in Sir Sayajirao General Hospital and Medical College, Baroda, Gujarat, India, over a period of 1 year. Data regarding age, sex, and complications associated with the disease were collected in the form of a questionnaire. The overall mean and standard deviation (SD) of FISH and Gilbert scores were calculated and correlated with the severity of the disease.

Results: The majority of cases (19) were between 20 and 40 years, and most (24) were diagnosed in childhood. All the subjects were male and all except one had hemophilia A. Family history was seen in only half of the cases. Nine had mild, 20 had moderate, and 11 had severe disease. Around 46% of the subjects had joint arthropathy with the knee joint most affected (60%) followed by the ankle (22.5%). The mean FISH score was 27.132 ± 4.0691 with a minimum score of 15 in severe disease suggesting more functional deficit. The average Gilbert score was 7.4 ± 2.985 with a maximum score of 14 in severe disease suggesting more joint damage.

Interpretations and conclusion: All subjects were male and except one all had hemophilia A. Majority were between 20 and 40 years but most were diagnosed before 10 years of age and only 50% had positive family history. Arthropathy is the most common complication with the knee joint being most affected. Majority of mild hemophiliacs achieved a maximum FISH score denoting maximum functional capacity. Compared to existing studies, our study showed better FISH scores in moderate hemophiliacs suggesting more functional independence. While comparing Gilbert’s score to other studies, moderate and severe hemophiliacs in our study showed less joint damage.

INTRODUCTION
Hemophilia is a hereditary disorder of the coagulation pathway. Both hemophilia A and B (which are the two main types) are single-gene disorders consisting of mutation in gene encoding factors VIII and IX, respectively, causing deficiency of these factors. Globally, one in 1,000 people manifest with bleeding disorders out of which hemophilia A constitutes 70% of cases.¹ In India, the prevalence of hemophiliacs is about 0.7 per 1 lakh population. Similarly, the prevalence of hemophilia B is 0.1 per 1 lakh in India; compared to 1.3 per 1 lakh in the United States (US) (13 times lower in India).¹ However, the US has a more robust surveillance system, whereas, in India, the underdiagnoses of cases is prevalent.¹

Male subjects show clinical symptoms, while females carrying the mutated gene are asymptomatic because of the X-linked recessive pattern of inheritance of the disease.² A male receives his only X chromosome from his mother; hence he has a 50% chance of inheriting the disease from a healthy mother, unlike a female who would have to inherit two defective alleles from both her parents. However, 30% of cases have no family history and 80% of those women are carriers of de novo mutated allele.

Due to the deficiency of clotting factors VIII and IX involved in the intrinsic and common coagulation cascades, the risk of hemorrhage or thrombosis is increased in disorders like hemophilia. The disease is clinically categorized into mild, moderate, and severe based on the deficient factor activity. Severe bleeding is commonly noticed at the sites such as joints (knee joints are most common), mucus membranes and gums, and genitourinary tract, with cases like intracranial, gastrointestinal tract (GIT), and neck bleeds posing a significant threat to life.

Bleeding from joints is a major problem, which is often recurrent and chronic, leading to extensive articular cartilage destruction, synovial hyperplasia, joint deformity, muscle atrophy, and contracture formation. Overtime, these lead to joint deformities, physical dependence, and functional disability. Therefore, the onus is on the treating physician to prevent this functional disability and hence more light has to be shed on factors leading to joint deformity.

The World Federation of Hemophilia Physical Examination (WFH-PE) (Gilbert) score measures the health of joints affected by bleeding by scoring the degree of pain, and bleeding, and performing a physical examination of the joint.³ To assess the functional ability of the joint objectively, however, another easily administrable scale called Functional Independence Score in Hemophilia (FISH) is used. Patients are evaluated for seven activities under three categories: self-care, transfers, and mobility.⁴

Here, we aimed to study the clinical profile, severity of disease, common sites of bleeding, and complications in 40 hemophilia patients along with evaluation of structural joint damage using the WFH-PE score and functional deficits using the FISH score.
Clinical Profile of Adult Hemophilia Patients

Materials and Methods

After obtaining approval and clearance from the Scientific Review Committee and Institutional Ethics Committee for human research, a population-based, observational cross-sectional study of 40 hemophilia patients was undertaken at a tertiary care hospital in Vadodara, Gujarat, India over a period of 1 year (2018–2019).

All hemophilia A and B patients over 12 years of age who were admitted into various wards, follow-up clinics, as well as those who came for replacement therapy, were included in the study. Some cases were enrolled from the Haemophilia Society Chapter One registry.

After getting written consent from patients, data was collected in the form of a questionnaire. Data were collected regarding sociodemographic characteristics, presenting complaints, age at diagnosis, clinical presentation, type of hemophilia, and past history. Patients were examined for the site of bleeding, severity, and deformity. The clinical severity of the disease (mild, moderate, and severe) was decided by the deficient factor activity (normal: 50–100%, mild: 5–40%, moderate: 1–5%, severe: <1%).

The WFH-PE (Gilbert) score was calculated for each patient which measures the health of joints most commonly affected by bleeding (knees, elbows, and ankles), by scoring the degree of pain (0–3), bleeding (0–3), and performing a physical examination of the joint (0–12) (Table 1). A score of zero denotes normal joints; 68 points correspond to the worst level of arthropathy.5

However, another scale called FISH was used to assess the functional ability of the joint. Patients were evaluated for seven activities under three categories (self-care, transfers, and mobility), and were marked between 4 and 1 in decreasing order of ability (Table 2).

Score 4: Able to perform the activity without any difficulty.

Score 3: Able to perform the activity without aids or assistance, but with slight discomfort.

Score 2: Needs partial assistance/aids/modified instruments/modified environment to perform the activity.

Score 1: Unable to perform the activity or needs complete assistance to perform the activity.

Scores range from 8 to 32, with 32 being the highest level of independence.7

The mean value with standard deviation (SD) was calculated for both scores and compared with the severity of the disease.

Results

Out of a total of 40 patients, 19 patients (48%) were between 20 and 40 years of age, whereas the least number of patients were above 60 years of age (n = 4, 10%) (Fig. 1). However, most of the patients (n = 24, 60%) were diagnosed before 10 years of age. The pediatric population (age <12 years) was excluded from our study.

All the patients were male. Female hemophiliacs were not identified in the study population. Almost all (n = 39, 97.5%) except one patient had hemophilia A. Although being an inherited disorder, family history has been observed in only half of the cases among the study population.

While categorizing according to severity, 22.5% of cases (n = 9) belong to mild hemophilia in the study population, about half (50%) belong to moderate (n = 20), and 27.5% (n = 11) belong to severe hemophilia.

As can be seen in Figure 2, the knee joint was the most common site of bleeding (60%), followed by the ankle joint (22.5%).

Almost half of the patients in our study had arthropathy as the most common complication (46%), followed by gastrointestinal bleeding (25%) which was further divided into gum bleeding (n = 8, 20%), hematemesis (n = 1, 2.5%), and bleeding per rectum (n = 1, 2.5%) (Fig. 3).

When the FISH score was calculated for objectively evaluating functional ability and

Table 1: World Federation of Hemophilia Physical Examination (WFH-PE) scoring based on physical examination of joints6

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>2</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Angular deformity</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>20–30° valgus (S° varus)</td>
<td>1</td>
</tr>
<tr>
<td>&gt;30° valgus (&gt;5° varus)</td>
<td>2</td>
</tr>
<tr>
<td>Intra-articular crepitation</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>ROM (%)</td>
<td></td>
</tr>
<tr>
<td>Total ROM loss: &lt; 30</td>
<td>0</td>
</tr>
<tr>
<td>Total ROM loss: 10–30</td>
<td>1</td>
</tr>
<tr>
<td>Total ROM loss: &gt;30</td>
<td>2</td>
</tr>
<tr>
<td>Flexion contracture</td>
<td></td>
</tr>
<tr>
<td>&lt;15°</td>
<td>0</td>
</tr>
<tr>
<td>&gt;15°</td>
<td>2</td>
</tr>
<tr>
<td>Instability</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present, but functions are not affected</td>
<td></td>
</tr>
<tr>
<td>Present, but functions are limited</td>
<td>2</td>
</tr>
<tr>
<td>ROM, range of movement</td>
<td></td>
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</tbody>
</table>

Table 2: Functional Independence Score in Hemophilia (FISH) score system

<table>
<thead>
<tr>
<th>Activity</th>
<th>Minimum score</th>
<th>Maximum score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating and grooming</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Bathing</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Dressing</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Transfers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Squatting</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Locomotion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Going up a step</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Walking</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Running</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 1: Patient proportion according to age-groups

Fig. 2: Most common site of bleeding
independence in the patients, only 7.5% of cases ($n = 3$) had a functional independence score below 25. The mean FISH score was $27.132 \pm 4.0691$. Further analysis of the FISH score with the severity of hemophilia showed that severe hemophilia patients had a more functional deficit with a minimum score of 15. Here, a score of 32 indicates the highest level of independence (Table 3).

The joint assessment was done by another score named Gilbert or the WFH-PE score. The majority of 30 (75%) patients of hemophilia had Gilbert score below 10. Mean score $7.4 \pm 2.985$. Correlating the Gilbert score with the severity of hemophilia showed that the severity of hemophilia manifested clinically only in males, while females are healthy carriers, females manifesting the disease are an extreme rarity. In our study also, all the patients were male.

Among 15% of cases in our study were diagnosed with hemophilia at $>20$ years of age, as in a study by Nigam et al., where 17% of cases were diagnosed after 20 years of age. Family history was present in 50% (20 out of 40 cases) of cases in our study. In a study by Mishra et al., 52.2% of patients had a positive family history of hemophilia which was comparable with our data.

While assessing the severity of hemophilia, it is observed that 22.5% of patients in our study had mild disease, 50% had moderate hemophilia, and 27.5% had severe disease. However, a study by Mishra et al. had the majority of patients with severe disease (80.5%), with mild to moderate disease observed in <20% of the study population.

The most common manifestation in our study was bleeding into joints ($n = 18, 45\%$), as seen in the study by Nigam et al. with 64.96% of patients presented with joint bleeding. Gum bleeding was the second most common presenting feature in both ours as well as in the study Nigam. Analysis from our study showed that the weight-bearing joints—knees (60%) and ankles (10%) were commonly affected by hemarthrosis. A similar finding was seen in the study by Mishra et al., involving knee joint in nearly 57.1% of the patients.

Functional Independence Score in Hemophilia is a reliable, inexpensive, performance-based assessment tool to objectively measure the patient’s functional ability that can be easily administered by a trained nurse, doctor, or therapist, therefore, constituting a good alternative to evaluate joint status. In our study, three (7.5%) patients with hemophilia had functional independence (FISH) scores of $<25$. The mean FISH score in our study was $27.132 \pm 4.0691$ which was comparable to another study by Choudhary et al. with a mean FISH score of 28.

In our study, patients with mild and moderate disease had a minimum FISH score of 24 and 25, respectively, whereas severe hemophiliacs had a minimum FISH score of 15. This finding suggests less functional independence. In the study conducted by Ferreira et al., the minimum FISH score in mild disease was 30, while scores of 16 and 14 were noted in moderate and severe disease, respectively. Compared to Ferreira et al’s study, in our study, patients with moderate disease had better FISH scores suggesting more functional independence.

The WFH-PE scale was developed in the 1980s to evaluate hemophilic arthropathy and is still widely used as it is easy to perform and capable of providing an extensive musculoskeletal assessment. The study conducted by Ferreira et al. showed a maximum Gilbert score of 6 in mild disease, 29 in moderate disease, and 34 in severe disease. However, our study reported a mean Gilbert score of $7.4 \pm 2.985$ and a maximum score of 10 in mild disease, 14 in moderate disease, and 14 in severe disease. As a maximum score suggests more joint damage, it can be said that patients with moderate to severe disease in our study suffered less joint damage compared to the study by Ferreira et al.

**Limitations**

- The sample size was small and taken predominantly from a single center. Therefore, generalization of the result to a larger population would not be appropriate.
- Due to the small sample size, we were not able to establish a statistically significant correlation between the severity of disease with FISH and Gilbert scores, for which larger studies are required.

**Conclusion**

Out of a total of 40 patients, almost all the patients had hemophilic A except one with hemophilia B, suggesting a higher prevalence.

---

**Table 3: FISH score and the severity of hemophilia**

<table>
<thead>
<tr>
<th>Severity</th>
<th>No. of patients</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>9</td>
<td>24</td>
<td>32</td>
<td>29.77</td>
</tr>
<tr>
<td>Moderate</td>
<td>20</td>
<td>25</td>
<td>32</td>
<td>27.35</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>15</td>
<td>32</td>
<td>24.277</td>
</tr>
<tr>
<td></td>
<td>Total mean</td>
<td></td>
<td></td>
<td>27.132</td>
</tr>
</tbody>
</table>

**Table 4: Joint assessment by Gilbert score and the severity of hemophilia**

<table>
<thead>
<tr>
<th>Severity</th>
<th>No. of patients</th>
<th>Gilbert score</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>9</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>20</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Total mean</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of hemophilic A. All patients were male in our study. Almost half of our study population was between 20 and 40 years of age. However, most of them were diagnosed below 10 years of age. Family history was present in half of the cases. Bleeding into joints was the most common presenting complaint followed by gum bleeding. Half of the study population had a moderate form of the disease. Recurrent bleeding into the joint progresses to chronic progressive hemophilic arthropathy, and the knee joint was involved the most among all weight-bearing joints.

The FISH and Gilbert scores are extremely useful instruments in clinical practice in the absence of imaging studies such as magnetic resonance imaging, which are considered very sensitive to detect early joint damage but are costly and relatively inaccessible. Only 7.5% of patients had a low FISH score (<25), whereas the majority of mild hemophiliacs achieved a maximum FISH score. Severe hemophiliacs had a maximum Gilbert score (14) compared to mild hemophiliacs, suggesting more joint damage.

In our study, we have studied several parameters such as age, gender, type of hemophilia, presence of family history, the severity of disease, site of bleeding, common complications, and assessment of functional independence and joint damage by FISH and Gilbert score respectively, along with its relation to severity. Therefore, this study outlines detailed clinical, treatment, and functional profiles of hemophilia patients in a single study group.

**References**

Knowledge Dissemination for elimination Role of Academic Institutions in Eliminating Viral Hepatitis

Tushar Prabhakar, Kanica Kaushal

Received: 04 November 2022; Revised: 24 February 2023; Accepted: 28 March 2023

**Abstract**

Introduction: India is looking to achieve hepatitis elimination status by 2030 through vaccination, diagnostic tests, medicines, and education campaigns. Awareness generation is essential to orient people regarding hepatitis B and C. The present study was done to assess the knowledge regarding hepatitis among students and staff of academic institutions and raise awareness through a series of webinars.

Materials and methods: A cross-sectional study was conducted in 12 academic institutes from across the country between February and March 2022. The study included the dissemination of knowledge in the form of a webinar and the administration of a pre and postwebinar survey to assess the difference in the knowledge levels.

Results: A total of 914 individuals participated in the sessions. The mean baseline score for general epidemiology (max = 13 points), treatment and complications (max = 7 points), and prevention (max = 5 points) were 10.9 ± 2.1, 4.6 ± 1.3, and 3.2 ± 1.3, respectively. Overall, the mean score increased from 18.5 ± 3.6 to 20.4 ± 3.4 postwebinar, with an increase of +7.3%.

Conclusion: The study observed significant improvement in knowledge among the participants following a low-cost 1-day training in webinar mode. Such training programs can be upscaled and help in educating the general public on hepatitis.

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**Introduction**

Viral hepatitis, especially B and C, is among the leading causes of cirrhosis of the liver, liver cancer, and acute liver failure. World Health Organisation, through its sustainable development goals, aims to reduce, by 2030, the incidence of chronic hepatitis infections by 90% and mortality by 65% as compared to baseline data of 2015.

Viral hepatitis has been recognized as a major global public health problem, and an estimated 254 million people are living with chronic hepatitis B and C, presently. Over 1.1 million people died in 2019 due to viral hepatitis B and C, exceeding the number of deaths due to human immunodeficiency virus. What makes hepatitis a public health issue of grave concern is the fact that of these, less than one in five (17.9%, 45.6 million) people living with hepatitis were aware of their hepatitis status, and only 6.3% (16 million) received treatment.

Academic institutions like medical colleges are an important cog in the wheel of awareness generation by engaging with the community at a grassroots level. Awareness generation workshops and webinars can bring about a positive change in the level of understanding about health issues and the significance of risk reduction measures. Recent studies have shown poor awareness and gaps in knowledge regarding the prevention and control of hepatitis in the staff of healthcare institutions in India.

Institute of Liver and Biliary Sciences (ILBS), Delhi, India, has conceptualized the “Empowering People Against Hepatitis: The EMPATHY Campaign,” under which initiatives are taken to engage academic institutions for community outreach activities and awareness generation. These activities act as an added service to the National Viral Hepatitis Control Program (NVHCP) of India, which aims to achieve hepatitis elimination by 2030.

The objective of the present study was to raise awareness regarding viral hepatitis among the students, faculty members, and staff in academic institutions and to motivate them to disseminate knowledge on the prevention and control of viral hepatitis among their peers and community members.

**Materials and Methods**

The cross-sectional study was conducted in 12 academic institutions from across the country. The study included the dissemination of knowledge in the form of a webinar and the administration of a pre and postwebinar survey to assess the difference in the knowledge levels. The webinars were conducted between the months of February and March 2022 via online mode, where participants attended the sessions either individually or as a group from their respective institutional lecture halls/ classrooms.

A broad scientific agenda for the webinar was developed in consultation with faculty from the Departments of Epidemiology, Virology, and Hepatology from ILBS. Each webinar was planned to be around 3 hours long with sessions under the broad topics of “burden of hepatitis B and C in India, transmission and prevention of hepatitis B and C at the community level, screening, vaccination strategy, and health education for hepatitis B and C at a community level, NVHCP, and postexposure prophylaxis for hepatitis B virus (HBV) and hepatitis C virus.”

All the participants who attended the webinar were administered a self-designed, pretested, and close-ended questionnaire in English. The questionnaire (Annexure 1) was carefully prepared after a thorough literature search and evaluation of the online resources. It was divided into two sections—section 1 included sociodemographic details of the participants (age, gender, educational level, marital status, and hepatitis B immunization status) and section 2 comprised 26 questions on knowledge and awareness regarding general epidemiology, prevention, and control and management strategies of hepatitis B and C. The questions were in the form of multiple-choice questions, and the participants were asked to choose the single best response. Finally, at the end of each event day, a question and answer session was conducted for the resolution of any pending queries from the participants.

Data collected from online proformas were coded, entered, and cleaned in IBM Statistical Package for the Social Sciences statistics for Windows Version 26.0. Quantitative assessment was done for baseline responses as well as postwebinar responses. All quantitative variables were analyzed in...
Knowledge Dissemination for elimination Role of Academic Institutions

terms of mean, standard deviation(SD), and proportions were calculated. Paired t-test was used to compare the mean scores pre and postwebinar to determine if there was any difference in knowledge levels before and after the webinar.

Results

The list of 12 participating academic institutions is given in Table 1. A total of 914 participants who attended the webinars successfully filled out the pre and posttest survey forms. Of these, 654 (71.6%) were females, and the remaining were males (Table 2). The mean age of the study participants was 29.0 ± 10.5 years (range = 18–66 years). All the participants had completed at least senior secondary schooling, and the majority (n = 710; 77.7%) had received a graduation degree or more. Close to two-thirds (65.4%) of respondents were aware that there are five common forms of hepatitis.

Knowledge regarding transmission through blood and blood products was the highest (94.7%), whereas participants were least aware of transmission through tattooing and usage of used razors (82.1%).

The majority of the participants were aware that complications of hepatitis B (86.8%) and C (84.1%) included cirrhosis and hepatocellular carcinoma. While most (90.7%) of the participants were aware that hepatitis B could be prevented by vaccination, only a third of the total (36.8%) were aware that hepatitis C could be treated completely with oral medication. Knowledge regarding hepatitis B vaccination doses and the schedule was appropriate in 62.6 and 51.3% of study participants, respectively.

The mean score of the participants prewebinar came out to be 18.5 ± 3.6 [median = 19; interquartile range (IQR) = 16–21], whereas, postwebinar it was 20.4 ± 3.4 (median = 21; IQR = 18–23) (Table 6).

Table 1: List of national webinars conducted by ILBS on creating awareness of viral hepatitis B and C

<table>
<thead>
<tr>
<th>S no.</th>
<th>Date</th>
<th>Name of organization</th>
<th>Total participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2nd February 2022</td>
<td>Engender Health, Delhi, India</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>3rd February 2022</td>
<td>Dr B R Sur Homoeopathic Medical College, Hospital &amp; Research Centre, Delhi, India</td>
<td>109</td>
</tr>
<tr>
<td>3</td>
<td>4th February 2022</td>
<td>Indian Medical Association, Nagpur, Maharashtra, India</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>8th February 2022</td>
<td>Department of Physiotherapy, Faculty of Allied Health Sciences, Manav Rachna International Institute of Research and Studies, Faridabad, Haryana, India</td>
<td>116</td>
</tr>
<tr>
<td>5</td>
<td>11th February 2022</td>
<td>Department of Nutrition &amp; Dietetics, Faculty of Allied Health Sciences, Manav Rachna International Institute of Research &amp; Studies, Faridabad, Haryana, India</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>14th February 2022</td>
<td>National Academy of Medical Science, Delhi, India</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>23rd February 2022</td>
<td>Department of Periodontology, Manav Rachna Dental College, Faridabad, Haryana, India, FDS, MRIIRS</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>25th February 2022</td>
<td>All India Institute of Medical Sciences, Deoghar, Jharkhand, India</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>28th February 2022</td>
<td>Department of Periodontology Manav Rachna Dental College, Faridabad, Haryana, India, FADS, MRIIRS</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>9th March 2022</td>
<td>All India Institute of Medical Sciences, Manglagiri, Andhara Pradesh, India</td>
<td>22</td>
</tr>
<tr>
<td>11</td>
<td>10th March 2022</td>
<td>United Way, Mumbai, Maharashtra, India</td>
<td>120</td>
</tr>
<tr>
<td>12</td>
<td>12th March 2022</td>
<td>Lady Irwin College, Delhi, India</td>
<td>87</td>
</tr>
</tbody>
</table>

FADS, Faculty of Architecture and Design; FDS, Faculty of Dental Sciences; MRIIRS, Manav Rachna International Institute of Research and Studies

Table 2: Gender-wise distribution of sociodemographic variables among study participants (N = 914)

<table>
<thead>
<tr>
<th>Sociodemographic variables</th>
<th>Males</th>
<th>%</th>
<th>Females</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;30 years</td>
<td>128</td>
<td>49.2</td>
<td>469</td>
<td>71.7</td>
<td>597</td>
<td>65.3</td>
</tr>
<tr>
<td>≥30 years</td>
<td>132</td>
<td>50.8</td>
<td>185</td>
<td>28.3</td>
<td>317</td>
<td>34.7</td>
</tr>
<tr>
<td>Level of literacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate/class 12</td>
<td>48</td>
<td>18.5</td>
<td>156</td>
<td>23.9</td>
<td>204</td>
<td>22.3</td>
</tr>
<tr>
<td>Graduate</td>
<td>80</td>
<td>30.8</td>
<td>288</td>
<td>44.0</td>
<td>368</td>
<td>40.3</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>110</td>
<td>42.3</td>
<td>165</td>
<td>25.2</td>
<td>275</td>
<td>30.1</td>
</tr>
<tr>
<td>Doctorate and above</td>
<td>22</td>
<td>8.5</td>
<td>45</td>
<td>6.9</td>
<td>67</td>
<td>7.3</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>132</td>
<td>50.8</td>
<td>453</td>
<td>69.3</td>
<td>585</td>
<td>64.0</td>
</tr>
<tr>
<td>Married</td>
<td>126</td>
<td>48.5</td>
<td>197</td>
<td>30.6</td>
<td>323</td>
<td>35.9</td>
</tr>
<tr>
<td>Divorced</td>
<td>2</td>
<td>0.8</td>
<td>4</td>
<td>0.6</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>Hepatitis B vaccination status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, all doses taken</td>
<td>164</td>
<td>63.1</td>
<td>365</td>
<td>55.8</td>
<td>529</td>
<td>57.9</td>
</tr>
<tr>
<td>Yes, partial doses taken</td>
<td>26</td>
<td>10.0</td>
<td>84</td>
<td>12.8</td>
<td>110</td>
<td>12.0</td>
</tr>
<tr>
<td>Not sure</td>
<td>37</td>
<td>14.2</td>
<td>106</td>
<td>16.2</td>
<td>143</td>
<td>15.6</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>12.7</td>
<td>99</td>
<td>15.1</td>
<td>132</td>
<td>14.4</td>
</tr>
</tbody>
</table>
There was a significant average difference of 1.9 points between pre and posttest study results and a moderate positive correlation of 0.635. Further, domain-wise mean preknowledge scores were 10.9 ± 2.1 out of 13 in general epidemiology, 4.6 ± 1.3 out of 7 in the treatment and complications domain, and 3.2 ± 1.3 out of 5 in the prevention domain. Posttraining mean knowledge scores for all the domains showed an increment, and all the increments were found to be statistically significant (p < 0.001). The prewebinar mean score for participants from medical institutions was 19.2 ± 3.3, whereas, for those from other institutions, it was 17.3 ± 3.8.

Table 3: Knowledge of study participants regarding general epidemiology (symptoms and modes of transmission) of hepatitis B and C (N = 914)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Correct response (N = 914)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major organs affected by hepatitis B and C</td>
<td>861</td>
<td>94.2</td>
</tr>
<tr>
<td>The causative agent of hepatitis</td>
<td>814</td>
<td>89.1</td>
</tr>
<tr>
<td>Number of common types of hepatitis</td>
<td>598</td>
<td>65.4</td>
</tr>
<tr>
<td>Most common signs and symptoms of acute hepatitis B infection</td>
<td>794</td>
<td>86.9</td>
</tr>
<tr>
<td>Spread of hepatitis B and C through infected blood and blood products</td>
<td>866</td>
<td>94.7</td>
</tr>
<tr>
<td>Spread of hepatitis B and C spread through the reuse of syringes and needles</td>
<td>840</td>
<td>91.9</td>
</tr>
<tr>
<td>Spread of hepatitis B and C spread through tattooing and sharing razors</td>
<td>750</td>
<td>82.1</td>
</tr>
<tr>
<td>Spread of hepatitis B and C spread through sexual contact with an infected person</td>
<td>786</td>
<td>86.0</td>
</tr>
<tr>
<td>Spread of hepatitis B and C spread from the infected mother to the fetus</td>
<td>787</td>
<td>86.1</td>
</tr>
</tbody>
</table>

Table 4: Knowledge of study participants regarding treatment and complications of hepatitis B and C (N = 914)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Correct response (N = 914)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B can result in cirrhosis or hepatocellular cancer if not treated in time</td>
<td>793</td>
<td>86.8</td>
</tr>
<tr>
<td>Hepatitis C can result in cirrhosis or hepatocellular cancer if not treated in time</td>
<td>769</td>
<td>84.1</td>
</tr>
<tr>
<td>Type of parenterally transmitted hepatitis infection that is completely curable</td>
<td>336</td>
<td>36.8</td>
</tr>
<tr>
<td>Hepatitis needs lifelong treatment</td>
<td>569</td>
<td>62.3</td>
</tr>
</tbody>
</table>

Table 5: Knowledge of study participants regarding prevention of hepatitis B and C (N = 914)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Correct response (N = 914)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of parenterally transmitted hepatitis that has an efficacious vaccine for prevention</td>
<td>829</td>
<td>90.7</td>
</tr>
<tr>
<td>Number of doses for complete vaccination of adults against hepatitis B infection</td>
<td>572</td>
<td>62.6</td>
</tr>
<tr>
<td>Schedule of hepatitis B vaccination among adults</td>
<td>469</td>
<td>51.3</td>
</tr>
</tbody>
</table>

Table 6: Mean score of study participants regarding knowledge of hepatitis B and C (N = 914)

<table>
<thead>
<tr>
<th></th>
<th>Pretest (mean ± SD)</th>
<th>Posttest (mean ± SD)</th>
<th>Mean difference percentage*</th>
<th>Correlation*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>General epidemiology (max = 13 points)</td>
<td>10.9 ± 2.1</td>
<td>11.7 ± 1.6</td>
<td>+5.4%</td>
<td>0.643</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment and complications (max = 7 points)</td>
<td>4.6 ± 1.3</td>
<td>5.1 ± 1.5</td>
<td>+7.3%</td>
<td>0.487</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevention (max = 5 points)</td>
<td>3.2 ± 1.3</td>
<td>3.8 ± 1.1</td>
<td>+9.7%</td>
<td>0.473</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total (max = 26 points)</td>
<td>18.5 ± 3.6</td>
<td>20.4 ± 3.4</td>
<td>+7.3%</td>
<td>0.635</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Paired t-test

**Discussion**

An estimated 4.5 million premature deaths from viral hepatitis could be prevented in low- and middle-income countries by 2030 through vaccination, diagnostic tests, medicines, and education campaigns. A comprehensive program for awareness generation, therefore, is the need of the hour to spread awareness about hepatitis B and C and to orient people who are infected so as to ensure optimum health-seeking behavior and live a life without being stigmatized. These webinars raised awareness amongst the participants regarding the cause and mode of transmission of hepatitis, signs and symptoms, associated complications, status of availability of treatment against hepatitis, and various steps to prevent the spread of hepatitis B and C.

The current study sought to assess the knowledge of hepatitis B and C in a mixed cohort of healthy individuals from medical as well as nonmedical academic institutions. Results of the study revealed that even though fair knowledge regarding hepatitis B and C was present in the majority of study participants, a significantly lower fraction had been fully immunized against hepatitis B from both participants from medical as well as nonmedical institutions. Those who had received full immunization coverage with three doses of the hepatitis B vaccine were similar to other studies conducted on college-going students. Participants from nonmedical institutes had a relatively lower overall mean prewebinar score as compared to those from medical institutes. Knowledge regarding vaccines for the prevention of hepatitis B and the availability of oral medication for the treatment of hepatitis C was relatively low among the study participants, which is similar to other studies done with community participants in different parts of the world.

Statistical analysis showed that the scientific module, along with the online presentations, helped the participants to enhance their
knowledge of viral hepatitis. With a one-day training session on viral hepatitis, we were able to statistically improve the mean knowledge score from 18.5 ± 3.6 in the pretest to 20.4 ± 3.4 in the posttest. A similar kind of improvement was reported in a study by Keshan et al. following a 1-day teaching session.

As per our findings from existing literature, this is a unique study that has assessed knowledge and awareness about viral hepatitis B and C among a mixed cohort of participants enrolled in various academic institutions across India while also assessing the effect of 1-day training via webinar mode in improving the knowledge level of the participants.

**Conclusion**

The study was able to assess the effect of a 1-day training in webinar mode regarding the knowledge level of the students and staff of academic institutions on the burden, modes of transmission, prevention, and diagnostic management of viral hepatitis. Overall, the study observed significant improvement in knowledge among the participants following the educational session. Such low-cost training programs can be upscaled and help in educating the general public on hepatitis and other various health-related topics across the country.

**Limitations**

There is a possibility of response-shift bias because of its default pre–post design.

**References**


Annexure 1: Questionnaire on knowledge and awareness regarding general epidemiology, prevention and control, and management strategies of viral hepatitis

<table>
<thead>
<tr>
<th>S No.</th>
<th>Theme</th>
<th>Questions</th>
<th>Pretest</th>
<th>Posttest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General epidemiology</td>
<td>Have you heard of the disease termed “hepatitis”?</td>
<td>885</td>
<td>898</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Have you heard of hepatitis B?</td>
<td>875</td>
<td>894</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Have you heard of hepatitis C?</td>
<td>843</td>
<td>891</td>
</tr>
<tr>
<td>4</td>
<td>General epidemiology</td>
<td>Which organ do hepatitis B and C mainly affect?</td>
<td>861</td>
<td>892</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>How many common types of viral hepatitis are there?</td>
<td>598</td>
<td>738</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>What is the cause of hepatitis B and C?</td>
<td>814</td>
<td>854</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>How do hepatitis B and C spread?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>General epidemiology</td>
<td>By contaminated water and food</td>
<td>602</td>
<td>676</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>By infected blood and blood products</td>
<td>866</td>
<td>894</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>By reuse of syringes and needles</td>
<td>840</td>
<td>857</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>By tattooing and sharing razors</td>
<td>750</td>
<td>827</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>By sexual contact with an infected person</td>
<td>786</td>
<td>867</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>By handshaking and hugging</td>
<td>813</td>
<td>788</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>From infected mother to fetus</td>
<td>787</td>
<td>861</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>By mosquito bite</td>
<td>739</td>
<td>765</td>
</tr>
<tr>
<td>16</td>
<td>Treatment and complications</td>
<td>What are the most common signs and symptoms of acute hepatitis B infection?</td>
<td>794</td>
<td>825</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>A person can be infected with hepatitis B and can still remain asymptomatic</td>
<td>779</td>
<td>824</td>
</tr>
<tr>
<td>18</td>
<td>Treatment and complications</td>
<td>Which of the following infections can result in cirrhosis or hepatocellular cancer if not treated in time?</td>
<td>716</td>
<td>723</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>Hepatitis A</td>
<td>793</td>
<td>818</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>Hepatitis B</td>
<td>769</td>
<td>804</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>Hepatitis C</td>
<td>285</td>
<td>438</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>Hepatitis D</td>
<td>722</td>
<td>736</td>
</tr>
<tr>
<td>23</td>
<td>Prevention</td>
<td>Which of the following infections is curable?</td>
<td>336</td>
<td>464</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>Treatment for the following needs to be taken lifelong as the disease is not curable.</td>
<td>569</td>
<td>674</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>Hepatitis A</td>
<td>585</td>
<td>663</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td>Hepatitis B</td>
<td>829</td>
<td>831</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td>Hepatitis C</td>
<td>468</td>
<td>554</td>
</tr>
<tr>
<td>28</td>
<td>Prevention</td>
<td>Complete vaccination (for adults) against HBV requires how many doses?</td>
<td>572</td>
<td>762</td>
</tr>
<tr>
<td>29</td>
<td></td>
<td>The hepatitis B vaccine schedule among adults is</td>
<td>469</td>
<td>644</td>
</tr>
</tbody>
</table>
Non-smoker COPD represents a clinically Distinct Phenotype: A Prospective Observational Study

Richa Rani1, Pawan K Singh2, Manjunath B Govindagoudar3, Tarana Gupta4, Parul5, Dhruva Chaudhry6*

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ABStract

Background: Chronic obstructive lung disease (COPD) has been characterized as a smoker’s disease, which has resulted in the usual exclusion of never-smokers from COPD studies. It is now recognized that never-smokers account for nearly one-fourth of all COPD cases, and thus airflow limitation in never-smokers needs further evaluation. Our study aims to elucidate the clinical and physiological aspects of COPD in nonsmokers and to compare smokers and nonsmokers with COPD.

Materials and methods: A total of 200 naïve sequential patients with COPD were recruited. The severity of airflow limitation in COPD patients was defined as per Global Initiative for COPD (GOLD) 2019 criteria, and the severity of breathlessness was assessed by the modified Medical Research Council (MRC) dyspnea scale. Data was collected using a patient pro forma, including risk factors for COPD and detailed clinical history. Phenotypic differences along with biomass exposure between never-smokers and smokers were analyzed.

Results: Compared to smokers, never-smokers presented at a younger age (55.69 ± 11.5 years; p < 0.001), with a longer duration of dyspnea (5.05 ± 9.46 vs 7.35 ± 6.98 years, p < 0.01). Chest radiographs revealed hyperinflation in a higher number of smokers as compared to never-smokers (82.9 vs 64.6%, p < 0.05). On spirometry evaluation, smokers were found to have significantly poorer lung function [forced expiratory volume in first second (FEV1) 40.36 ± 17.76%; forced vital capacity (FVC): 58.16 ± 17.02%] as compared to never-smokers (FEV1: 47.1 ± 16.47%; FVC: 67.38 ± 17.02%) with p < 0.05. With respect to severity at presentation, most (45.8%) never-smokers presented with stage 2 COPD as compared to the majority of smokers (46.7%) who presented with stage 3 COPD (p-value of <0.05). Absolute eosinophil count (AEC) and eosinophil proportion in total leucocyte count (TLC) was significantly higher in never-smokers as compared to smokers (56.02 vs 6.28; p-value of <0.001). Risk factor analysis showed mean biomass exposure index was significantly higher in never-smokers as compared to smokers (204.2 vs 309 ± 238.8, p < 0.05). Absolute eosinophil count (AEC) and eosinophil proportion in total leucocyte count (TLC) was significantly higher in never-smokers as compared to smokers (204.2 ± 238.8, p < 0.05). Risk factor analysis showed mean biomass exposure index was significantly higher in never-smokers as compared to smokers (56.02 vs 6.28; p-value of <0.001).

Conclusion: Compared to smokers, COPD in never-smokers presents at a younger age, with a longer duration of dyspnea and higher eosinophil count. Biomass exposure is one of the major contributors to etiologies for COPD in nonsmokers.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disability, adjusted life years, and deaths worldwide.¹ As per the 2001 report of the GOLD, COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways following exposure to noxious particles or gases.² Due to progressive loss of lung parenchyma in COPD, patients tend to have an adverse impact on the health-related quality of life.³

Historically COPD has been considered a smokers’ disease, which has resulted in the usual exclusion of nonsmokers from the studies pertaining to COPD,⁴ -⁷ but it’s now recognized that never-smokers account for nearly one-fourth of all COPD cases⁸ ¹⁰ and thus the airflow limitation in nonsmokers needs further evaluation.¹¹ Data on the pathogenesis of COPD in nonsmokers is limited compared to that in smokers. Some studies have explored risk factors other than smoking that play a role in the development of COPD among nonsmokers, like air pollution, occupational exposure, asthma, and antiprotease deficiency.¹² ¹⁻¹⁸ A study on phenotypic comparison by Salvi et al. showed that compared to COPD in smokers, nonsmokers present with the obstructive pulmonary disease at a younger age with a predominant small airway disease with less emphysema, preserved lung diffusion, and a slower rate of decline in lung functions.¹⁹ A study on COPD among nonsmokers done by Jindal et al. further demonstrated the higher rate of exacerbations and healthcare resource utilization among the subgroup with no smoking history.²⁰

Despite this, there is a dearth of evidence, both prospective and cross-sectional which delves into the subject of nonsmokers’ COPD and associated risk factors. The evidence from India is further scarce.

The present study is an attempt to elucidate the clinical and physiological aspects of COPD in nonsmokers and to compare the smoker’s COPD phenotype with that of a nonsmoker, with a particular interest in the risk factors associated with the development of the disease.

MATERIALS AND METHODS

Study design and setting: The present study is a prospective cross-sectional observational study conducted in the Medicine, Pulmonary, and Critical Care Department at a tertiary care teaching hospital in Northern India. The study was conducted over a period of 1 year and 6 months (July 2019–December 2020). Prior Ethical and Institutional Review Board clearance was taken vide letter number BREC/293/Ins/HR/2013/RR-19 dated 1st February 2020.

Sample size and study participants: The study sequentially recruited 200 naïve patients with COPD from the outpatient department. Inclusion criteria included >40 years of age, history of cough, expectoration, and/or breathlessness for over 3 months in 1 year for 2 or more years, and spirometry showing post bronchodilator forced expiratory volume in first second (FEV1)/forced vital capacity (FVC) ratio of <0.70 in past 2 months and having insignificant bronchodilator reversibility. Patients with a history of tuberculosis were excluded from the study. Additional exclusion criteria used were the presence of alternate causes of chronic dyspnea or pulmonary symptoms, such as obstructive sleep apnea, neuromuscular

REFERENCES


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disorders (diaphragmatic paralysis and myasthenia gravis), thoracic wall disease (such as flail chest and kyphoscoliosis), congestive heart failure, pleural effusion, pneumothorax, pulmonary embolism, pulmonary edema, interstitial lung diseases, or pulmonary artery hypertension. Patients suffering from any active malignancy or history of hospitalization in the recent 1 month or prior thoracic surgery were also excluded. Bronchial asthma was considered in all cases, and the presence of atopy with the variability of clinical symptoms was used as a criterion of exclusion.

Diagnostic criteria For COPD: Spirometry was performed for diagnosis and classification of the severity of COPD by GOLD 2019 criteria. The severity of airflow limitation in COPD patients was defined by GOLD criteria, and the severity of breathlessness was assessed by a modified Medical Research Council (MRC) dyspnea scale. Bronchodilator reversibility was used to rule out the diagnosis or overlap of bronchial asthma.

Data collection and statistical analysis: A patient pro forma including detailed clinical history, risk factors for COPD, health status, and comorbidities was administered. Patients also underwent routine laboratory investigations, including baseline biochemical investigations along with Absolute eosinophil count (AEC). The data was initially collected in paper format and later entered in a coded format in Microsoft excel® version 2019, and the final analysis was done using IBM® Statistical Package for the Social Sciences version 26.0. Descriptive statistics were used to summarize demographic characteristics, and an unpaired t-test was used for quantitative data comparison of all clinical indicators between two independent groups. The Chi-squared test and Fisher exact test were used for qualitative data. For multivariate analysis, the Pearson correlation test was done. The level of significance was set at \( p \leq 0.05 \).

Ethical considerations: The study was approved by the Institutional Review Board and Ethics Committee. Confidentiality of the data was maintained, and no personal identifier was used or shared in the study analysis.

**Results**

Over the period of study duration, 450 subjects were screened, of which 200 patients were included in the study (Fig. 1). The mean age of recruited subjects was 60 ± 9.9 years, with 41 females and 159 males. There were 48 nonsmokers and 152 smokers among the participants. The mean age of nonsmokers was 55.69 ± 11.5 years, and of smokers was 60.65 ± 9.10 years (\( p \)-value of <0.001). Most patients belonged to the age group between 60 and 69, both smokers 38.1% (58/152) and nonsmokers 35.4% (17/48) (Table 1). The majority of the study participants were from rural areas and constituted nearly 61% of the total study subjects.

Table 2 summarizes the phenotypic differences among smokers and nonsmokers with their associated \( p \)-values. Nonsmokers were found to have a longer duration of shortness of breath at presentation as compared to smokers, with a mean difference of 2.30 years (5.05 ± 4.96 vs 7.35 ± 6.98 years, a \( p \)-value of <0.01). Duration of other respiratory symptoms in the nonsmoker COPD population was also higher when compared to the smokers COPD subgroup, albeit the difference was not found to be statistically significant.

Upon evaluation of chest radiographs, 82.9% (126 out of 152) of smokers showed hyperinflation, in contrast to nonsmokers, where only 64.6% (31 out of 48) showed features of hyperinflation (\( p < 0.05 \)). High-
Nonsmoker COPD represents a clinically Distinct Phenotype

### Discussion

The present study sequentially enrolled 200 naïve cases of COPD after objectively confirming the diagnosis and found that there were significant phenotypic differences among smokers and nonsmokers with COPD.

Smoking has been considered the single most important risk factor for COPD, but there is mounting evidence that the disease also affects people who have never smoked.10

In addition to biomass exposure, other risk factors have also been associated with COPD among nonsmokers like outdoor pollution, occupational exposure to dust and fumes, history of repeated lower respiratory tract

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**Table 2: Phenotypic characteristics of the COPD patients**

<table>
<thead>
<tr>
<th>Phenotypic characteristics</th>
<th>Smoker</th>
<th>Nonsmoker</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms (in years)</td>
<td>4.79 (6.002)</td>
<td>5.35 (6.15)</td>
<td>0.57</td>
</tr>
<tr>
<td>Chronic Cough</td>
<td>1.92 (3.102)</td>
<td>2.58 (3.712)</td>
<td>0.22</td>
</tr>
<tr>
<td>Wheezing</td>
<td>4.92 (6.706)</td>
<td>4.96 (5.87)</td>
<td>0.97</td>
</tr>
<tr>
<td>Sputum production</td>
<td>5.05 (4.96)</td>
<td>7.35 (6.98)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiological findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperinflation on chest radiography</td>
<td>82.9% (126/152)</td>
<td>64.6% (31/48)</td>
<td>0.03</td>
</tr>
<tr>
<td>Bronchial wall thinking on HRCT chest</td>
<td>(21/42)</td>
<td>(6/10)</td>
<td>0.56</td>
</tr>
<tr>
<td>Bullae on HRCT chest</td>
<td>(12/42)</td>
<td>(2/10)</td>
<td>0.26</td>
</tr>
<tr>
<td>Emphysema on HRCT chest</td>
<td>(26/42)</td>
<td>(6/10)</td>
<td>0.64</td>
</tr>
<tr>
<td>Spirometry findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (in L)</td>
<td>2.24 (0.75)</td>
<td>2.17 (0.93)</td>
<td>0.56</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>58.16 (17.02)</td>
<td>67.38 (17.02)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV (in L)</td>
<td>1.28 (0.63)</td>
<td>1.38 (0.64)</td>
<td>0.34</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>40.36 (17.76)</td>
<td>47.1 (16.47)</td>
<td>0.02</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>51.25 (10.007)</td>
<td>51.25 (9.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>COPD severity (GOLD staging)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>8</td>
<td>2</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage 2</td>
<td>36</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>71</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>37</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Blood picture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>2.23 (2.02)</td>
<td>3.06 (2.81)</td>
<td>0.06</td>
</tr>
<tr>
<td>AEC</td>
<td>232.49 (204.15)</td>
<td>309.63 (238.76)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total leukocyte count (TLC)</td>
<td>4347.37 (3473.85)</td>
<td>4051.67 (3510.32)</td>
<td>0.6</td>
</tr>
<tr>
<td>% Granulocytes</td>
<td>4.99 (2.52)</td>
<td>4.42 (2.58)</td>
<td>0.17</td>
</tr>
<tr>
<td>% Lymphocytes</td>
<td>2.16 (1.701)</td>
<td>2.06 (1.52)</td>
<td>0.71</td>
</tr>
<tr>
<td>% Monocytes</td>
<td>2.53 (2.38)</td>
<td>2.77 (2.66)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

HRCT, high-resolution computed tomography; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; GOLD, Global Initiative for COPD; The bold values highlight observations

---

resolution computed tomography thorax was done in 42 smokers and 10 nonsmokers to look for bronchial wall thickening, the presence of bullae, and/or emphysematous changes. The bronchial wall changes were seen in 60% of nonsmokers as compared to 50% of smokers, and bullae were seen in 28% of smokers and 20% of nonsmokers. Similarly, emphysema was observed in 60% of nonsmokers and nearly 62% of smokers; however, none of the differences in these findings were statistically significant.

Spirometry evaluation revealed that mean FEV1 was 40.36 ± 17.8% in smokers and 47.1 ± 16.5% in nonsmokers, and mean FVC was 58.16 ± 17% among smokers and 67.38 ± 17% among nonsmokers; both the values were greater in nonsmokers as compared to smokers and the difference was statistically significant (p < 0.001 and p < 0.05, respectively). FEV1/FVC ratio was similar in the two groups.

At the time of presentation, all the patients were graded for their severity of COPD according to the GOLD staging. The distribution of COPD severity is provided in Table 2. It was observed that among nonsmokers majority of the patients presented with stage 2 (moderate) COPD, whereas among smokers, 46.7% of the total cases presented with severe COPD in stage 3 (p < 0.05).

Analysis of data of complete hemograms of the participants revealed a lower, but statistically insignificant, TLC among nonsmokers as compared to smokers. However, the AEC and eosinophil proportion in TLC were higher in nonsmokers as compared to the smokers (232 ± 204.15 vs 309 ± 238.76, p < 0.05).

Biomass exposure as a risk factor for the development of COPD was also assessed. Analysis showed that 50% of the never smokers had a history of biomass fuel exposure as compared to only 19.1% among smokers. The mean biomass exposure index (measured as the average number of hours spent with ambient biomass combustion daily multiplied by the total number of years spent in cooking) was 56.02 in the nonsmoker group vs 6.28 in the smoker’s subgroup (p < 0.001). Similarly, it was noted that as the index of exposure increased, the severity of COPD increased amongst the participants; however, this did not reach statistical significance (p-value: 0.65).
infections during childhood, pulmonary tuberculosis, asthma, preterm birth, and intrauterine growth retardation, as well as exposure to incense stick combustion.\(^{18,22,23}\) But the physiological difference between COPD caused by smoking and nonsmoking risk factors is poorly studied.

In the index study, nonsmokers constituted 24% of the total cases. These proportions coincide with findings from previous studies from the United States of America (25%),\(^{1,10}\) the United Kingdom (22.9%),\(^{24}\) and Spain (23.4%),\(^{25}\) where a similar prevalence of nonsmokers amongst COPD patients has been reported.

Additionally, Hagstads et al., in their study from China, reported that around 20% of the participants from a random sample of 2,470 COPD patients were nonsmokers.\(^{26}\) Gender-related finding of our study is also consistent with studies performed in Spain, Austria, South Africa, Iceland, Poland, and Australia.\(^{27,28}\) The majority of nonsmoker patients were females (62.5%), which may be attributed to relatively higher exposure of females to biomass fuel and indoor air pollution in developing countries.\(^{29}\) In the population-based Burden of Chronic Obstructive Lung Disease study,\(^{28}\) similar findings were encountered, with nonsmokers constituting 27.7% of all COPD cases, with females making up nearly 71%.

Another interesting finding of the index analysis was that the mean age of nonsmokers was significantly less than the mean age of smokers (55.69 vs 60.6 years, \(p < 0.05\)). This observation contrasts with the Western (Lee et al.) studies where the mean age was more in nonsmokers at (65.7 vs 62.8 years), however, results from an Indian study by Salvi et al. corroborate our findings.\(^{30,31}\) The likely reason might be the early initiation of exposure to noxious gases in the form of biomass fuel exposure and indoor air pollution among the nonsmoker group, especially among females. Additionally, the genetic predisposition towards the development of chronic airway inflammation may also contribute to the early onset of COPD among these subjects.

Biomass exposure has been a major cause of COPD in nonsmokers, especially in developing countries, in particular the rural population where it is used as a cooking fuel.\(^{31}\) Since our study populations constituted mostly rural participants, this risk factor was particularly prominent. Out of a total of 200 COPD cases, 26.5% gave a history of biomass fuel exposure, and 50% of nonsmokers had a history of biomass fuel exposure. In contrast, a case-control study from Turkey by Ekiç et al. reported that only\(^{22}\) 23% of nonsmokers have a history of biomass exposure, which reflects upon the geographical heterogeneity of the use of biomass fuel. The present study also demonstrated a linear correlation between the severity of COPD and increasing exposure to biomass fuel combustion, which is in coherence with the findings demonstrated by Mahmood et al.\(^{11}\) in their cross-sectional study from Allahabad, India.

The relationship between smoking and a decline in FEV1 has been well-established in the general population.\(^{14}\) In our study, the percent predicted FVC and FEV1 were significantly higher in nonsmokers as compared to smokers. This contrasts with the study published by Salvi et al., where it was shown that the degree of airflow obstruction measured by FEV1% predicted was higher in nonsmokers (smokers COPD: 43.1% vs nonsmoker COPD: 40.7%).\(^{11}\) This contradiction can be attributed to the delay in the diagnosis of COPD among nonsmokers as well as the lack of awareness about the entity of nonsmoker COPD. This is further reflected in the finding of the duration of dyspnea which was higher in nonsmokers (7.35 vs 6.05 years).

Investigations like laboratory and radiological findings in our study also corroborate with earlier studies. In the present study, radiological abnormalities like emphysema and hyperinflation were significantly more prevalent in smokers than nonsmokers (83.3 vs 63.6%), which was anticipated in view of the casual association of smoking with the destruction of alveolar walls.

Among the analysis of hematological investigations, the overall TLC count was found to be higher in smokers as compared to the never smokers’ group, albeit it was not statistically significant. However, the AEC and eosinophil percentage in DLC were significantly higher among nonsmokers as compared to smokers. The result was supported by previous studies by Bajpai et al.\(^{32}\) and Salvi et al.\(^{33}\)

One of the major strengths of our study was that we sequentially recruited only naive cases of COPD, which decreases bias and provides a clear picture of the proportion of never-smokers among naive cases of COPD. Never smokers have a longer duration of illness, with relatively preserved lung functions and hematological features suggestive of eosinophilic inflammation. Despite the methodology, there are some lacunae in our study, like selection bias as our center is a tertiary care hospital which may result in referral bias, a relatively small number of cases given the high prevalence of COPD, and the inability to account for other risk factors like air pollution. Also, the sputum examination could have added further value to the study. Due to financial constraints, inflammatory cytokine levels were not done, which would have been a better marker of eosinophil inflammation.

**Conclusion and Recommendations**

There is an increasing burden of COPD among nonsmokers with various associated risk factors like biomass exposure, air pollution, and tuberculosis, among others. The present study shed some light on the presentation of COPD in nonsmokers, which can be atypical with a longer duration of dyspnea and earlier age of presentation with higher eosinophil count. Also, there is a higher proportion of females among nonsmokers presenting with COPD, mostly from rural backgrounds reflecting upon the menace of biomass fuel exposure. Nonsmoker COPD remains a heterogenous, common, and neglected phenotype, which requires bigger and more prospective studies to further elucidate its pathogenesis.

**Site Where Study was Conducted**

Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

**Author Credit Statement**

- Conceptualization: DC and TG
- Methodology: PKS, MBG, and RR
- Ethical and review board approvals: RR
- Data collection: RR and PKS
- Data entry and curations: RR, MBG, and PKS
- Formal Analysis: P, PKS, and DC
- Writing-original draft: P, RR, and MBG
- Review and editing: DC and TG
- Overall supervision: DC

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We would like to thank the support staff of the Pulmonary Function Laboratory and patients for their immense support and faith.

**References**

Nonsmoker COPD represents a clinically Distinct Phenotype


The Role of Monocyte to High-density Lipoprotein Cholesterol Ratio in Predicting the Severity of Acute Ischemic Stroke and its Association with the NIHSS

Deepti Sharma1, Sreede Aravind2*, Sony Joseph3, Narendra Fagera4, Gopikrishnan Rajagopalan5

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ABSTRACT

Background: Atherosclerosis, an underlying abnormality, plays a significant role in the progression of ischemic stroke. Inflammation, oxidative stress, platelet activation, endothelial dysfunction, and lipid abnormalities are the primary factors involved in the development of atherosclerosis. Monocytes, key contributors to chronic inflammation, actively participate in the development, progression, and rupture of atherosclerotic plaques within blood vessels. Therefore, the objective of this study is to investigate the monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) in acute ischemic stroke (AIS) and its correlation with the National Institute of Health Stroke Scale (NIHSS) to predict the severity of the condition.

Materials and methods: A prospective observational study was conducted on 100 AIS patients and age/gender-matched controls at a hospital in Kota. Diagnostic methods included clinical examination, imaging, and laboratory tests. MHR was measured using a hematology analyzer and correlated with reference values and stroke severity.

Results: The mean MHR of AIS patients were higher (14.12 ± 2.95) than controls (7.09 ± 1.48) (p = 0.0001). Besides, a statistically significant positive correlation was obtained between MHR and NIHSS scores at admission and discharge. MHR values were significantly greater from a reference point in patients who deteriorated (18.48 ± 4.02) compared to significantly lower values in patients who improved (13.66 ± 2.44).

Conclusion: In our study, the MHR shows an increased value in patients with AIS, and a linear correlation is found with the NIHSS score. Thus, the method is a pocket-friendly, easily available, and simple-to-use novel inflammatory marker that may predict the severity of a disease.

INTRODUCTION

In recent decades, stroke has caused a significant load on the healthcare system. Ischemic stroke is the leading cause of mortality and disability among low-income people. Therefore, it is highly desirable to detect ischemic stroke at the onset so that primary defence is the keystone of management.

Atherosclerosis, particularly intracranial atherosclerosis, plays a crucial role in the progression of ischemic stroke. Pathophysiological studies have identified intracranial plaques that can lead to interarterial embolism, hemodynamic depression, in situ thromboembolism, and focal branch occlusion, thereby contributing to the development of ischemia.1,2 Clinical studies have also shown a high incidence of intracranial atherosclerosis in patients with ischemic stroke across different races, as revealed by advanced imaging techniques or autopsy.3–6 However, these imaging techniques are expensive, time-consuming, require specialized settings, and are primarily used as supplementary data in clinical and research studies. Therefore, there is a need for a new marker for early diagnosis and prevention of ischemic stroke.

Inflammation, oxidative stress, platelet activation, endothelial dysfunction, and lipid abnormalities have been proposed as key components in the pathophysiology of atherosclerosis growth and progression.7,8 Monocytes, the primary players in chronic inflammation, interact mainly with platelets and endothelial cells, contributing to the aggravation of prothrombotic and inflammatory pathways. Their active involvement in the growth, progression, and rupture of atherosclerotic plaques at the vascular level is well established.9,10 Monocytes and T lymphocytes play an essential role in stroke pathogenesis by increasing the production of inflammatory cytokines, promoting infiltration and lipid core formation, and exacerbating brain damage. On the other hand, high-density lipoprotein cholesterol (HDL-C) protects endothelial cells from inflammation to oxidative stress by regulating monocyte activation and the proliferation of monocyte progenitor cells. It also suppresses macrophage migration and low-density lipoprotein (LDL) molecule oxidation.11,12 Based on the pathogenesis of atherosclerosis, HDL-C levels have antioxidant and anti-inflammatory properties as lipid parameters. They can mitigate the adverse effects of LDL-C on endothelial cells, limiting atherosclerosis. Conversely, monocytes are a hematological marker that increases during inflammation. Thus, based on literature findings, while HDL-C levels decline, monocyte levels increase in atherosclerosis, which in turn is expected to elevate the monocyte to HDL-C ratio (MHR) value.

Building upon these observations, the MHR has emerged as a preferred model for assessing the prognosis of cardiovascular events and evaluating atherosclerosis.13 The National Institutes of Health Stroke Scale (NIHSS) is a well-standardized and widely used tool for assessing stroke severity, predicting patient outcomes and prognosis, and monitoring treatment efficacy. However, the use of MHR in acute ischemic stroke (AIS) and its correlation with NIHSS is relatively unexplored.

Therefore, the aim of this study was to evaluate the MHR in AIS patients and its correlation with the NIHSS for predicting stroke severity. By comparing the MHR value with the NIHSS score, we can determine whether there is a correlation between the two. This study sought to assess the ratio of MHR in AIS and its correlation with NIHSS to predict the severity of AIS.

MATERIALS AND METHODS

This hospital-based, prospective, observational study was conducted at...
Medical College and Associated MBS Hospital, Kota, from 2020 to 2021 on 100 AIS patients. An Institutional Review Board approval was taken, and a comparison with the same number of controls (age and gender-matched) was made.

**Inclusion Criteria**
The patients included in this study were individuals diagnosed with AIS.

**Exclusion Criteria**
Patients with hemorrhagic stroke, venous sinus thrombosis, autoimmune disease, hepatic or renal disease, connective tissue disorders, moribund condition, seizure disorders, mental or physical illness, and refusal to participate in the study were excluded.

The clinical examination, the temporal profile of the clinical syndrome, and computed tomography or magnetic resonance imaging of the brain were applied to diagnose acute stroke. For detecting the risk factors (nonmodifiable and modifiable) of ischemic stroke, a detailed history, clinical investigations, and routine laboratory examinations were performed. The stroke severity was determined using the National Institute of Health Stroke Scale (NIHSS) among all patients at admission and release. Stroke severity was categorized as minor strokes (1–4), moderate strokes (5–15), moderate to severe strokes (16–20), and severe strokes (21–42).

An in-house, fully automated hematology analyzer performed the fasting lipid profile and complete blood count (CBC) test to measure the MHR. A peripheral venous sample (2 mL) was collected just after admission before any treatment with all aseptic precautions. A second sample was taken just before discharge, and the samples were processed immediately. Therefore, we performed a CBC test in which the ratio of monocytes to HDL was obtained by dividing the absolute number of monocytes by HDL. This MHR ratio was further correlated to calculated reference values from a control group (same age and sex) and NIHSS severity scores (at admission and discharge).

### Statistical Analysis
Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Independent t-tests compared parameters between cases and controls. Chi-squared tests analyzed the correlation between categorical variables. Unpaired Student’s t-tests and Chi-squared tests examined the relationship between MHR ratio and stroke severity. A significance level of p < 0.05 indicated statistical significance. Pearson correlation coefficient assessed MHR-NIHSS correlation at admission and discharge.

### Results
Of 100 patients, 55 males and 45 females were matched with a control group containing 57 males and 43 females. Most patients with AIS were between 50 and 69 years (73%), and their age had a mean of 62.26 ± 9.12 years.

The average HDL ratio of male cases was 39.3 mg/dL, and that of female cases was 47.2 mg/dL. The mean duration of onset of symptoms is 38 hours (1.5 days), with a range of presentation from 8 to 140 hours (5.8 days). We have not taken the patients presented in the window period. The mean discharge period was 6.3 days, showing a negative correlation with MHR.

Right hemiparesis with or without cranial nerve involvement was the very common focal neurological deficit, accounting for 49% of the cases when compared to 45% of the cases with left hemiparesis with or without cranial nerve involvement. Approximately 6% of cases showed features of posterior circulation stroke, such as dizziness and incoordination.

The stroke severity in patients of different groups based on NIHSS score showed the maximum was in NIHSS score group 5–15 (moderate stroke). A total of 71 patients had NIHSS scores between 5 and 15, and 61 patients had NIHSS scores between 5 and 15 at discharge.

The most common risk factor was hypertension, with a prevalence of approximately 50% in our study group. This was followed by smoking (40%), diabetes (36%), and alcoholism (35%) (Table 1).

The absolute numbers of monocytes in the study and control groups were 590.84 ± 84.6 and 394.61 ± 65.8 (Table 2).

### Table 1: Comparison of absolute monocyte count between groups

<table>
<thead>
<tr>
<th>Monocyte</th>
<th>Control</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>394.61</td>
<td>590.84</td>
</tr>
<tr>
<td>SD</td>
<td>65.8</td>
<td>84.6</td>
</tr>
<tr>
<td>t</td>
<td>18.307</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

High-density lipoprotein cholesterol (HDL-C) levels in the study and control groups were 42.57 ± 5.01 and 56.37 ± 6.29, respectively (Table 3).

Monocyte to HDL-C ratio (MHR) ratios for both groups were calculated by dividing monocyte counts (per mm3) by HDL-C levels (mg/dL). MHR with a p-value of 0.0001 was significantly higher in the AIS group (14.12 ± 2.95) than in the control group (7.09 ± 1.48) (Table 4 and Fig. 1).

The NIHSS score was calculated in patients with AIS on admission. Monocyte counts increased proportionally with increasing NIHSS scores.

Table 5 and Figure 2 found a moderately strong and statistically significant correlation between monocyte counts at admission and NIHSS scores (Fig. 2).

As NIHSS scores decreased, HDL levels decreased proportionally. The correlation between his HDL level on admission and his NIHSS score was negative, moderately strong, and statistically significant (Fig. 3).

Monocyte to HDL-C ratio (MHR) was calculated in patients with different NIHSS scores. It was lowest in NIHSS score groups 1–4, that is, 11.02 ± 1.15, increased to 13.66 ± 2.10 in NIHSS groups 5–15, and MHR in NIHSS

### Table 2: Comparison of absolute monocyte count between groups

**Table 3: Comparison of HDL levels between groups**

<table>
<thead>
<tr>
<th>HDL</th>
<th>Control</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>56.37</td>
<td>42.57</td>
</tr>
<tr>
<td>SD</td>
<td>6.29</td>
<td>5.01</td>
</tr>
<tr>
<td>t</td>
<td>17.14</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: Comparison of MHR between acute ischemic stroke between groups**

<table>
<thead>
<tr>
<th>MHR</th>
<th>Control</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.09</td>
<td>14.12</td>
</tr>
<tr>
<td>SD</td>
<td>1.48</td>
<td>2.95</td>
</tr>
<tr>
<td>t</td>
<td>21.247</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1:** Comparison of MHR between acute ischemic stroke between groups
The Role of Monocyte to High-density Lipoprotein Cholesterol Ratio

Scores 16–20 was 16.60 ± 2.47, and the ratio was highest in NIHSS groups 21–42, 22.04 ± 1.14 (Table 5 and Fig. 4).

At admission, a statistically significant correlation was found between MHR and NIHSS scores (Table 5 and Fig. 5).

**Table 5:** Monocyte to HDL-C ratio (MHR) comparison according to NIHSS score at admission

<table>
<thead>
<tr>
<th>NIHSS score</th>
<th>No. of patients</th>
<th>MHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>11</td>
<td>11.02 ± 1.15</td>
</tr>
<tr>
<td>5–15</td>
<td>71</td>
<td>13.66 ± 2.10</td>
</tr>
<tr>
<td>16–20</td>
<td>14</td>
<td>16.60 ± 2.47</td>
</tr>
<tr>
<td>21–42</td>
<td>4</td>
<td>22.04 ± 1.14</td>
</tr>
</tbody>
</table>

Among 100 patients, 77 improved, eight worsened, and 15 were static, according to the clinical status of the various NIHSS score groups assessed at discharge. Most patients who improved were shown to have much lower mean heart rates than those who deteriorated (Table 7).

**DISCUSSION**

Our study involved AIS patients (100) and the same number of age- and sex-matched controls. In our study, the largest cases (73%) were in the 50–69-year-old group. This was similar to the study by Ojha et al.14 Most patients were over 45 years of age in Grau et al.15 study. In this study, the mean age of cases was 61.04 ± 8.65 years. In a study by Yilmaz et al.16 The median age group was 68.36 ± 16.2 years old. The male-to-female ratio in our study was 1.3, such that the population is 57% male and 43% female.

Our study results were similar to those of Grau et al.,15 and Altafi et al.17 also found similar proportions of males and females with stroke. Therefore, the prevalence of stroke is slightly higher in men than women.

In our study, hypertension was the most common risk factor for ischemic stroke, with a prevalence of 50% of patients.

**Table 6:** Comparison between MHR of AIS patients and NIHSS at admission

<table>
<thead>
<tr>
<th>NIHSS score</th>
<th>No. of patients</th>
<th>MHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>11</td>
<td>11.02 ± 1.15</td>
</tr>
<tr>
<td>5–15</td>
<td>71</td>
<td>13.66 ± 2.10</td>
</tr>
<tr>
<td>16–20</td>
<td>14</td>
<td>16.60 ± 2.47</td>
</tr>
<tr>
<td>21–42</td>
<td>4</td>
<td>22.04 ± 1.14</td>
</tr>
</tbody>
</table>

**Table 7:** Mean monocyte count, HDL level, and MHR at admission and its relation to the outcome of the patient

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>Admission (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monocyte (per mm³)</td>
</tr>
<tr>
<td>Improved</td>
<td>77</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>8</td>
</tr>
<tr>
<td>Static</td>
<td>15</td>
</tr>
</tbody>
</table>

Fig. 2: Correlation between monocyte count of patients suffering from acute ischemic stroke with NIHSS at admission

Fig. 3: Correlation between HDL levels of patients suffering from acute ischemic stroke with NIHSS at admission

Fig. 4: National Institute of Health Stroke Scale (NIHSS) score MHR

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Mauricio et al., in their research, found that the group had hypertension in 64% of stroke cases. Dalal et al. and Alverez et al. in their studies had prevalence of hypertension at 40, 22.6 and 23.3%, respectively. Hypertension can adversely affect cerebrovascular autoregulation. Diabetes is a known risk factor for macrovascular complications.

Our study found diabetes mellitus in 36% of stroke patients, similar to Soliman et al. and Tallawy et al. 34.7 and 36.5% of patients had diabetes, respectively. The increased risk of stroke in diabetes is due to elevated clotting factors and hyperinsulinemia, which play an important role in developing microangiopathic stroke.

In our study, 40% of cases had a smoking history, consistent with the study of Kaul et al. Comparable. Also, Dalal et al. showed a 40% smoking prevalence. The possible mechanisms include carboxy hemoglobinemia, increased platelet aggregation, increased fibrinogen levels, decreased HD cholesterol, and reduced levels of compounds such as 1,3-butadiene, a gas phase component of environmental tobacco smoke. Includes direct toxic effects. Accelerate arteriosclerosis. In our study, 23% of stroke patients had a history of ischemic heart disease (IHD). This is consistent with research by Fogelhalm and Murros et al. found that 18% of patients had previously suffered from IHD. People with a history of IHD are more likely to have a stroke because they are at greater risk of embolism.

High-density Lipoprotein (HDL) Levels and Acute Ischemic Stroke

In our study, HDL levels in cases and controls were 42.57 mg/dL and 56.37 mg/dL respectively. In another study by Ralph et al. in stroke, HDL levels in cases were 40 mg/dL compared to 47 mg/dL in control group. This lower level of HDL compared to controls may be due to its protective effects against arteriosclerosis, including reverse cholesterol transport, antioxidant, anti-inflammatory, antithrombotic effects, and modification of endothelial function.

Monocyte to HDL-C Ratio (MHR) and Acute Ischemic Stroke

In our study, the mean MHR, calculated by dividing the absolute number of monocytes by the HDL-C ratio, was significantly higher than the mean MHR value in patients with AIS, 14.12 ± 2.95, was 7.09 ± 1.48 obtained in control subjects. Another study by Bolayir et al. compared MHR values in AIS cases and controls, which showed values of 13.58 ± 4.67 and 9.46 ± 1.13, respectively. Another study by Liu et al. found MHR values of 12.37 in cases and 11.21 in controls. This increase in MHR is because inflammation and dyslipidemia have been proposed as key factors in atherosclerosis development and progression pathophysiology.

Furthermore, monocytes, known as indicators of chronic inflammation, primarily interact with platelets and endothelial cells, exacerbating inflammatory and prothrombotic processes. They actively contribute to the formation, progression, and rupture of atherosclerotic plaques. Conversely, HDL-C protects endothelial cells from inflammation to oxidative stress by regulating monocyte activation and proliferation. It also inhibits macrophage migration and LDL molecule oxidation. Considering the pathogenesis of atherosclerosis, HDL-C levels possess antioxidant and anti-inflammatory properties, which help mitigate the detrimental effects of LDL-C on endothelial cells and limit atherosclerosis. Simultaneously, monocytes serve as hematological markers that increase during inflammatory conditions.

Monocyte to HDL-C Ratio (MHR) and Clinical Outcome

In our study, among 100 patients, 77 showed improvement, eight worsened, and 15 remained static. At admission, the MHR in 77 patients who improved was 13.66 ± 2.44. Eight deteriorated patients had an MHR value of 18.48 ± 0.02. This suggested that the MHR value at admission was low for those who improved and high for those who deteriorated. As a result of this data, it is possible to conclude that admission MHR values predict severity and prognosis in stroke patients.

Li et al. reported the MHR ratio in predicting the prognosis of aortic arteriosclerosis and ischemic stroke; increased MHR was associated with aortic arteriosclerosis and ischemic stroke at three months. It was associated with an increased risk of poor outcomes in functional outcomes of stroke. In another study by Liu et al. multivariate logistic regression analyses showed that higher MHR scores in stroke patients were independently associated with poorer outcomes at 3 months.

Limitations of our study include small sample size, single-center patient inclusion, lack of long-term follow-up to assess MHR as a predictor of prognostic outcomes in AIS, and absence of blinding among researchers.

CONCLUSION

The MHR is a simple, inexpensive, and readily available method that may help predict disease severity and functional outcomes in AIS patients. There is a proven linear correlation between this ratio and NIHSS scores. Moreover, this ratio can be calculated even in limited-resource health setups. However, further investigations are necessary to validate our results. Our study strongly supports the routine calculation of this ratio and its potential contribution to risk stratification in AIS patients.

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REFERENCES


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(ENDORSED BY)
AMERICAN ACADEMY OF ALLERGY, ASTHMA AND IMMUNOLOGY & CENTER FOR GLOBAL HEALTH, UNIVERSITY OF COLORADO, USA

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Course Commencement: Jan 2024
Last date for receipt of completed application: 30th August 2023
Download application form: https://www.cmch-vellore.edu/SITES/DA/main.html
E-mail: daacmc@gmail.com
Diabetes in India’s North East Study: Prevailing Insulin Usage and Insulin Injection Practices amongst Type 2 Diabetes Mellitus Patients

Manash P Baruah1*, Sonali B Bhuyan2, Sanjay Kalra3, Mangesh H Tiwaskar4

Received: 06 April 2022; Accepted: 25 May 2023

ABSTRACT

Objective: Insulin therapy is mostly advised in patients with poorly controlled type 2 diabetes mellitus (T2DM). However, wide variation exists in insulin practice and usage across the Indian geography.

Materials and Methods: In this cross-sectional study, a retrospective audit of the medical records of T2DM patients who were receiving insulin and attending an urban referral clinic in Northeast India during the period from 2006 to 2017 was conducted to analyze the insulin utilization pattern and injection technique variation. A total of 1,454 patients were included, 60% were male and 40% were female.

Results: At presentation, the mean duration of T2DM was 12.13 (7.45) years. Insulin with or without oral anti-diabetic (OADs) was received by 52.27% and 47.73% of patients, respectively. The majority (62.93%) used a pen device for insulin administration. The patient-reported reasons for insulin therapy initiation were OAD failure (33.15%), glucotoxicity (30.26%) and diabetes-associated complications (20.36%). The mean ± standard deviation (SD) total daily dose (TDD) of insulin was 33.05 ± 17.09 (0.53 ± 0.30 units/kg/day). The breakup for the number of injection(s) per day was one (234, 16.09%), two (970, 66.71%), three (166, 11.42%), four (78, 5.36%), and five (6, 0.41%). The majority (67.88%) used premixed insulin, while 10.90% used basal insulin alone. Compared to those without lipohypertrophy (LH), patients with LH were less likely to rotate the site of injection (0.85 vs 17.90%; p = 0.000), space the injections (10.71 vs 23.91%; p = 0.000), more likely to use wrong angles (10.08 vs 22.73%; p = 0.000) and reuse the needles (5.63 vs 14.86%; p = 0.000). Also, 34.87% of patients were not storing their insulin device at the right temperature and 8.87% experienced at least one episode of a hypoglycemic event.

Conclusion: This audit depicts important attributes of current injection practices amongst T2DM patients on insulin and suggests the possible benefits of adopting correct practices for avoiding complications such as LH and hypoglycemia.

INTRODUCTION

India has the second-largest diabetic population after China in the world.1 The prevalence of diabetes mellitus (DM) in India has increased from 67 million in 2014 to 73 million in 2017. The number of people expected to have DM by 2045 is over 134 million. In fact, young adults (<35 years) in India are at a higher risk of developing DM.2 DM in the Indian working-age population (20–59 years) raises the risk of premature death and has a significant influence on work productivity, emphasizing the relevance of disease management in health care.3

In the DiabCare India survey of 5,907 Indian patients with type 2 DM (T2DM), mean glycated hemoglobin (HbA1c) was 8.9 ± 2.1% and only a few patients (19.7%) had <7.0% despite the fact that many were receiving multiple oral anti-hyperglycemic drugs [oral anti-diabetics (OADs)].4 Tight glycemic control has been established as the cornerstone of effective diabetes management in European and US studies, as well as in studies of Asian patients.5 Guidelines suggest an HbA1c target of <7% and also recommend simultaneous monitoring of fasting plasma glucose and peak postprandial glucose level to make an accurate therapeutic decision like early initiation of insulin in patients not meeting HbA1c targets.6

The introduction of insulin therapy (insulin glargine 100 U/mL or Gla-100) in 2003 showed an increasing adoption rate of basal insulin therapy among the Indian population.7 However, wide variation exists in insulin practice and usage across the Indian geography.79 In fact, depending on the inappropriate insulin injection techniques, the glycemic outcome can vary, leading to higher insulin consumption and HbA1c values that result in higher frequencies of hypoglycemia and glucose variability.

Thus, this cross-sectional study was designed to audit the various aspects of insulin use, tolerability, and efficacy of insulin regimens, degree of variability in injection technique and its causes, interactions, associations with glucose control, and other outcomes.

MATERIALS AND METHODS

Study Setting

Data for this cross-sectional retrospective study was collected from the Insulin prescription registry set up at the urban referral clinic in Northeast India. This referral clinic is a private tertiary care clinic catering to the needs of the population of Assam and surrounding areas of other Northeastern states.

Patients

This cross-sectional registry-based retrospective trial captured all patients diagnosed with T2DM from January 2006 until December 2017. The patients have been using insulin for >3 months. Patients were excluded if they had no initial HbA1c level at registration or either before or after 3 weeks of the first point of contact.

Assessments

A customized, user-friendly software called Diabetes, Endocrinology and Metabolic Disease Information Management System was used to collect information on (1) patient demography; (2) risk factors (smoking and alcohol consumption); (3) clinical measurements (weight, waist circumference, etc.).

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Diabetes in India’s North East Study

HbA1c, fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, eye and extremities examinations; (4) other diabetes complications (cardiovascular and renal disorders); (5) family history of diabetes; (6) current diabetes management (type, dose and the number of insulin injections per day); (7) other medications (treatments for hypertension and hyperlipidemia); (8) insulin injection practice [injection site, rotation, needle reuse, gap between injection and meal, and lipohypertrophy (LH)]; (9) self-monitored blood glucose (SMBG); (10) lifestyle management (exercise and diet) and (11) hypoglycemic events experienced in the past 6 months.

Statistical Analysis
Statistical Package for the Social Sciences (SPSS) software (version 17.0, Chicago, Illinois, United States of America: SPSS Inc) was used to perform statistical analyses. Diabetes and insulin duration are expressed as the median (interquartile range). Other quantitative variables are expressed as the mean ± standard deviation (SD). The HbA1c variation from baseline was analyzed using the paired student t-test. The relationship between initial characteristics and outcome measures was analyzed with logistic regression and a Chi-squared test for binary outcomes. Additionally, correlations between quantitative parameters were assessed using the Pearson correlation coefficient and a p-value of <0.05 was considered to denote significance.

Results

Baseline Characteristics, Demographic, and Anthropometric Profile
A retrospective study of medical records of 1454 patients (aged 18–85 years) diagnosed with T2DM who were receiving insulin and attending an urban referral clinic in North East India during the period from 2006 to 2017 was conducted. Table 1 gives the population statistics for T2DM patients. Around 60.39% of the patients with T2DM were male. The patients’ mean age was 54.63 years (range, 18–85 years), with a mean duration of diabetes of 12.13 years (±7.45 years). The majority (72.64%) were under 60 years of age, with the 51–60 years age group being the major contributor (39.42%) to insulin utilization. Almost all patients had completed at least their primary education (97.94%). While the majority (72.08%) had hypertension as major comorbidity, dyslipidemia was present in about two third (68.98%) of patients (total cholesterol; 169.63 mg/dL [±48.54]; HDL: 42.09 mg/dL [±12.24]; LDL: 99.64 mg/dL [±39.83]), and 28.61% patients had hypertriglyceridemia (167.74 mg/dL [±117.40]). Table 1 narrates other significant comorbidities found in the study.

Antihyperglycemic and Other Therapies
Of 1454 patients, 694 (47.73%) were on insulin alone, and 760 (52.27%) were on insulin plus any one or more classes of OADs. The median (range; min: max) duration of insulin treatment was 2.00 (0.25:37) years; the mean dose of insulin was 33.0 ± 17.8 units/day; overall 234 (16.09%), 970 (66.71%), 166 (11.42%), 78 (5.36%), and six (0.41%) patients took insulin injections once, twice, thrice, four, and five times per day respectively. Body mass index (BMI) was linearly related to the duration of insulin treatment, though not significant (p = 0.313). Table 2 provides the detailed status of diabetes management.

Statin was used by 33.70%, anti-renin-angiotensin-aldosterone system agents by 50.14%, and anti-platelet medication by 22.21% of patients. Only 67.8% of patients with hypertension and 44.67% with dyslipidemia were taking respective treatments.

Reasons for Initiating Insulin Therapy
Around >90% of patients with T2DM reported only one reason to initiate insulin (91.75%), followed by 7.98 and 0.28% with two and three reasons, respectively. Figure 1 shows the common patient-reported reasons for insulin therapy initiation. By far, secondary OAD failure and glucotoxicity remain the most prominent reasons for initiating insulin therapy.

Glycemic Control
Mean HbA1c was 9.20 ± 2.16% (male: 9.16 ± 2.21; female: 9.25 ± 2.09). Only 219 (15.06%) had HbA1c of <7%. HbA1c levels between

Table 1: Baseline characteristics of patients with diabetes mellitus on insulin therapy

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>Diabetic patients (N = 1454)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>54.63 (10.80)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>64.70 (11.84)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>25.14 (4.49)</td>
</tr>
<tr>
<td>Waist circumference (cm), mean (SD)</td>
<td>94.44 (10.95)</td>
</tr>
<tr>
<td>HbA1c (%), mean (SD)</td>
<td>9.20 (2.16)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>878 (60.39)</td>
</tr>
<tr>
<td>Female</td>
<td>576 (39.61)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>123 (8.46)</td>
</tr>
<tr>
<td>Secondary</td>
<td>237 (16.30)</td>
</tr>
<tr>
<td>Senior Secondary</td>
<td>351 (24.14)</td>
</tr>
<tr>
<td>Graduation</td>
<td>596 (40.99)</td>
</tr>
<tr>
<td>Postgraduation</td>
<td>133 (9.15)</td>
</tr>
<tr>
<td>Postdoctorate</td>
<td>14 (0.96)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1048 (72.08)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1003 (68.98)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>238 (16.39)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>52 (3.58)</td>
</tr>
<tr>
<td>Cancer</td>
<td>10 (0.69)</td>
</tr>
<tr>
<td>Hypothyroidity</td>
<td>379 (26.07)</td>
</tr>
<tr>
<td>Peri-arthritis</td>
<td>44 (3.03)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>28 (1.93)</td>
</tr>
<tr>
<td>Diabetic microvascular complication, n (%)</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>203 (13.96)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>302 (20.77)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>200 (13.76)</td>
</tr>
<tr>
<td>Current lifestyle status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>139 (9.56)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>149 (10.25)</td>
</tr>
<tr>
<td>Family history (% of first-degree relatives), mean (SD)</td>
<td></td>
</tr>
<tr>
<td>T2DM</td>
<td>19.62 (19.79)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.87 (11.11)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>1.27 (4.27)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.52 (6.45)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.82 (5.52)</td>
</tr>
</tbody>
</table>

T2DM, type 2 diabetes mellitus


are given in Table 3. About 66.62% of patients had HbA1c > 8%, including a larger proportion of female patients (68.5%) than males (65.3%). Duration of diabetes treatment (p < 0.001) was significantly associated with glycemic control; however, neither duration of insulin treatment (p = 0.391) nor duration from diagnosis till initiation of insulin since diagnosis (p = 0.228) had a significant association. Mean HbA1c (10.14%) was higher in patients with less than one year of diagnosis, while it decreased to 8.97% in patients with >10 years of disease (p < 0.001). Similarly, the patients with >10 years of insulin therapy had a mean HbA1c of 8.58%, which was lower than the mean value of 9.33% in <1 year of therapy. Age at diagnosis, systolic and diastolic blood pressure were not significantly associated (p > 0.05).

It was further observed that HbA1c >8% was 2.2 times more likely to occur in overweight patients as compared to patients with normal BMI [odds ratio (OR) (95% confidence interval) = 2.234 (1.278–3.904)]. In addition, it was found that obese patients were 2.4 times more likely to have HbA1c >8% [OR (95% CI) = 2.347 (1.274–4.324), p = 0.006] than overweight patients.

A total of 77.68% of the patients had average to good dietary compliance; while 59.42% of the patients claimed to engage in regular physical activity, 40.58% of the patients did not. In terms of the relationship between glycemic control and individual lifestyle, there was a nonsignificant relationship between glycemic control with self-certified dietary compliance (p = 0.70) as well as with regular physical activity (p = 0.80), while those performing SMBG with glucometers at home have significantly lower HbA1c (p < 0.001).

Insulin Injection Practices
The assessment of insulin injection technique and insulin pen storage practice revealed that 947 (65.13%) patients were storing their insulin device at the right temperature while 507 (34.87%) were not. Around 66.71% received two injections daily, followed by 16.09, 11.42, 5.37, and 0.41%, who received one, three, four, and five injections per day, respectively. About >80% of patients maintained the right time gap between injections and meals (87.35%). About 82.12% of patients followed the ideal injection hygiene. The abdomen, thigh, arm, and buttocks are the preferred injection sites, which were used by 78.40% of the patients, while 21.60% used the wrong sites. An incorrect rotation technique was observed in 983 patients (67.61%). Nearly 1190 (81.84%) patients injected insulin at the correct angle.
Hypoglycemia

In the 6-month retrospective assessment period, 8.87% (129/1454) of patients with T2DM experienced at least one episode of a hypoglycemic event. The incidence of objectively confirmed hypoglycemic events was not significantly associated with the type of insulin. The estimated incidence rates of any hypoglycemic events over the past 6 months were highest (12.07%) in patients using both human and analog insulin, compared to those using human insulin (9.0%) and analog insulin (8.35%) alone. The association of insulin dose with hypoglycemia did not vary by regimen type, insulin type (9.0%) and analog insulin (8.35%) compared to those using human insulin, compared to those using human insulin (9.0%) and analog insulin (8.35%) alone.

The improper time gap between meals and insulin injection was significantly linked with perceived hypoglycemia, with 13.41% of patients reporting hypoglycemic episodes (p < 0.05). A small percentage of patients (6.90%), who maintained the proper gap between insulin injection and meal, also experienced hypoglycemic events.

We did not find a significant difference in incidental hypoglycemia with regard to right versus wrong execution of parameters such as injection site selection, site rotation, angle, needle reuse, storage, and also the device used (pen vs syringe) in our audit study.

**Discussion**

The present study revealed that despite the clinical benefits and the recommendations of international treatment guidelines, glycemic control with insulin therapy remains suboptimal due to inappropriate insulin injection practice, resulting in inadequate glycemic control in most patients.

Our study population comprised T2DM individuals on insulin therapy with a mean HbA1c level of 9.20% and a mean duration of diabetes of 8.61 ± 6.32 years. A similar trend of mean HbA1c has also been observed in the DiabCare India survey (8.9 ± 2.1%) and in the study of Gulf countries (8.3 ± 2.0%). Approximately 31.38% of patients in the present study had an HbA1c level >10%. This confirms that treatment intensification and the initiation of insulin therapy are still being delayed in Asian patients, irrespective of international and regional guidelines. This finding is not unique to Asian countries as Cardiovascular Risk Evaluation in People with T2DM on Insulin Therapy registry has reported 11 years as the mean duration of T2DM along with mean HbA1c level as 9.50 ± 2.0% at baseline in 3031 patients of Northern America, Europe, and Asia who recently started insulin therapy. Similarly, the MOSAIC (Multinational Observational Study Assessing Insulin use: understanding the challenges associated with progression of therapy) study (i.e., a longitudinal, observational study on the care of diabetes patients) involving 18 countries (including India) showed initiation of insulin after a mean disease duration of 12 ± 8 years. This audit found the use of different types of insulin among people of Northeast India with T2DM to improve their glucose control, as 890 were prescribed premixed insulin, 503 with rapid insulin, and 58 with a combination of rapid and premixed insulin. It highlighted the fact that physicians were less likely to be familiar or comfortable with the use of basal insulin in comparison to premixed insulin. Simple start and intensification with the same insulin type, thus improving adherence, compliance, and quality of life, maybe the main driver for such a choice.

Asian populations have a higher risk of developing T2DM at lower BMIs than the Western population because of their structural variations. Thus, International Obesity Task Force has proposed lower BMI cut-off values for defining overweight and obesity among the Asian population. The insulin demand in the Asian population is lower compared to the non-Asian population. In Asian patients, a conservative titration goal is generally set depending on their BMI and increased risk of hypoglycemia compared with the Western population. Low BMI (25.14 kg/m²) compared with 28 kg/m² in a European study and 32 kg/m² in the Treat to Target study in North American patients attributed to low weight-adjusted TDD for any insulin regimen. A study from the United States on non-Hispanic Asians and the White population showed a mean BMI of 24.0 and 26.8 kg/m², respectively. Low insulin dose may also signify physicians’ inertia for treatment intensification. As a result, only 15.07% of patients achieved an HbA1c level of <7.0% in this audit.

Correct insulin injection technique is crucial for better glycemic control. It has been recommended that insulin should be administered into clean sites using clean hands with a 30–45-minute gap between injection and meal. The same was maintained by 87.3% of participants in the present audit. Regular and biphasic insulin storage at 32°C and 37°C for 28 days reduces its potency by 14–18% and 11–14%, respectively. In the present audit, almost 1/3rd patients did not store their insulin at the correct temperature and injected it at the correct site as recommended by the guidelines. It has been recommended that the needle should not be reused as it may impair sterility and lubrication of the needle, increasing the risk of infection, pain, irritation, damage, and LH. An Indian survey reported the reuse of pen needles at least two >10 times by 92.5%, whereas the reusing of a syringe by 80.5% of patients. Another study from India reported an average of six times when a single needle was used to inject insulin. This audit also found needle reuse in 73.11% of patients. Poudel et al. have reported cost-effectiveness and convenience as the major reasons for

### Table 3: HbA1c levels at enrollment by duration of diabetes and insulin initiation, number of insulin injections per day and TDD of insulin

<table>
<thead>
<tr>
<th>DM duration (years)</th>
<th>HbA1c (%) mean ± SD</th>
<th>Duration of insulin therapy (years)</th>
<th>HbA1c (%) mean ± SD</th>
<th>Injection per day(n)</th>
<th>HbA1c (%) mean ± SD</th>
<th>TDD of insulin (units)</th>
<th>HbA1c (%) mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>10.14 ± 3.05</td>
<td>&lt;1</td>
<td>9.33 ± 2.43</td>
<td>1</td>
<td>9.01 ± 2.20</td>
<td>&lt;10</td>
<td>7.72 ± 1.76</td>
</tr>
<tr>
<td>1–5</td>
<td>9.16 ± 2.33</td>
<td>1–5</td>
<td>9.16 ± 1.98</td>
<td>2</td>
<td>9.28 ± 2.19</td>
<td>10–20</td>
<td>8.90 ± 2.45</td>
</tr>
<tr>
<td>5–10</td>
<td>9.33 ± 2.08</td>
<td>5–10</td>
<td>9.23 ± 2.10</td>
<td>3</td>
<td>9.04 ± 2.08</td>
<td>20–40</td>
<td>9.24 ± 2.19</td>
</tr>
<tr>
<td>&gt;20</td>
<td>8.70 ± 1.84</td>
<td>&gt;15</td>
<td>8.58 ± 1.82</td>
<td>5</td>
<td>9.53 ± 1.88</td>
<td>&gt;60</td>
<td>9.45 ± 1.78</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HbA1c, glycated hemoglobin; TDD, total daily dose

The incidence of objectively confirmed hypoglycemic events was not significantly associated with the type of insulin. The estimated incidence rates of any hypoglycemic events over the past 6 months were highest (12.07%) in patients using both human and analog insulin, compared to those using human insulin (9.0%) and analog insulin (8.35%) alone. The association of insulin dose with hypoglycemia did not vary by regimen type, irrespective of international and regional guidelines. This finding is not unique to Asian countries as Cardiovascular Risk Evaluation in People with T2DM on Insulin Therapy registry has reported 11 years as the mean duration of T2DM along with mean HbA1c level as 9.50 ± 2.0% at baseline in 3031 patients of Northern America, Europe, and Asia who recently started insulin therapy. Similarly, the MOSAIC (Multinational Observational Study Assessing Insulin use: understanding the challenges associated with progression of therapy) study (i.e., a longitudinal, observational study on the care of diabetes patients) involving 18 countries (including India) showed initiation of insulin after a mean disease duration of 12 ± 8 years. This audit found the use of different types of insulin among people of Northeast India with T2DM to improve their glucose control, as 890 were prescribed premixed insulin, 503 with rapid insulin, and 58 with a combination of rapid and premixed insulin. It highlighted the fact that physicians were less likely to be familiar or comfortable with the use of basal insulin in comparison to premixed insulin. Simple start and intensification with the same insulin type, thus improving adherence, compliance, and quality of life, maybe the main driver for such a choice.

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needle reuse. This audit also found poor insulin injection practice among patients with LH as they were less likely to rotate the site of injection, space the injections, inject less often in the right site, and more likely to use the wrong angles and reuse the needles. LH can be avoided through improvement in insulin injection technique, which was followed by about 70% of patients of the present audit and over one-third of them well-accepted insulin. Inappropriate timing of insulin administration results in mismatching of postprandial carbohydrate absorption and postinjection insulin peak. In this audit, the improper time gap between meals and insulin injection was significantly linked with perceived hypoglycemia, with 13.41% of patients reporting hypoglycemic episodes ($p < 0.05$).

Limitations of this study include: (1) it was an audit, and the characteristic of the patients in different groups were not comparable; (2) there were considerable differences in the timing of insulin initiation and the use of OADs. However, the present audit can be explained in the context of the above-mentioned limitations. In addition, the data presented here support the findings of the previous registry study, indicating underused insulin therapy and suboptimal glycemic control in Indian T2DM patients. The First Basal Insulin Evaluation Asia study reported at least 9 years of delay in the initiation of basal insulin therapy, though it was one of the best options for T2DM patients.

In conclusion, this cross-sectional retrospective audit suggested the effectiveness and well-tolerance of insulin therapy in T2DM patients who showed a failure to OAD therapy. Insulin usage and injection practice among T2DM patients have a wide variation. Adopting correct injection practices like proper rotation of the injection site and avoidance of needle reuse can minimize associated complications like LH and hypoglycemia, apart from helping the patient to achieve glycemic targets. Further study in this direction, including a wider Indian diabetic population, will provide more inputs for improving the standard of care, wherein the efficacy and safety issues are optimally addressed.

References
Abridged Prescribing Information

**Active Ingredients:** Metformin hydrochloride (as sustained release) and glimepiride tablets

**Indication:** For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycaemic control.

**Dosage and Administration:** The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed.

**Adverse Reactions:**

- For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur; allergic reactions or pseudo allergic reactions may occur occasionally.

- For Metformin: GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in Vit B12 absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders.

**Warnings and Precautions:**

- For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders.

**Contraindications:** Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma). Severe renal failure (GFR < 30ml/min). In pregnant women. In lactating women. Acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents; acute or chronic disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock; hepatic insufficiency; acute alcohol intoxication; alcoholism. Use in a special population: Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

**Additional information is available on request.**

Last updated: March 13, 2023

*In case of any adverse events, kindly contact: pv@usv.in*
In T2DM, HF & CKD,

UDAPA

Dapagliflozin 5mg & 10mg

Manufacturing plant
Global Accreditation

Quality API
USFDA ANDA Approval

Formulation
• PURE 3 Technology
• Bioequivalent & Therapeutically Equivalent to Innovator
• FAST 10 Technology

Manufacturing
Automated Manufacturing Plant

Quality Check
U 10 Quality Assurance

Packaging
Automated Packaging

Patient
• Most Affordable
• Widely Available
• Real World Evidence

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4-FOLD ADVANTAGE

DPP4 inhibition

95% \(\text{Vildagliptin}^2\) VS 86.9% & 80% 

\(\text{Sitagliptin}^2\) \(\text{Linagliptin}^4\)

HbA1c reduction

1.3% \(\text{Vildagliptin}^2\) VS 0.8% & 0.8% 

\(\text{Sitagliptin}^2\) \(\text{Linagliptin}^4\)

TIR

18.9 hrs \(\text{Vildagliptin}^2\) VS 15.9 hrs & No data 

\(\text{Sitagliptin}^2\) \(\text{Linagliptin}^4\)

Hypoglycemia incidences*

0.1% \(\text{Vildagliptin}^2\) VS 0.3% & 0.2% 

\(\text{Sitagliptin}^2\) \(\text{Linagliptin}^4\)

*Data from different studies


1. Intended for the use of registered medical practitioner only
2. For AE reporting, contact pv@usv.in
In Drug Naive people with Diabetes

RX
UDAPA-M
Dapagliflozin 5mg/10mg + Metformin Extended Release Tablets (500mg/1000mg)

Better Turn with superior Weight + A1c reduction

LATEST UPDATE FROM AACE 2023
Recommends,
For recently diagnosed individuals with T2DM & an A1C ≥ 7.5%, Start Early with combination of Metformin + SGLT2i

In T2DM patients uncontrolled on monotherapy with complications

RX
UDAPA-S 10/100
Dapagliflozin 10 mg + Sitagliptin 100 mg Tablets

↑ turn to a life ‘IN RANGE’

bring your Patients ‘IN RANGE’
always stay true to its values

Rx in Anaemia associated with

- Pregnancy & Lactation
- Menorrhagia
- Nutritional & Iron Deficiency
- Chronic Gastrointestinal Blood Loss
- General Weakness
- Chemotherapy-induced anaemia
- Lack of Appetite
- Chronic Kidney Disease
ADVANCE to ADVANCE-ON: Unfolding the “Legacy Story” in Diabetes

Sanjay Kalra*

Received: 27 March 2019; Accepted: 06 February 2023

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a progressive disease. The importance of early intensive glucose lowering in preventing vascular complications in diabetes is well established. Sulfonylureas (SU) is recommended by most guidelines and widely used for the management of T2DM. However, there has been ambiguity around the long-term benefits with regard to microvascular and macrovascular outcomes with SUs. The United Kingdom Prospective Diabetes Study (UKPDS) provided evidence of sustained cardiovascular (CV) and microvascular benefits of previous intensive glycemic control with SUs or insulin in T2DM patients. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release (MR) Controlled Evaluation (ADVANCE) trial, another landmark study in T2DM patients and its posttrial observational follow-up (FU) study (ADVANCE-Observational Study (ADVANCE-ON)) together provide definite evidence for sustained renal benefits of gliclazide MR based intensive glucose control initiated early during the course of diabetes. These effects, however, may be specific to gliclazide. Evidence from other studies and reviews also suggests that gliclazide MR may hold a distinct place among currently available SUs and reinforce its utility in diabetes management.

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INTRODUCTION

Diabetes is a growing health issue worldwide. The global diabetes prevalence in 2021 was estimated to be 536.6 million people, which is expected to rise to 783.2 million in 2045. Diabetes is associated with micro and macrovascular complications leading to debilitating or often fatal outcomes.

Type 2 diabetes mellitus (T2DM) accounts for 90–95% of cases. A comprehensive approach addressing hyperglycemia along with lipid, blood pressure, and weight abnormalities, and additionally preventing or delaying the associated complications, can help manage T2DM as a whole. Sulfonylureas (SUs) are secretagogues that act by stimulating insulin secretion from pancreatic B-cells. Since their introduction in clinical practice in the 1950s, SUs have remained the mainstay of pharmacotherapy in the management of T2DM. Despite the advent of several new antihyperglycemic drugs, SUs remains the most prescribed oral antihyperglycemic agents for managing T2DM. Modern SUs, including gliclazide modified release (MR) and glimepiride, have been preferred. Nevertheless, there has been ambiguity regarding their long-term benefits, especially on the cardiovascular (CV) and mortality risks associated with SUs. Many contrasting reports have been published about this. In a meta-analysis comparing SU vs non-SU agents, the use of SUs was associated with increased mortality and risk for stroke in patients with T2DM; however, the overall incidence of major CV events was similar for both the agents. Few reports suggest an increased risk of CV events, mortality, and hypoglycemia with certain SUs. A review of 15 head-to-head trials comparing SUs with active comparators reported no increased CV risk with SUs. This review aims to revisit the available data on the long-term microvascular and macrovascular effects of intensive hypoglycemic therapy in T2DM, particularly with the modern SU, gliclazide MR, and provide clinically relevant insights.

THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS): LEGACY EFFECT OF INTENSIVE GLYCEMIC CONTROL IN NEWLY DIAGNOSED T2DM

Large, randomized trials on diabetes patients have demonstrated that early intensive glucose lowering confers microvascular benefits. In the UKPDS, patients with newly diagnosed T2DM were randomly assigned for intensive glucose lowering with either an SU (chlorpropamide or glibenclamide) or insulin, or conventional diet-based therapy. A 25% risk reduction in overall microvascular complications was observed with intensive vs conventional treatment in patients with newly diagnosed diabetes. This reduction in microvascular risk was maintained over ~10 years of posttrial follow-up (FU).

Long-term CV [15% reduction in myocardial infarction (MI)] benefits with previous intensive therapy emerged during the 10-year posttrial FU.

United Kingdom Prospective Diabetes Study (UKPDS) 44-year FU demonstrated that the legacy effect of implementing intensive blood glucose control soon after diagnosis continues to remain for up to 44 years. Early intensive blood glucose control with insulin or sulfonylurea led to 11% fewer deaths and 26% fewer diabetic complications like kidney failure or vision loss. The use of metformin led to 31% fewer heart attacks and 25% fewer deaths. This glycemic legacy effect strengthened the early intervention in diabetes.

OTHER LANDMARK TRIALS: WHAT THEY ADD TO THE EXISTING KNOWLEDGE

In the early 21st century, three large long-term trials were conducted by Action to Control CV Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), to evaluate the relationship between intensive glycemic control and CV outcomes in T2DM patients at high risk for CV events. A long-term FU study was commissioned for each of these trials to evaluate possible legacy effects. The results from these trials and their posttrial FU studies are summarized in Table 1.

In contrast to the results from previous epidemiological studies and the UKPDS, no significant CV benefit was observed with intensive glucose lowering in the initial active comparison phase of the ACCORD trial or the VADT. In fact,
the glucose-lowering arm of the ACCORD trial was terminated early, and all patients were transitioned to a standard glucose control regimen due to increased all-cause [hazard ratio (HR), 1.20 [95% confidence interval (CI), 1.04–1.39]; p = 0.01] and CV mortality (1.49 [1.19–1.87]; p < 0.0001) with intensive treatment. The risk of CV mortality with prior intensive therapy remained high at the end of the posttrial FU (1.20 [1.03–1.39]; p = 0.02). In the VADT, a significant reduction in major CV events was noted with previous intensive vs standard therapy (0.83 [0.70–0.99]; p = 0.04) nearly 10 years after completion of the active intervention phase. A post hoc analysis of the ACCORD study revealed that intensive glycemic control did not reduce composite microvascular outcomes or renal failure but delayed the onset of albuminuria and certain measures of retinopathy. A total of 5 years of intensive glycemic treatment in the VADT was associated with reduced progression to macroalbuminuria but did not significantly alter the onset or progression of retinopathy. A 6-year FU of the VADT showed improved renal outcomes [34% greater odds of maintaining estimated glomerular filtration rate (eGFR) >60 mL/minute/1.73 m²] with previous intensive therapy, particularly among patients who were at higher risk of chronic kidney disease (CKD).

However, it is unclear whether early intensive hypoglycemic therapy reduces the risk of end-stage kidney disease (ESKD).

**Table 1: Baseline characteristics and outcomes from landmark trials in T2DM**

<table>
<thead>
<tr>
<th>Characteristic/outcome</th>
<th>UKPDS18,19</th>
<th>ACCORD20,23</th>
<th>VADT21,24</th>
<th>ADVANCE22,25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age, years</td>
<td>53</td>
<td>62</td>
<td>7.1</td>
<td>8.3</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>NAa</td>
<td>10</td>
<td>6.0</td>
<td>12</td>
</tr>
<tr>
<td>Baseline HbA1c, %</td>
<td>7.1</td>
<td>8.3</td>
<td>9.4</td>
<td>9.8</td>
</tr>
<tr>
<td><strong>Trial characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>Prospective RCT in patients with newly diagnosed T2DM</td>
<td>Multicenter, RCT in T2DM patients with established CV disease or CV risk factors</td>
<td>Open-label RCT in patients with poorly controlled T2DM</td>
<td>Multinational RCT in T2DM patients</td>
</tr>
<tr>
<td>Treatments for glycemic control (I vs S)</td>
<td>Metformin, SU, or insulin vs diet</td>
<td>Multiple drugs in both arms</td>
<td>Multiple drugs in both arms</td>
<td>Current therapy + gliclazide vs current therapy (physician-directed)</td>
</tr>
<tr>
<td>Glycemic target (I vs S)</td>
<td>Fasting plasma glucose: &lt;6 mmol/L vs &lt;15 mmol/L</td>
<td>A1c: &lt;6% vs 7–7.9%</td>
<td>A1c: &lt;6% vs &lt;9%</td>
<td>A1c: &lt;6.5% vs per local guidelines</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Micro and macrovascular complications</td>
<td>Composite of MI, stroke, or CV death</td>
<td>Composite of MI, stroke, CV death, hospitalization for HF, revascularization, or amputation</td>
<td>Major macrovascular and microvascular events</td>
</tr>
<tr>
<td>Duration of FU, years</td>
<td>10.0</td>
<td>3.7</td>
<td>5.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Results</td>
<td>HbA1c (I vs. S), %</td>
<td>7.0 vs 7.9</td>
<td>6.4 vs 7.5</td>
<td>6.9 vs 8.4</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>–12%*</td>
<td>–9%*</td>
<td>–17%*</td>
<td>–10%*</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>nd</td>
<td>–13%*</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>CV death</td>
<td>nd</td>
<td>NA</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>MACE</td>
<td>nd</td>
<td>–15% (0.01)</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>–25%*</td>
<td>–24%*b</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nephropathy/ESKD</td>
<td>nd</td>
<td>NA</td>
<td>decreased</td>
<td>NA</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>–29%*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* p < 0.01 for intensive vs standard glucose-lowering groups; ** the UKPDS included patients with newly diagnosed T2DM; 19 in UKPDS, the composite microvascular endpoint included vitreous hemorrhage, retinal photocoagulation, and renal failure; CV, cardiovascular; ESKD, end-stage kidney disease; FU, follow-up; HbA1c, glycated hemoglobin; HF, heart failure; I, intensive glycemic control; MACE, major adverse cardiovascular event; MI, myocardial infarction, NA, data not available; nd, no significant difference between intensive and standard treatment groups; S, standard glycemic control

**Evaluation (ADVANCE) to Advance-Observational Study (ADVANCE-ON): Further Unraveling the Legacy Story**

The ADVANCE trial evaluated the effect of an intensive [gliclazide MR-based regimen; target glycated hemoglobin (HbA1c) ≤6.5%] vs standard glucose control (target HbA1c per local guidelines) on vascular outcomes in patients with T2DM. A total of 11,140 patients were randomized at 215 centers across 20 countries, including 471 Indian patients. After a median FU of 5 years, the mean HbA1c level was significantly lower in the intensive group vs the standard group (6.5 vs 7.3%). The incidence of the primary endpoint, a composite of major macrovascular and microvascular events, was significantly lower in the intensive group vs the standard group (6.5 vs 7.3%). The incidence of the primary endpoint, a composite of major macrovascular and microvascular events, was significantly lower in the intensive group vs the standard group (6.5 vs 7.3%).
lower with intensive vs standard control (18 vs 20%; HR, 0.90 [95% CI, 0.82–0.98]; p = 0.01). Major microvascular outcomes were also significantly lower in the intensive group (9.4 vs 10.9%; 0.86; [0.77–0.97]; p = 0.01), primarily driven by the reduction in the incidence of nephropathy (4.1 vs 5.2%; 0.79; [0.66–0.93]; p = 0.006).

Of the 11,140 patients selected, 8,494 participated in the posttrial FU ADVANCE-ON (Fig. 1). During the 5.4-year FU (i.e., total 10-year FU of ADVANCE study), despite the early loss of glycemic differences, the renal benefits observed during the active trial persisted during the posttrial FU, HR (95% CI) for ESKD was 0.54 (0.34–0.85); p = 0.007. This observational FU of the ADVANCE study demonstrated the legacy effect of an oral antihyperglycemic drug, with respect to the hard endpoint like ESKD and provided strong evidence supporting early treatment with a gliclazide MR-based regimen, even in patients with established CKD.26

**Gliclazide: beyond ADVANCE-ON**

Several reports have suggested that gliclazide is unique among all SUs.8,27,28 A population-based observational study that compared the impact of gliclazide vs glimepiride on kidney outcomes supported the nephroprotective effect of gliclazide which was observed in the ADVANCE study.27 Gliclazide was associated with reduced risk of doubling of creatinine in patients with preserved kidney function (eGFR ≥60 mL/minute/1.73 m²), good glycemic control (HbA1c <7%), and in older patients (>60 years). In another population-based study of Danish residents, gliclazide was associated with a lower risk of CV events compared to other insulin secretagogues, irrespective of the presence of CV risk.28 A systematic review comparing glimepiride with other SUs reported significantly lower hypoglycemia events and equal or greater glucose-lowering effect with gliclazide. Further, the authors concluded that amongst the currently available SUs, gliclazide had the lowest potential for macrovascular and microvascular events, including CV mortality.3,4 This potential beneficial effect may be attributed to its binding specificity for the pancreatic SU receptor (SUR1) and not for SU receptors in the myocardium (SUR2A) or blood vessels (SUR2B). Understandably, the Dutch, South African guidelines, and South Asian Federation of Endocrine Societies consensus statement specifically recommend gliclazide as the preferred SU for the management of type 2 diabetes.29,30,31

**SUMMARY**

The results from the ADVANCE study showed that early intensive treatment with a gliclazide MR-based regimen provides effective glycemic control and confers vascular benefits in patients with T2DM. The long-term posttrial FU during the ADVANCE-ON study also showed a favorable legacy effect on hard renal endpoints, such as ESKD, without increased risk of CV events or mortality. Gliclazide MR is associated with a lower risk of hypoglycemia compared to other SUs. Overall, the results confirmed the legacy effects of gliclazide MR, reinforcing its utility in routine diabetes management.

**REFERENCES**


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**Fig. 1: Flow of patients from ADVANCE to ADVANCE-ON; T2DM, type 2 diabetes mellitus; R, randomization; MR, modified release**
Over 30 Years of Omeprazole
Praveen Sharma*
Received: 08 May 2023; Accepted: 29 June 2023

ABSTRACT
Background: In the last 3 decades, omeprazole has proved its mettle in managing acid peptic diseases (APDs). It has established itself as the first line of therapy for duodenal and gastric ulcers, gastroesophageal reflux disease (GERD), ulcers due to nonsteroidal anti-inflammatory drugs (NSAIDs), and Zollinger-Ellison syndrome (ZES).
Objectives: The purpose of this literature review is to assess the effectiveness of omeprazole as compared to the other proton pump inhibitors (PPIs) currently in use and its safety and efficacy in special populations, including the pediatric and geriatric populations.
Results: Omeprazole was found to be the most effective PPI in the management of APDs due to its rapid action, good antioxidant effects, and effectiveness against nocturnal acid breakthroughs. Its safety and tolerance have been proved in various randomized controlled trials.
Conclusion: Omeprazole is the prototypical drug in the management of APDs and has withstood the test of time. After 3 decades, omeprazole remains the drug of choice in managing APD.

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INTRODUCTION, BACKGROUND, AND HISTORY
Acid peptic disease (APD) is a group of conditions where the impaired gastric mucosa has been damaged by gastric acid. Gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) belong to this group of conditions. Individuals with APD have an impaired quality of life (QoL) along with significant morbidity and mortality.1

Gastric acid secretion is a complex process coordinated by various stimuli. Histamine, gastrin, and postganglionic muscarinic acetylcholine regulate this process. Although anticholinergics and histamine 2 receptor antagonists (H2RA) are used to manage gastric hypersecretion, proton pump inhibitors (PPIs) are more effective as they block the acid pump response to all types of parietal cell stimulation. They are longer-acting than H2RA and can maintain a pH of >4 for 15–20 hours a day. Additionally, they are effective against a postprandial and nocturnal rise in gastric acid. Therefore, PPIs are pivotal in managing a plethora of gastric conditions, such as esophagitis, PUD, nonerosive reflux disease (NERD), ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs), functional dyspepsia, and Zollinger-Ellison syndrome (ZES).2 A meta-analysis of 19 trials in NERD patients has shown that PPIs are superior to prokinetics and H2RAs against heartburn.3

The various PPIs that are currently available are omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole, of which omeprazole and lansoprazole have been in use for the longest time.4 It is essential for health professionals to possess a thorough knowledge of the indications and dosages of these drugs. Omeprazole is the most used and the most cost-effective of all.5 A meta-analysis of 98 randomized controlled trials (RCTs) and 45,964 patients that compared the efficacy of 40 mg omeprazole once daily (OD), 80 mg pantoprazole OD, and 80 mg famotidine OD found that omeprazole had the best performance in both symptom relief and drug tolerance. Omeprazole (20 mg) was 10 times more effective in healing and four times more effective in symptom relief than a placebo in patients with GERD; patients also had a 39% greater tolerance to the drug than the placebo.6 Similarly, a systematic review comparing PPIs, H2RAs, potassium-competitive acid blockers, and alginate in treating reflux disease demonstrated that omeprazole (20 mg OD; taken for 2–4 weeks) ranks first in complete symptom relief.7

Omeprazole strongly inhibits gastric acid secretion without serious adverse effects. A study evaluating the effectiveness of quadruple therapy for 2 weeks with bismuth subcitrate, antibiotics, and omeprazole (20 mg) indicated that the regimen could effectively eradicate Helicobacter pylori (H. pylori) and that the treated individuals tolerated this regimen well.8 In a systematic review of the safety and effectiveness of omeprazole and lansoprazole in managing GERD, four studies demonstrated that omeprazole (40 mg) was significantly more effective than lansoprazole (30 mg) in raising gastric pH (p < 0.05) and that the effects of omeprazole lasted for a longer time than those of lansoprazole.9 Omeprazole was also observed to be more effective than H2RAs in healing ulcers in a pooled analysis of RCTs. When used for maintenance therapy, no relapses occurred, and tolerance to omeprazole was good. In addition, omeprazole was found to be effective in patients refractory to H2RAs, with individuals experiencing relief from the very first day of treatment.10

Omeprazole can be used to treat various conditions such as GERD, duodenal, and gastric ulcers, ulcers infected with H. pylori, ulcers due to NSAIDs, and ZES.5 However, apart from these conventional uses, omeprazole has also been repurposed for use in treating coronavirus disease 2019 (COVID-19) as it is hypothesized to inhibit viral replication.10 In addition, when patients with diabetes were given hypoglycemic agents along with omeprazole, better glycemic control was achieved than when the hypoglycemic agents were taken alone. There seems to be some potential for the use of omeprazole in patients with diabetes, with an established safety profile in these patients.11 This review aims to explore the aspects of omeprazole that make it unique; these include its effectiveness in preventing nocturnal breakthroughs, rapid action, and antioxidant effects. In addition, this review also aims to evaluate the use of omeprazole in treating individuals with comorbidities.

Omeprazole was first discovered 30 years ago.1 Servier, a pharmaceutical company from France, reported the antisecretory activities of CMN 131, a thioacetamide derivative; however, most thioacetamide derivatives showed acute toxicity in animals. Later, scientists in Hässle, Sweden, investigated other structural analogs of these molecules that showed no toxicity. These scientists hypothesized that the thiaoamide group in the molecules was responsible for toxicity and added a

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A Review of Omeprazole

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The introduction of omeprazole as a drug to treat APDs was followed by the invention of six other PPIs varying slightly in their structures and having similar efficacies as omeprazole in controlling heartburn, healing erosive esophagitis, and reducing relapses of erosive esophagitis.14 Despite the introduction of newer PPIs, omeprazole has remained relevant and the most studied drug in the clinical management of APD.1

Currently, India exports omeprazole to >158 countries. Between April 2020 and November 2022, India exported 163.88 million USD worth of omeprazole. This is equivalent to roughly 4,323,030 tablets, demonstrating the extensive use of and demand for omeprazole.15

**Mechanism of Action**

Omeprazole inhibits the parietal cell H⁺K⁺-adenosine triphosphate (ATP) pump, which leads to the suppression of acid secretion. The inhibitory effects set in rapidly, within 1–2 hours of administration, and continue for approximately 72 hours; once the administration of omeprazole is stopped, the baseline activity of the H⁺K⁺-ATP pump returns to normal within 5 days (Fig. 2).16 Intake of food delays the absorption of omeprazole (as the area under the plasma curve [AUC] is reduced), increases absorption variability, and decreases the maximum concentration of the drug in the stomach; therefore, administration under fasting conditions is recommended.17

As PPIs are prodrugs, they need to be activated in the secretory canaliculi of parietal cells to inhibit the H⁺K⁺-ATP pump. Since food affects omeprazole bioavailability,18 the drug is administered 30 minutes to one hour before a meal.16

Omeprazole is metabolized by the hepatic cytochrome P450 (CYP) enzyme and is excreted in the urine. It has a half-life of 30 minutes to one hour in healthy individuals and 3 hours in those who are hepatically impaired. Nevertheless, the pharmacological effects of omeprazole last much longer as it is preferentially accumulated in the parietal cells and binds covalently with H⁺K⁺-ATPase.16 Omeprazole was found to increase the gastric pH to a greater extent in CYP2C19-poor metabolizers (PMs) than in early metabolizers (EMs). In PM, the phenotype is common in the Chinese population; therefore, omeprazole was found to be more effective in reducing bleeding in peptic ulcers in the Chinese population.19

In contrast, the Clinical Pharmacogenetics Implementation Consortium guidelines for PPI dosing and CYP2C19 mention that PPIs were less effective in normal metabolizers in the Asian population, who, thus, require higher doses of the drug.20 A study in Tamil Nadu, India, phenotypically classified individuals as EMs, heterozygous EMs, PMs, heterozygous ultra-metabolizers, and ultra-metabolizers.19

**Pharmacokinetics of Omeprazole**

The bioavailability of omeprazole (20–40 mg OD) is 30–40%. Omeprazole attains peak plasma concentrations in 0.5–3.5 hours which increases proportionally up to a dose of 40 mg. Doses >40 mg show a nonlinear increase in peak plasma concentration and AUC due to the saturation of the first-pass effect above 40 mg.21

Despite the nonlinear relationship between AUC and the inhibition of gastric acid release at doses >40 mg, the AUC

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**Fig. 1: Evolution of omeprazole**

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A Review of Omeprazole

symptom resolution is observed in patients with esophagitis who were administered PPIs when compared to those on H2RA or prokinetics. Omeprazole is as effective as pantoprazole and lansoprazole and superior to cisapride, cimetidine, or ranitidine in promoting healing in patients with acute GERD with esophagitis. Patients are treated with 20 mg omeprazole (OD) for 4–8 weeks.9,23

• Pathological hypersecretory conditions such as ZES: Though surgical excision of the neuroendocrine tumor remains the mainstay in patients with ZES, medical management of acid peptic complications in these patients is necessary as they experience a constitutive release of gastrin. Gastric hypersecretion can be managed by the use of PPIs. A longitudinal study demonstrated the safety and effectiveness of omeprazole when administered for a period of up to 4 years in patients with ZES. Patients are treated with 60 mg omeprazole (OD); however, dosage and duration vary based on the clinical situation and patient response.9,23

• Maintenance of acid-mediated GERD-led erosive esophagitis: Omeprazole alone or combined with cisapride as maintenance therapy for 12 months was significantly more effective in maintaining endoscopic remission than cisapride alone (p = 0.003), ranitidine alone (p < 0.001) or ranitidine and cisapride combined (p = 0.003) after a year of maintenance therapy. Patients are prescribed 20 mg omeprazole (OD).9,23

In acid-mediated GERD-led erosive esophagitis, 20 mg omeprazole OD for 4–8 weeks has been recommended in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Omeprazole 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_{1/2} (hour)</td>
<td>0.5–1.2</td>
</tr>
<tr>
<td>t_{max} (hour)</td>
<td>1–4</td>
</tr>
<tr>
<td>C_{max} (µmol/L)</td>
<td>0.23–23.2</td>
</tr>
<tr>
<td>AUC (µmol·hour/L)</td>
<td>0.58–3.47</td>
</tr>
<tr>
<td>V (L/kg)</td>
<td>0.13–0.35</td>
</tr>
<tr>
<td>CL (mL/minute)</td>
<td>400–620</td>
</tr>
</tbody>
</table>

AUC, area under the plasma concentration curve; CL, clearance; C_{max}, maximal plasma concentration; t_{1/2}, elimination half-life; t_{max}, time to maximal plasma concentration; V, apparent volume of distribution

Fig. 2: Mechanism of action of omeprazole

Table 1: Pharmacokinetic characteristics of omeprazole 20 mg

In acid-mediated GERD-led erosive esophagitis, 20 mg omeprazole OD for 4–8 weeks has been recommended in

**Clinical Uses**

Omeprazole (20 mg) capsules are indicated by the United States Food and Drug Administration (USFDA) in the management of the following conditions:

- Symptomatic GERD: Damage to the esophageal mucosa is noticed in GERD due to the reflux of the gastric contents into the esophagus. The prevalence of GERD in Indian patients is around 7.6%. Omeprazole has shown rapid and better symptom relief than cisapride, ranitidine, and placebo in symptomatic GERD. Omeprazole (20 mg OD) is prescribed for up to 4 weeks to reduce pain, inflammation, and heartburn.9,23

- Active duodenal ulcers: Omeprazole has shown greater healing of duodenal and gastric ulcers over 2 weeks as compared to cimetidine and ranitidine. Omeprazole (20 mg OD) is prescribed for 4 weeks, and if found refractory, the same dosage is continued for another 4 weeks.9,23

- Active benign gastric ulcers: Patients with PUD refractory to high-dose, 450 mg, ranitidine OD have demonstrated healing of ulcers with the administration of 40 mg omeprazole (OD) for a period of 2–8 weeks. Bleeding of the upper gastrointestinal tract from PUD results in significant mortality, morbidity, and healthcare expenses. Early administration of PPIs has been associated with a reduction in the proportion of patients with rebleeding ulcers and the need for surgery. Patients are treated with 40 mg omeprazole (OD) for 4–8 weeks.9,23

- H. pylori eradication: It has been established that H. pylori is one of the etiological factors associated with gastroduodenal ulcer disease. A high level of evidence supports the use of PPIs along with antibiotics to effectively eradicate H. pylori. Omeprazole eradicates H. pylori by a urease-independent mechanism by inhibiting the growth of the organism at a low pH. Studies have demonstrated that omeprazole as triple therapy (with two antibiotics) is more effective against H. pylori than lansoprazole, ranitidine, or bismuth. The therapy aims to reduce the risk of recurrence of duodenal ulcers. Omeprazole is prescribed concomitantly with antibiotics as dual therapy (40 mg omeprazole (OD) with clarithromycin (500 mg) thrice a day for 2 weeks) or triple therapy (20 mg omeprazole with amoxicillin (1000 mg) and clarithromycin (500 mg), all prescribed two times a day for 10 days).9,23

- H. pylori eradication: Omeprazole combined with clarithromycin (500 mg) and amoxicillin (1000 mg) for 10 days is effective in eradicating H. pylori.9,23
A Review of Omeprazole

adults, and weight-based dosing has been recommended in children of age one month and above. In newborn infants and children up to 1 year of age, the recommended weight-based dosage of omeprazole is 0.3–3.5 mg/kg/day.

According to the prescribing information for omeprazole provided by the USFDA (first approved in 1989), omeprazole is indicated for the management of GERD in children over 1 year of age with a body weight of >10 kg. Omeprazole is safely used along with antibiotics to eradicate H. pylori infections in children >4 years of age and in adolescents. The common adverse reactions to omeprazole are nausea, vomiting, headache, diarrhea or constipation, stomach pain, and flatulence. The uncommon side effects are dizziness, vertigo, insomnia, swelling of feet and ankles, hives, and lethargy.

OTHER USES
Role of Omeprazole in NSAID-associated Gastrointestinal Effects
The mainstay therapies for the management of arthritis, visceral pain, headache, postoperative pain, and musculoskeletal disorders are NSAIDs. However, they can cause significant adverse reactions, such as gastrointestinal complications, hypertension, renal injury, and cardiovascular disease. A meta-analysis demonstrated that treatment with NSAIDs and PPIs lowered the risk of developing dyspepsia by 66% as compared to that when treatment consists of NSAIDs alone. A systematic review demonstrated that PPIs are significantly more effective than H2RAs and antacids in managing nonspecific dyspepsia. Antacids provided only symptomatic relief and did not reduce the risk of peptic ulcers and their complications. Omeprazole, however, also reduced the risk of bleeding caused by low-dose aspirin usage in managing cardiovascular disease.

Role of Omeprazole in Diabetes Mellitus
Diabetes mellitus is a growing health concern, particularly in developing countries. Although various hypoglycemic agents have been used to manage diabetes, a combination of therapies has been recommended to avoid long-term complications of the disease. It has been suggested that PPIs increase the mass of islet cells, decrease the speed of gastric emptying, and reduce glucagon secretion. This is because PPIs increase the secretion of gastrin, which, due to its resemblance to incretin, may stimulate the pancreatic cells to secrete insulin and mediate other metabolic effects similar to those of incretin. A trial reported that the addition of omeprazole to metformin treatment significantly improved fasting blood glucose and glycated hemoglobin levels in 3 months. A retrospective study of almost 400,000 individuals with data over 5 years demonstrated a statistically significant (p < 0.001) dose-dependent decrease in the risk of diabetes development in individuals being treated with PPIs to manage an upper gastrointestinal disease.

Role of Omeprazole in Respiratory Diseases
An association between chronic rhinosinusitis and GERD has been found, probably due to the high sensitivity of the upper airway mucosa to acid content. Omeprazole (20 mg) has been shown to reduce the symptoms and signs of chronic rhinosinusitis and laryngopharyngeal reflux when used for 8 weeks. Individuals with asthma and GERD showed improved lung function and QoL when treated with PPIs. Omeprazole has also had a beneficial effect on individuals with idiopathic pulmonary fibrosis.

Role of PPI in Preventing Esophageal Ulcers Postendoscopic Ligation of Varices
Portal hypertension is the underlying cause of esophageal varices. While endoscopic variceal band ligation (EVL) is an effective procedure for controlling and preventing variceal bleeding in these patients, it can be complicated by bleeding from post-EVL ulcers. In a retrospective cohort study, 505 cirrhotic patients with high-risk esophageal varices who underwent primary prophylactic EVL were evaluated, and it was found that bleeding after prophylactic EVL was associated with coexisting gastric varices and the nonadministration of PPIs. Another retrospective cross-sectional study of 46 cirrhotic patients with bleeding gastroesophageal varices (GEV) who underwent EVL demonstrated that PPIs lower the occurrence of early bleeding and adverse events after EVL. The study also reported that nonsuppression of PPIs and the presence of GEVs were significantly associated with a higher risk of bleeding.

Role of Omeprazole in the Management of COVID-19
The COVID-19 pandemic has followed an unpredictable course in its effects on human health, with most people having mild-to-moderate symptoms and recovering rapidly, but others developing grave symptoms. A multidisciplinary approach has been employed in the management of COVID-19, including the use of antisecretory agents. Omeprazole can inhibit the replication of the virus by interfering with the acidification of lysosomes. At concentrations much higher than the therapeutic concentrations currently being used, omeprazole impairs the formation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A synergistic action was observed when the antiviral agent remdesivir was used with aprotinin (a protease inhibitor) and therapeutic concentrations of a PPI. The antiviral efficacies of PPIs are also related to their antioxidative and anti-inflammatory actions. Omeprazole reduces the symptoms of COVID-19 by decreasing oxidative stress in endothelial and gastric epithelial cells and reducing the production of cytokines in duodenal epithelial cells. Another hypothesis regarding the mechanism of action of omeprazole rests on its ability to block vacuolar-type ATPase pumps or by its pH buffering action, both of which interfere with the functioning of the viral spike (S1) protein and contains the ingress of the SARS-CoV-2. Due to the decreased rate of hospitalization and duration of symptoms seen in COVID-19-positive individuals on NSAIDs, these drugs are commonly prescribed to them. Omeprazole helps protect these individuals from gastric damage caused by the NSAIDs.

GLOBAL AND LOCAL TRENDS IN OMEPRAZOLE USE
Omeprazole is on the list of essential medications that have been drawn up by the World Health Organization. It is one of the most prescribed drugs across the globe, with >2 million tablets of omeprazole being prescribed in March 2018 in the United Kingdom alone. In the United States, between 2006–2019, omeprazole prescriptions increased by 44 million. Omeprazole is popular in North America, Latin America, Asia Pacific, Europe, Africa, and the Middle East.

Globally, 10–15% of the population experiences gastric ulcers. In 2020, the geographic region with the maximum use of omeprazole was North America due to the increased incidence of H. pylori infection observed there. Around 4.5 million people in the United States are affected by PUD, and ~10% of the population by duodenal ulcers. The reasons for the increasing prevalence of GERD are an increase in the aging population; delayed stomach emptying; lifestyle changes, such as increased consumption of fatty food, alcohol, and smoking; and obesity. A similar increase in H. pylori infections and omeprazole use has been predicted in the Asia Pacific region. The Asia Pacific region ranks third
in the use of omeprazole, following North America and Europe. \(^{39}\)

Although India exports medicines globally, the affordability of these drugs to the local population is limited by the prices of the drugs, which remain highly variable, and the use of such drugs adds to the out-of-pocket expenses borne by patients. An Indian study has demonstrated that the tablet rabeprazole (20 mg) has the highest cost ratio (9.15) and percentage cost variation (815.78) in India. A single vial of injectable omeprazole (40 mg) has the lowest cost ratio (1.47) and percentage cost variation (47.95). In a country like India, where 80% of health-related costs are borne by the patient, physicians have an important role in prescribing cost-effective drugs. \(^{40}\) Another study from India has shown that 20 and 40 mg of omeprazole are the most cost-effective drugs in both injectable and oral forms, whereas 10 mg of ilaprazole is the most expensive oral PPI, and 40 mg of rabeprazole is the most expensive injectable PPI. This information is important as PPIs are commonly prescribed drugs, and the prescription of expensive drugs affects the patient’s health-seeking behavior and healthcare expenses. \(^{41}\)

**Recent Research on Omeprazole**

Details on the systematic reviews, RCTs, and observational studies on omeprazole included in this review are provided in Table 2.\(^{4,6–8,42}\)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design and setting</th>
<th>Sample size</th>
<th>Exposure</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barberio et al., 2022</td>
<td>A systematic review and meta-analysis</td>
<td>23 RCTs with 10,735 subjects</td>
<td>Efficacy and safety of PPIs, H2RA, potassium-competitive acid blockers, and alginites in reflux disease.</td>
<td>Omeprazole 20 mg, taken OD, ranked first in complete symptom relief between 2–4 weeks.</td>
</tr>
<tr>
<td>Javed et al., 2020</td>
<td>A systematic review using PRISMA guidelines</td>
<td>9 studies with 418 participants</td>
<td>Medline, Embase, and CENTRAL were searched for studies on the effectiveness and safety of omeprazole and lansoprazole in the management of GERD.</td>
<td>Omeprazole lowered gastric pH faster, and the effects lasted for a longer time than with lansoprazole.</td>
</tr>
<tr>
<td>Zhang et al., 2017</td>
<td>A network meta-analysis and GRADE system</td>
<td>9 RCTs with 45,964 participants</td>
<td>Effectiveness and tolerability of different recommended doses of PPIs and H2RAs in GERD.</td>
<td>Omeprazole 40 mg/day ranked first in both symptom relief and drug tolerance.</td>
</tr>
<tr>
<td>Salmanroghani, Mirvakili, Baghbanian, et al., 2018</td>
<td>Randomized, open-label clinical trial</td>
<td>228 participants</td>
<td>To evaluate the effectiveness of quadruple therapy with bismuth subcitrate, antibiotics, and omeprazole for 2 weeks on eradication of <em>H. pylori</em> and patient compliance with treatment.</td>
<td>The results of the study indicated effective eradication of <em>H. pylori</em> and good tolerance of the regimen among the individuals treated.</td>
</tr>
<tr>
<td>Lazebnik et al., 2021</td>
<td>Multicountry, multicenter, observational study</td>
<td>18,724 participants</td>
<td>Patient-reported outcomes to 40 mg and 20 mg omeprazole on measures of heartburn due to varying etiologies.</td>
<td>Better patient-reported outcomes were found with omeprazole 40 mg compared to 20 mg omeprazole.</td>
</tr>
</tbody>
</table>

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**Comparing the Relative Effectiveness of Omeprazole, Lansoprazole, and Pantoprazole**

Omeprazole exhibits dual action in protecting the gastric mucosa by suppressing acid secretion and by acting as a potent antioxidant. Its ability to scavenge free radicals was far superior to pantoprazole and lansoprazole and at par with esomeprazole. \(^{43}\)

A systematic review comparing the efficacies of 20 mg omeprazole and 30 mg lansoprazole found that omeprazole was consistently better at reducing gastric acidity and increasing gastric pH. Omeprazole was also more effective in controlling nocturnal gastric pH and reducing nocturnal acid breakthroughs. Four studies demonstrated that omeprazole (40 mg) lowered gastric pH significantly more than lansoprazole (30 mg) \((p < 0.05)\) in both healthy individuals and patients with GERD. \(^{4}\)

A single-center, three-way crossover, open-label study compared the effectiveness of immediate-release omeprazole (20 mg)/sodium bicarbonate (1100 mg) with delayed-release lansoprazole (15 mg). Omeprazole was significantly better at decreasing the median intragastric pH level as compared to lansoprazole on the 7th day of administration; omeprazole exerted this effect as early as 10–15 minutes after the dose was administered and showed sustained effects up to 115–120 minutes after administration. Even on day 1, omeprazole was able to decrease intragastric acidity more rapidly than lansoprazole. Furthermore, omeprazole maintained a pH of >4 for a significantly longer duration than lansoprazole over 24 hours on the 7th day \((p < 0.007)\). Thus, the study demonstrated that omeprazole had significantly better acid suppression effects and faster onset of action than lansoprazole. \(^{44}\)

Omeprazole is used as a first-line drug in eradicating *H. pylori*. The emergence of clarithromycin resistance has caused triple therapy to often be ineffective in eradicating *H. pylori* infections. Even quadruple therapy using bismuth may be ineffective as the bioavailabilities of the drugs are variable, and many patients cannot tolerate the drugs/drug combinations. Therefore, PPIs, such as omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole, have been widely used as first-line acid inhibitors to treat *H. pylori* infections. \(^{45}\) A meta-analysis that evaluated the efficacy of omeprazole and lansoprazole in the management of *H. pylori*-associated duodenal ulcers found no significant differences between the two drugs in their ulcer healing rates; in addition, patients showed no serious adverse reactions to either drug. The two drugs also had similar efficacies in managing *H. pylori*-associated duodenal ulcers. \(^{46}\)

A meta-analysis of RCTs found that new-generation PPIs and omeprazole exhibit...
similar efficacies in controlling GERD, healing esophagitis, and preventing the relapse of symptoms. Though several studies claim that one PPI is more effective than another, the World Health Organization Collaborating Centre for Drug Statistics Methodology has stated that 20 mg omeprazole, 30 mg esomeprazole, 30 mg lansoprazole, 40 mg pantoprazole, 20 mg rabeprazole, and 30 mg dexlansoprazole were equally efficacious in managing GERD. Kirchheiner et al. reviewed 57 clinical studies and reported that the relative potencies of pantoprazole, lansoprazole, and omeprazole were 0.23, 0.90, and 1.00, respectively. Similar results were obtained by Graham and Tansel in 2018, who analyzed data from RCTs that tested the gastric pH of patients after they were administered oral doses of omeprazole, rabeprazole, esomeprazole, pantoprazole, and lansoprazole for at least 5 days. They concluded that these PPIs, based on their potencies, may be used interchangeably. Omeprazole (20 mg) and lansoprazole (30 mg) were found to be equivalent to 20 mg esomeprazole and rabeprazole.

A meta-analysis that compared the efficacies of 40 mg omeprazole OD, 80 mg pantoprazole OD, and 80 mg famotidine OD demonstrated that omeprazole ranked first in both symptom relief and drug tolerance. Additionally, omeprazole has withstood the test of time, is the most used PPI, and is also the most affordable.

**Use of Omeprazole in Special Populations**

According to the FDA, PPIs are effective and safe in children (1–17 years of age). A study has demonstrated that the administration of 1 mg/kg omeprazole in infants aged 6–12 weeks increased gastric and intraesophageal pH in cases of GERD resulting from esophageal atresia or congenital diaphragmatic hernia. The recommended dose in children from 1–16 years of age is based on their body weight (Table 3).

Data from a retrospective analysis found that the common adverse effects of omeprazole seen in children were not serious and mainly included gastrointestinal and skin manifestations. Headache, nausea, diarrhea, or constipation were seen transiently. The USFDA has approved the use of most PPIs in pediatric patients (children >1 year of age) for treating conditions like GERD and erosive esophagitis. However, pantoprazole is not suitable for use in children <5 years of age because it is currently not available in a formulation suitable for children <5 years of age; in addition, this drug is not effective in infants <1 year of age. A systematic review of PPI usage, including omeprazole, in children showed that PPIs were superior to placebos, alginic acid, and ranitidine in the management of GERD. Observational studies have reported that in children, omeprazole in doses of 1–2 mg/kg body weight twice a day was effective in treating eosinophilic esophagitis.

An interventional study examined the response of children <16 years of age to 1 mg/kg/day of omeprazole administered in 2 doses for the management of eosinophilic esophagitis. Follow-ups for 6 months indicated that remission occurred, but only if the patients adhered strictly to the treatment. An RCT comparing the administration of omeprazole alone with omeprazole administered along with the imposition of a 4-food elimination diet to treat eosinophilic esophagitis in children found that the combination of omeprazole and diet therapy was more effective.

A study compared the triple-therapy regimens of clarithromycin, amoxicillin, and omeprazole with amoxicillin, omeprazole, and azithromycin for the eradication of *H. pylori* in children and found both treatments to be equally effective. Another similar study found that triple therapy with clarithromycin, amoxicillin and omeprazole for 7 days was effective in eliminating *H. pylori* in children <15 years of age. Omeprazole also improved asthma control in asthmatic children (4–16 years) with GERD.

Around 40–85% of pregnant women experience GERD due to both mechanical and hormonal factors. Estrogen and progesterone have a role in the relaxation of the lower esophageal sphincter. Additionally, hormonal changes during pregnancy are believed to affect gastric motility (GM) by altering the enteric nervous system and musculature, leading to decreased GM, which may contribute to GERD. In a cohort study that included 6051 nulliparous women on PPI, PPI use during pregnancy was linked to an increased risk of overall preeclampsia; however, after 28 weeks, a protective effect against preterm preeclampsia was observed. According to a recent systematic review, there is evidence of birth defects, including cardiac defects, with PPI use during pregnancy, but there exists no evidence supporting a causal association between PPI use and these birth defects. The review also concluded that omeprazole has a low risk at doses of 20–60 mg/day during the first trimester. However, due to a lack of comprehensive prospective clinical studies on its use during pregnancy, the FDA has not altered its classification of omeprazole as a category C drug.

On assessing the safety of PPIs during lactation, it was observed that pantoprazole and omeprazole are both excreted into breast milk in quantities 300–600 times lower than those administered to neonates. The excretion of PPIs into breast milk is negligible, and the acidic environment of the infant’s stomach may further break down PPIs; thus, PPIs in breast milk are unlikely to get absorbed systemically.

Another population where PPIs are increasingly being used is the elderly. In adults <40 years of age, fewer than 10% of individuals are prescribed PPIs, while in those >80 years of age, 30% of individuals are prescribed PPIs. This increase could be because PPIs decrease the risk of the development of adenocarcinomas and Barrett’s esophagus, both of which are likely to develop in old age. Bleeding from peptic ulcers is also more common in the elderly, probably because many people in this age group are also prescribed NSAIDs. The administration of PPIs can protect against bleeding peptic ulcers associated with NSAID use. These drugs have been demonstrated to be safe in the short term for the elderly.

The classification by Child-Turcotte-Pugh (CTP) for cirrhosis has been considered to guide the use of PPIs in patients with cirrhosis. It has been recommended that in patients with CTP A and B, a reduced dose of rabeprazole and omeprazole be given, and in those with CTP C, a maximum of 20 mg OD of esomeprazole may be administered. Lansoprazole and pantoprazole were unsafe due to a four to eight-fold increase in their exposure in patients with cirrhosis.

When considering the use of PPIs in patients with kidney disease, although omeprazole use has been associated with injury to the kidneys, most cases of chronic kidney disease and acute kidney injury were associated with the administration of lansoprazole and dexlansoprazole as per the FDA Adverse Event Reporting System. The American College of Gastroenterology (ACG), 2022 guidelines mention that patients with renal insufficiency can be prescribed PPIs following a nephrologist consultation along with monitored renal function.

Studies have also associated PPI use with deficiencies of vitamins, bone fractures due

**Table 3:** Recommended dose in children from 1 to 16 years based on body weight

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Dose of omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–&lt;10 kg</td>
<td>5 mg OD</td>
</tr>
<tr>
<td>10–&lt;20 kg</td>
<td>10 mg OD</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>20 mg OD</td>
</tr>
</tbody>
</table>
to osteoporosis, and intestinal infections. However, these studies had protopathic bias as well as residual confounding and could not establish causality. High-quality evidence has demonstrated that PPIs do not pose a risk for any of these adverse events except for intestinal infections. The ACG guidelines mention that neither vitamin D nor calcium intake needs to be increased in patients on PPIs without other risk factors for osteoporosis, nor does vitamin B12 intake effectively that treatment failure is more likely to indicate a misdiagnosis of GERD. A study on individuals refractory to PPIs showed that those who were prescribed omeprazole twice a day and given appropriate instructions on its use got relief from heartburn. A comparison of the relative acid-suppression abilities of PPIs (based on the average intragastric pH for 24 hours) to those of omeprazole is called an omeprazole equivalent (OE). Omeprazole has an OE of 1.00, pantoprazole 0.23, lansoprazole 0.90, esomeprazole 1.60, and rabeprazole 1.82.66

The National Health Service (NHS), United Kingdom, recommends using 20 mg omeprazole OD as a full dose, 10 mg omeprazole OD as a low on-demand dose, and 40 mg omeprazole OD as a double dose. The NHS also recommends the use of PPIs in the following conditions:

- Suspected upper gastrointestinal bleeding.
- Peptic ulcer.
- Gastroesophageal reflux disease (GERD).
- Barrett’s esophagus.
- Dyspepsia.
- Functional dyspepsia.
- Esophageal dilatation.
- For gastro-protection.
- Esophagitis.67

The Indian recommendations on PPIs suggest prescribing PPIs for 12 weeks (long term) for GERD with peptic stricture or erosive esophagitis. In patients with GERD without complications, a short-term PPI course (<6 weeks) is prescribed. For patients demonstrating unusual symptoms of GERD (noncardiac chest pain), PPIs are prescribed on a trial basis for 2 weeks and in nonresponsive patients, further investigations are recommended to determine the etiology of the problem. Patients on NSAIDs with a high risk of ulcerative bleeding are prescribed PPIs. For patients with dyspepsia and acidity-related symptoms, such as epigastric pain syndrome, PPI therapy for a short-term is recommended. Long-term evaluation of the PPI dose is recommended periodically to ensure that the lowest dose of PPI required for effectiveness is prescribed to manage APDs.68

**Comparative Pricing of Various Brands of PPI Available in India**

Details about the various PPIs available in India are provided in Table 4.22,69–71

**Conclusion**

Omeprazole is the first line of treatment for APD. Omeprazole is effective in managing active and benign gastric ulcers, treating symptomatic GERD, managing active duodenal ulcers, H. pylori eradication, preventing ulcers due to NSAIDs, managing acid-mediated GERD-led erosive esophagitis, treating pathological secretory conditions such as ZES, and the maintenance of erosive esophagitis due to acid-mediated GERD. Apart from these, omeprazole has also recently been investigated as a treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg)</th>
<th>Half-life (hours)</th>
<th>Mode of metabolism</th>
<th>Price range (INR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Tablet 10</td>
<td>0.6–1.5</td>
<td>Metabolized to omeprazole hydroxy sulphone by the action of CYP2C19 &amp; CYP3A4</td>
<td>24.50–39.60</td>
</tr>
<tr>
<td></td>
<td>Capsule 10–40</td>
<td></td>
<td></td>
<td>28–78.33</td>
</tr>
<tr>
<td></td>
<td>Injection 40</td>
<td></td>
<td></td>
<td>23.25–23.75</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Tablet 20–40</td>
<td>1.1–1.6</td>
<td>Metabolized to esomeprazole sulphone by the action of CYP2C19 and CYP3A4</td>
<td>27–60</td>
</tr>
<tr>
<td></td>
<td>Injection 40</td>
<td></td>
<td></td>
<td>77–95.75</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Capsule 15–30</td>
<td>0.9–1.6</td>
<td>Metabolized to lansoprazole sulphone by the action of CYP2C19 and CYP3A4</td>
<td>26.25–100</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Tablet 20–40</td>
<td>0.9</td>
<td>Metabolized to pantoprazole sulphate by the action of CYP2C19 and CYP3A4</td>
<td>58–78</td>
</tr>
<tr>
<td></td>
<td>Injection 40</td>
<td></td>
<td></td>
<td>44.80–79.50</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Tablet 20</td>
<td>1–1.1</td>
<td>Metabolized to rabeprazole sulphone by the action of CYP2C19 and CYP3A4</td>
<td>18.50–76.50</td>
</tr>
<tr>
<td></td>
<td>Injection 20</td>
<td></td>
<td></td>
<td>50–89</td>
</tr>
<tr>
<td>Dexrabeprazole</td>
<td>Tablet 5–10</td>
<td>3.5</td>
<td>Metabolized by CYP450 isoenzymes in the liver.</td>
<td>18.00–120.00</td>
</tr>
<tr>
<td>Ilaprazole</td>
<td>Tablet 5–10</td>
<td>0.5–2</td>
<td>Ilaprazole is catalyzed mainly by CYP3A4 via its sulfoxide oxidation. The CYP3A4 enzyme has a prime role in ilaprazole clearance.</td>
<td>45.00–85.00</td>
</tr>
</tbody>
</table>

CYP, cytochrome; INR, Indian rupee
option for patients with both APD and diabetes to understand its effect on blood glucose levels. In addition, omeprazole was also prescribed to patients with COVID-19 who were on multiple medications that caused drug-induced acidity. The general advantages of using omeprazole are that it is effective in reducing gastric pH, acts rapidly, and is suitable for children as young as 1-month-old. Unlike in the case of H2RAs, patients prescribed omeprazole do not show tachyphylaxis. Omeprazole is well tolerated by most people, and the most common adverse effects are mild, ranging from headaches to tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribed omeprazole do not show rapid tachyphylaxis. Omeprazole is well tolerated by patients prescribe...
A Review of Omeprazole


In hypertensive patients with CAD

Initiate with

**Tazloc-Beta 25**

Telmisartan 40 mg + Metoprolol Succinate 25 mg PR

**Assured Control on Sympathetic Over Activity**

[Visual arrow and icon indicating 74% HCPs prefer the combination of Telmisartan + Metoprolol]

1. Data on file

In hypertensive patients with CAD

**Tazloc-Beta 50**

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**Superior Cardiovascular Protection**

**In Post PCI**

METOPROLOL$^1$ & TELMISARTAN$^2$

Reduces risk of

MACE

Recurrent MI

In patients with hypertension & diabetes,

Tazloc®-AM

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The Complete Protection

Amlodipine offers a significant reduction of

57%

in Coronary Revascularisation and Progression of Carotid Artery Atherosclerosis

Reference: J Assoc Physicians India. 2018 Mar;66(3):64-9
Gastroesophageal reflux disease (GERD) is among the most prevalent gastrointestinal (GI) disorders. It is known to often coexist with other chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD), obesity, diabetes mellitus (DM), and hypertension. Upper endoscopy, esophageal manometry, and impedance-pH monitoring are a few invasive diagnostic options that are reserved for selected GERD patients. Symptom assessment by using questionnaires, such as the frequency scale for the symptoms of GERD (FSSG), is simple, convenient, noninvasive, and inexpensive. These questionnaires are widely used to facilitate diagnosis and appropriate treatment. Early diagnosis of GERD and timely management may improve clinical outcomes in patients. Proton pump inhibitors (PPIs) are the preferred therapy for GERD. However, evidence indicates that excessive and extended use of PPIs is linked to adverse events. An overview of the diagnosis and management of GERD, as well as an evidence-based overview of the relationship between GERD and asthma, COPD, obesity, DM, and hypertension, is presented in this review. Expert opinions and recommendations for diagnosing GERD using invasive tests and validated questionnaires have also been mentioned.

Background

Gastroesophageal reflux disease (GERD) is among the most prevalent GI disorders. According to a systematic review, the prevalence of GERD ranges between 18.1 and 27.8% in North America, 8.8 and 25.9% in Europe, 2.5 and 7.8% in East Asia, 8.7 and 33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America. The prevalence of the disease ranges from 7.6 to 30% in India, according to an Indian consensus on GERD in adults. In the Southern part of India, a GERD prevalence of 22.2% was reported in 2016, which was comparable with the data of Western countries. According to the recent American College of Gastroenterology (ACG) clinical guideline, GERD is described as a chronic condition where the esophagus is repeatedly invaded by the contents of the stomach, resulting in symptoms, complications, or both. Acid reflux is the result of improper closure of the lower esophageal sphincter after the ingestion of food. The acid then returns through the esophagus into the pharynx and oral cavity. The phenotypic presentation of GERD is divided into three categories based on the results of endoscopy and histopathology. Nonerosive reflux disease (NERD) is the most common phenotype, affecting around two-thirds (60–70%) of patients. This is followed by erosive esophagitis (30%) and Barrett’s esophagus (6–12%).

This review article aims to describe the connection between GERD and comorbidities such as asthma, COPD, obesity, DM, and hypertension and assesses the usage of a simple symptom-based questionnaire such as the FSSG score for the early diagnosis of GERD. In addition, the review aims to provide expert comments and recommendations on the evaluation and management of GERD in the Indian population.

Association of GERD with Comorbidities

The most frequently reported GERD comorbid conditions include asthma, COPD, hypertension, DM, and obesity (Table 1).

The Link between GERD and Respiratory Diseases

There are wide variations reported in the incidence of GERD in respiratory diseases, and it varies between 10 and 90% for the majority of respiratory disorders. GERD can be a direct cause of various respiratory diseases and may impact disease regulation or worsen them. Even though substantial gastroesophageal reflux can occur in people with respiratory conditions, it does not always manifest with typical reflux indications such as heartburn and/or regurgitation. In certain respiratory diseases, damage to the lung tissue causes changes in lung mechanics, which manifest as alterations in lung volumes and compliance. These alterations impact abdominal and chest pressures during breathing, inducing esophageal reflux and shifting the location of the diaphragm, affecting the esophagogastric junction. Overall, respiratory variables that might affect gastroesophageal reflux include alterations in lung volume, lower lung compliance, dyspnea, and coughing. The respiratory diseases associated with GERD include asthma, COPD, chronic cough, cystic fibrosis, vocal cord dysfunction, interstitial lung disease (ILD), bronchiolitis obliterans syndrome, and aspiration pneumonitis.

How to cite this article: Dumra H, Sainani R, Pratap N, et al. Expert Recommendations on Optimizing the Diagnosis and Management of Gastroesophageal Reflux Disease Associated with Comorbidities in the Indian Population. J Assoc Physicians India 2023;71(8):73–78.
Gastroesophageal Reflux Disease and Asthma

In individuals with asthma, the prevalence of GERD ranges from 30 to 90%.1,11 Furthermore, the reported mean prevalence of abnormal esophageal pH was 50.9% in patients with asthma.12 Studies on this subject, on the other hand, support the idea of reflux-induced asthma and suggest that GERD and asthma may aggravate each other.13 Gastroesophageal reflux exacerbates respiratory conditions by triggering the sensitized neuronal esophageal-bronchial circuit (in cases of chronic cough or asthma) or through aspiration into the airways.6 Coughing and exerted breathing may further aggravate GERD by increasing the pressure difference over the lower esophageal sphincter.11,12 Acid reflux may cause asthma through two different mechanisms—sputum from the pulmonary network after direct exposure to acid refluxate (reflux theory) or a stimulus to the vagal nerve terminals in the esophagus leading to bronchial constriction (reflex theory).12

In terms of symptoms, heartburn, regurgitation, and swallowing difficulties were experienced by 77, 55, and 24% of patients with asthma, respectively.14 However, literature has revealed that a significant proportion of asthma cases were associated with GERD without the classic heartburn or regurgitation symptoms.15,16 A study reported that 43% of asthmatic patients had esophagitis, Barrett’s esophagus, or both.17

Gastroesophageal Reflux Disease and COPD

According to questionnaire-based assessments of symptoms, the mean prevalence of GERD in COPD patients was 24.4% (range 9–29%).11 According to esophageal pH tests, GERD was present in 19–78% of COPD patients (at an average of 42.8%).11 Additionally, a significant correlation has been reported between COPD exacerbation and GERD in the meta-analysis of 10 observational studies involving 13,245 patients.18

In patients with severe COPD, asymptomatic GERD is common. Objective verification of the diagnosis of GERD is crucial as silent reflux frequently affects individuals with COPD (16–74%).18 GERD is also linked to poor health status in COPD patients.19 Aspiration into the airways (microaspiration) and impairments in laryngopharyngeal mechno-sensitivity and swallowing have been reported in COPD patients.8 The relationship between GERD and pulmonary disorders may be attributed to microaspiration of gastric contents or bronchosplasm following vagal nerve stimulation as a result of esophageal inflammation.20

The Link between GERD and Obesity

According to a meta-analysis, body mass index (BMI) has a direct correlation with GERD symptoms; moreover, an increase in obesity significantly enhances the risk of it.21 Obesity in adults has been linked with GERD prevalence in studies conducted in South India and Central India.22,23 In a study conducted in Brazil, GERD was prevalent in 42.7% of obese patients who met the eligibility criteria for bariatric surgery.24

The pathophysiology of GERD is different among obese and lean individuals.25 Compared to lean individuals, obese individuals are more vulnerable to esophageal acid. Furthermore, hiatal hernia, which increases the likelihood of GERD through multiple pathways, is more common in obese individuals. Additionally, they have higher intraabdominal pressure, which results in the displacement of the lower esophageal sphincter and an increase in the gastroesophageal gradient. Furthermore, obesity-related vagal anomalies may result in increased production of bile in the liver and enzymes from the pancreas, making the refluxate hazardous to the esophageal mucosa.25

The Link between GERD and DM

A review by Punjabi et al. determined type 2 DM (T2DM) as a prognostic factor for symptomatic GERD. Reflux symptoms were shown to occur more frequently in patients with three primary diabetic complications, namely nephropathy, retinopathy, and neuropathy. Furthermore, the usage of oral hypoglycemic drugs, BMI, duration of diabetes, and level of diabetes control impacted the occurrence of GERD.26 Studies from Saudi Arabia and China found that patients with T2DM had GERD prevalence rates of 45 and 16%, respectively.27,28 Patients with T2DM and neuropathy exhibited a 25% greater incidence of GERD symptoms than those without the condition.29

Atypical GERD symptoms of dysphagia, globus sensation, and extraesophageal manifestations are frequently experienced by patients with T2DM.30 Numerous pathophysiological conditions, including obesity, metabolic syndrome, peripheral neuropathy, and inadequate glycemic management, aggravate symptoms of GERD in patients with T2DM.28

Obesity and diabetes can cause hormonal changes, particularly in the levels of motilin and ghrelin, which impede stomach motility and cause GERD. Diabetes and hyperglycemia can cause neuropathy, which can affect GI motility, in addition to gastroparesis and/or esophageal dysmotility, which can lead to GERD.28

The Link between GERD and Hypertension

The occurrence of silent GERD and GERD in hypertensive patients was found to be 15.1 and 31.4%, respectively.31 According to Li et al., individuals with essential hypertension were associated with a GERD prevalence of 44.2%.32 The common factors that influenced silent GERD and hypertension included age, BMI, male gender, alcohol intake, smoking, and educational status.31

Diagnosis of GERD

Classical signs of heartburn and regurgitation are often not reliable diagnostic indicators of GERD. The diagnosis of GERD is established based on symptoms along with additional evaluations, including endoscopy of the mucosa of the esophagus, monitoring of gastric reflux, and therapeutic compliance to empirical PPIs.33 Upper endoscopy is reserved for evaluating GERD patients and cases involving dysphagia, vomiting, bleeding, odynophagia, weight loss, and/or anemia (alarm features).34 A total of 24 hours of esophageal pH and impedance monitoring is a sensitive approach for evaluating GERD. Esophageal manometry can be safely performed, but it is limited to the screening of dysphagia in cases with GERD.35 Noninvasive methods for the diagnosis of GERD include a questionnaire-based screening of GERD symptoms, which is a simple and inexpensive method that may aid in early and accurate diagnosis.36 Diagnosis of GERD in the presence of extraesophageal symptoms/conditions such as hoarseness, chronic cough, asthma, globus, or laryngitis can be challenging (Table 1). In individuals with extraesophageal manifestations, empirical PPI treatment is often recommended as a screening tool and therapeutic option.37

In 2022, an algorithm published by the ACG to diagnose GERD suggested that patients presenting with heartburn and regurgitation with no alarm symptoms should be treated with PPI once daily for 8 weeks. Patients with complete symptomatic relief are to be diagnosed with GERD, while upper GI endoscopy or reflux monitoring should be recommended for patients with incomplete symptomatic relief or recurrence of symptoms after completion of PPI therapy.37

Expert opinions and recommendations are presented in Table 2.
**Questionnaire-based Screening of GERD**

Questionnaires are considered to play an important part in the quick and accurate diagnosis of GERD. They also help in choosing patients for empirical treatment, eliminating the requirement for expensive investigations. Many questionnaires have been developed and used to assess GI symptoms. A few commonly used questionnaires include quality of life and utility evaluation survey technology, medical outcomes study 36-item short form, GERD questionnaire, and Carlson–Dent questionnaire (CDQ).

**Frequency Scale for the Symptoms of GERD Questionnaire**

The FSSG questionnaire was created to assess the compliance of GERD symptoms to medical treatment. The questionnaire consists of 12 items, each of which is scored to evaluate symptom frequency. This questionnaire has a few advantages over other available questionnaires. It is a self-administered questionnaire that is easy for the patient to use. It may also allow for the objective evaluation of the treatment effect of various PPIs, including on-demand therapy. Additionally, it is useful in the assessment of supraesophageal symptoms of GERD as a part of respiratory and otorhinolaryngology evaluations.

Several studies have assessed the utility of the FSSG questionnaire in clinical settings. In a study conducted in India with 60 patients who had confirmed diagnoses of bronchial asthma, the FSSG questionnaire revealed that regurgitation-related symptoms were more common (89%) than other symptoms. In another study, the FSSG score was utilized to evaluate GERD in individuals who had antiinflammatory drug therapy for persistent moderate-to-severe asthma. The intensity of the cough and reflux symptoms were significantly correlated. The FSSG was utilized to assess symptoms of GERD in Japanese individuals with T2DM. In a study by Hirata et al., metabolic syndrome and low serum adiponectin were correlated with FSSG scores of ≥8 and higher grades of GERD symptoms in patients with T2DM. Another study showed that the postprandial plasma glucose levels and self-rating depression scale (SDS) scores of T2DM patients were correlated with their FSSG scores. Notably, in cases with type 1 DM, the FSSG questionnaire detected a higher frequency of GERD than the CDQ.

**Management of GERD**

A multimodal approach to GERD management is followed by clinicians, considering the presenting symptoms, upper endoscopy results, and related complications. Medical management comprises lifestyle changes and pharmacologic treatment. The ACG clinical guideline has listed PPIs as the most efficacious medical intervention for GERD. As per the guideline, PPI, along with lifestyle modifications, should be the first line of approach if patients have typical symptoms like heartburn and regurgitation of GERD and no alarm symptoms. If patients have atypical, high-risk alarm symptoms, upper GI endoscopy is advised. If symptoms are resolved within 8 weeks of PPI treatment, it is advised to stop therapy or continue the lowest effective dose as maintenance therapy. If symptoms are not resolved with once-daily PPI, then PPI is prescribed twice a day (BID) instead of once daily (OD). If needed, histamine 2 receptor antagonist (H2RA) is added in the nighttime. If symptoms persist, patients are diagnosed with refractory GERD, which must be managed as per the refractory GERD treatment strategy.

For managing extraesophageal GERD in cases with extraesophageal manifestations without typical symptoms of GERD, reflux testing is advised. For patients with extraesophageal and typical GERD symptoms, PPIs are recommended for 8–12 weeks twice daily on a trial basis. If extraesophageal symptoms improve with PPI therapy, patients are treated for GERD. For patients who are unresponsive to PPI therapy for extraesophageal symptoms, reflux monitoring is recommended after discontinuing PPIs for 2–4 weeks. These patients are further treated for GERD if reflux monitoring is suggestive of reflux disease.

Proton pump inhibitors (PPIs) are the most often recommended therapy for both erosive esophagitis and NERD; however, a systematic review showed that the response rates to PPIs were significantly lower in cases with NERD than erosive esophagitis (37 vs 56%; p < 0.0001). In NERD patients, the overall rate of symptomatic improvement with PPIs was reported to be 51.4%. Findings of another study indicated that PPIs reduce symptoms in approximately 57–80% of erosive esophagitis patients and approximately 50% of NERD patients. Furthermore, the resolution of erosive esophagitis (all grades) was noted in >85% of GERD cases managed with conventional PPI doses. Regarding the comparative efficacy of different PPIs, a meta-analysis reported that the newer PPIs (rabeprazole, lansoprazole, and pantoprazole) were comparable to omeprazole in terms of heartburn control, healing erosive esophagitis, and relapse rates. All PPIs had higher efficacy than ranitidine and placebo in terms of healing and lowering relapse rates of erosive esophagitis.

**Table 1: Expert opinions on prevalence, symptoms, and common comorbidities in GERD patients**

<table>
<thead>
<tr>
<th>Symptoms/Comorbidities</th>
<th>Prevalence (% of GERD patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn and regurgitation</td>
<td>Typically 50%</td>
</tr>
<tr>
<td>Chest pain or discomfort</td>
<td>Frequently encountered</td>
</tr>
<tr>
<td>Belching, nausea, bloating</td>
<td>Very common</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>Common</td>
</tr>
<tr>
<td>Persistent throat irritation</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>Occasionally seen</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Rare</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

**Classical symptoms of GERD**

Prevalence of GERD symptoms in patients with respiratory diseases.

<table>
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<tbody>
<tr>
<td>&gt;50% of adults with diabetes over the age of 30 years</td>
</tr>
<tr>
<td>Intolerance to metformin in 20–30% of patients with diabetes results in severe GERD.</td>
</tr>
</tbody>
</table>

**Comorbidities**

- Respiratory conditions such as asthma, COPD, ILD, chronic cough, upper airway allergy.
- Type 1 and T2DM.
- Obesity.
- Hypertension.
- Others: Sleep apnea, ischemic heart diseases.

**Management**

- Medication-related GERD
- Antidiabetic drugs: Metformin, acarbose, voglibose.
- Antiplatelet drugs: Aspirin, clopidogrel.
- Antihypertensive drugs.
- Heartburn and regurgitation.
- Chest pain or discomfort.
- Belching, nausea, bloating.
- Epigastric pain.
- Persistent throat irritation.
- Chronic cough.
- Hoarseness.
- Laryngitis.
Table 2: Expert comments and recommendations on the diagnosis of GERD

<table>
<thead>
<tr>
<th>Expert comments</th>
<th>Expert recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of GERD is based on the patient’s medical history and symptoms.</td>
<td>For patients with typical symptoms of heartburn and regurgitation and/or belching without alarm symptoms, lifestyle changes are recommended along with a 4–6–week trial of empiric PPIs taken once daily before a meal.</td>
</tr>
<tr>
<td>There is a subset of patients who have nonacid reflux, whereas most patients have both acid and nonacid reflux symptoms.</td>
<td>If symptoms persist in a patient after PPI therapy, he/she should be referred to a gastroenterologist for upper GI endoscopy.</td>
</tr>
<tr>
<td>Noninvasive methods such as questionnaires can be used for the diagnosis of GERD.</td>
<td>If endoscopic findings are normal, the patient is diagnosed with NERD.</td>
</tr>
<tr>
<td>No additional tests are necessary for individuals with typical symptoms of heartburn and regurgitation and/or belching but without any alarm symptoms (dysphagia, GI bleeding, weight loss) and the condition is diagnosed as uninvestigated GERD.</td>
<td>If endoscopic findings are abnormal, the diagnosis of GERD in the patient is confirmed.</td>
</tr>
<tr>
<td>Patients are sometimes prescribed empirical PPIs to diagnose GERD.</td>
<td>If patients with alarm symptoms (dysphagia, GI bleeding, weight loss), upper GI endoscopy is recommended.</td>
</tr>
<tr>
<td>The most common invasive diagnostic methods for GERD are upper GI endoscopy and reflux monitoring (pH or impedance-pH).</td>
<td>For patients with alarm symptoms (dysphagia, GI bleeding, weight loss), upper GI endoscopy is recommended.</td>
</tr>
</tbody>
</table>

Table 3: Expert comments and recommendations on diagnosing GERD using the FSSG questionnaire

<table>
<thead>
<tr>
<th>Expert comments</th>
<th>Expert recommendations</th>
</tr>
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<tbody>
<tr>
<td>Panel members stated that questionnaires are used by gastroenterologists to assess the extent of GERD in clinical trials and communities and not to diagnose the condition. Experts unanimously agreed that the FSSG score can be used in everyday clinical practice. The questionnaire, according to experts, is simple, short, less time-consuming, and structured. Experts opined that this questionnaire would be effective in:</td>
<td>The primary objective of the FSSG questionnaire is to assist the physician in diagnosing GERD, following up with the patient, and planning treatment.</td>
</tr>
<tr>
<td>• Capturing some of the atypical symptoms of GERD.</td>
<td>The FSSG questionnaire will aid general physicians, pulmonologists, and ENT specialists in diagnosing GERD and prescribing PPI therapy to patients, particularly when gastroenterologists are unavailable or patients are reluctant to undergo any procedure.</td>
</tr>
<tr>
<td>• Resolving the issue of under and over-diagnosis to some extent, along with clinical assessment.</td>
<td>The FSSG questionnaire will be especially useful for clinicians other than gastroenterologists in diagnosing GERD in patients where it coexists with other chronic diseases and referring only undiagnosed cases to gastroenterologists.</td>
</tr>
<tr>
<td>• Helping the physicians to focus on both the primary presentation, such as diabetes, hypertension, asthma and GERD symptoms based on the score.</td>
<td>This questionnaire should be validated and correlated with endoscopic findings in the Indian population before being recommended for diagnosing GERD.</td>
</tr>
<tr>
<td>• Aiding both qualitative and quantitative analysis of the condition.</td>
<td>Despite its many benefits, this questionnaire’s limited specificity and sensitivity are one of its shortcomings.</td>
</tr>
<tr>
<td>• Save time and direct the patients to the appropriate treatment.</td>
<td>ENT, ear, nose, and throat; FSSG, frequency scale for the symptoms of GERD; GERD, gastroesophageal reflux disease; H2RA, histamine type 2 receptor antagonist; ILD, interstitial lung disease; NERD, nonerosive reflux disease; PPI, proton pump inhibitor</td>
</tr>
<tr>
<td>• Assisting in the scaling-up and scaling-down of treatment with good prognostic value.</td>
<td>Aiding both qualitative and quantitative analysis of the condition.</td>
</tr>
<tr>
<td>• According to experts, this questionnaire will be useful in determining the treatment response after 8 weeks of PPI therapy.</td>
<td>Aiding both qualitative and quantitative analysis of the condition.</td>
</tr>
</tbody>
</table>

Although all PPIs have a similar clinical spectrum, changing to a different PPI is a common approach followed in patients with chronic symptoms despite receiving once-daily PPI therapy. Switching to a different PPI is also considered for minor adverse effects like headache, abdominal pain, nausea, vomiting, constipation, diarrhea, and flatulence. For instance, switching patients with persistent heartburn on lansoprazole (30 mg once a day) to esomeprazole (40 mg once a day) was just as effective in controlling heartburn symptoms as increasing the dosage of lansoprazole (30 mg) to twice daily. Furthermore, a 40 mg dose of pantoprazole was as effective as esomeprazole 40 mg for treating GERD symptoms. Patients on pantoprazole experienced quicker relief from GERD-related symptoms, significantly fewer symptoms, and a much lower risk of relapse. Evidence suggests that PPIs are among the most beneficial treatment modalities for GERD when compared to H2RAs and other pharmacological treatments. In particular, PPIs substantially enhance the symptom response rate in NERD patients when compared to H2RAs. A meta-analysis reported that PPI medication was considerably more effective in healing erosive esophagitis than H2RA or H2RA plus prokinetics. Several publications report a wide range of side effects with the long-term use of PPIs, including pneumonia, intestinal infections, osteoporosis-related bone fractures, and stomach cancer. Conversely, evidence-based studies have reported that PPIs are not associated with any of these side effects except for intestinal infections. The usage of PPIs for acute prophylaxis, along with corticosteroids without concomitant nonsteroidal anti-inflammatory drug use, and for stress ulcer prophylaxis in noncritically ill patients is considered inappropriate. Long-term PPI usage may be appropriate in Zollinger–Ellison syndrome,
Table 4: Expert comments and recommendations on the management of GERD

| Expert comments | \- A PPI is typically administered as an OD dose for patients, although a BID dose may improve response rates. \
| | \- In many individuals, gastroenterologists prescribe prokinetic agents such as domperidone, itopride, or cinitapride together with a PPI for a short period for associated functional dyspepsia. \
| | \- All PPIs are considered to have similar clinical efficacy. However, pantoprazole is the most prescribed PPI in clinical practice, with the least drug interactions. \
| | \- Previous reports suggested that the most frequent adverse effects associated with PPIs are infections, such as Clostridium difficile infections. Short-term use of PPIs is generally safe. \
| | \- Long-term use of PPIs has been linked to interstitial nephritis and renal toxicity in published literature. In clinical practice, experts opined that they infrequently encountered adverse events. However, meta-analyses findings on the major side effects of PPIs are conflicting. \
| | \- According to estimates, about 5–10% of highly symptomatic patients are over-treated. Patients presenting with throat problems in the ENT setting are over-treated with concomitant antiallergic and antireflux medications to treat allergies and refluxes. \

| Expert recommendations | PPI is the first line of therapy along with lifestyle modifications in cases presenting with typical GERD symptoms of heartburn and regurgitation and/or belching. \
| | For patients presenting with alarm symptoms (dysphagia, GI bleeding, and weight loss), upper GI endoscopy is advised. For patients whose typical GERD symptoms do not get fully resolved: \
| | \- PPI should be prescribed BID rather than OD. \
| | \- If necessary, an H2RA can be added at night. \
| | \- PPI therapy should be stopped or reduced to the lowest effective dose as maintenance therapy in patients whose symptoms have been resolved after initial therapy. \
| | If symptoms persist with twice daily PPI, patients should be diagnosed with refractory GERD, which must be managed according to the refractory GERD treatment strategy. \
| | For patients diagnosed with NERD with reflux hypersensitivity, recommended treatment includes serotonin reuptake inhibitor, cognitive behavioral therapy, and lifestyle changes. \
| | An H2RA is used alone for tapering therapy and recommended over a PPI for on-demand therapy. \
| | A PPI dose of either OD or BID is recommended in patients with daytime symptoms. However, in patients with nighttime reflux symptoms, a BID dose is preferred. In patients presenting with GERD symptoms associated with respiratory diseases (asthma, COPD, and ILD), treatment should be initiated with a double dose of PPI for 8 weeks, and the dose should be gradually reduced if the patient’s response is favorable. In case of no response, the patient should be referred to a gastroenterologist for further evaluation. For patients who have been on PPIs for more than 8 weeks, the dose is halved for 4 weeks, followed by on-demand therapy. \
| | PPIs are recommended for a duration of 4–6 weeks in patients with mild esophagitis (grades A and B). In patients with grade C esophagitis, PPIs are recommended for 8–10 weeks for symptom prophylaxis, followed by maintenance therapy. In patients with Barrett’s esophagus, lifelong PPI treatment is recommended. In individuals who require long-term therapy, PPIs should be prescribed for symptom prophylaxis for 8–10 weeks before switching to a low dose for the long term. Patients are advised to continue PPI therapy for a minimum of 6–8 weeks to prevent the return of symptoms upon therapy discontinuation. \
| | Amongst the various PPIs available, dexlansoprazole is recommended for patients with nocturnal symptoms due to its 24-hour acid-control action. In the LA 3 and 4 subgroups, esomeprazole is favored over other PPIs, despite its high cost. Omeprazole is not recommended for cardiac patients as it interacts with cardiac medications. \
| | Regarding switching from one PPI to another: \
| | \- If a patient’s symptoms are not controlled by pantoprazole OD and BID, it is recommended to switch to rabeprazole or esomeprazole. \
| | \- Switching to lansoprazole should be considered if a patient has nocturnal symptoms. \
| | \- Given the safety concerns associated with long-term use, PPIs should be prescribed judiciously for a certain duration based on the indication, when needed, and de-prescribed once symptoms have resolved. \

Barrett’s esophagus, idiopathic peptic ulcer disease, or PPI-responsive eosinophilia. Short-term usage (4–12 weeks) for Helicobacter pylori eradication, stress ulcer prophylaxis, before and after endoscopy for acute upper GI bleeding, or treating peptic ulcer disease is also considered appropriate.54

Expert opinions and recommendations are presented in Table 4.

Conclusion
Gastroesophageal reflux disease (GERD) is a highly prevalent condition that is frequently linked with chronic diseases such as asthma, COPD, obesity, DM, and hypertension. It is important to carefully diagnose patients that present with GERD symptoms, especially in nongastroenterology settings. The FSSG questionnaire is simple and useful for early and appropriate diagnosis of GERD, especially in nongastroenterology settings. Empirical PPI therapy can be given to patients who present with no alarm symptoms. Patients presenting with alarming diagnostic clues of the disease need further evaluation to determine the management approach. PPIs are the most efficient treatment modalities for managing the symptoms of various phenotypic manifestations of GERD when compared to all other pharmacological treatments. Although short-term prescription of PPIs is usually safe, there are concerns related to long-term PPI usage. However, meta-analyses findings on the major side effects of PPIs are conflicting and do not prove a causal link between PPIs and adverse effects. PPIs can be prescribed as per need but should be eventually stopped after the symptoms have been resolved.
Expert Recommendations

Author Contribution Details
All authors have contributed to the conception, design, development of the draft, review and finalization of the manuscript.

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A Historical Perspective on Chronic Obstructive Pulmonary Disease: From Past to Present

Surya Kant1,*, Ajay Kumar Verma2, Anuj Kumar Pandey3

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ABSTRACT
René-Théophile-Hyacinthe Laennec in his book “Treatise of the Diseases of the Chest” discussed the emphysema in 1821. Chronic obstructive pulmonary disease (COPD) has been around for at least 202 years, from 1821 to 2023 (but the disease itself is much older than that). It is believed that William Briscoe first used the term COPD in June 1965, at the 9th Aspen Emphysema Conference. COPD was first defined by the CIBA guest symposium in 1959 and the American Thoracic Society Committee on Diagnostic Standards in 1962; recent definition of COPD was released by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2023. In 1990, it was sixth leading cause of death and in 2020 COPD becomes third leading cause of death. GOLD update 2023 also proposed taxonomy (etiotypes), classification of COPD based on risk factors, and ABE assessment tool for COPD. Now concept of early-COPD, pre-COPD, and, mild-COPD are also emerging, which are helpful in better understanding of COPD. Here, we have discussed historical landmarks, definition, burden, taxonomy, classification, different concept of disease, ABE assessment tool, personalized medicine, and brief description of GOLD and World COPD Day from past to present.

INTRODUCTION
Earlier in 1821, RTH Laennac, a physician, pathologist, and the inventor of the stethoscope wrote a magnificent description of the emphysema component of disease in “Treatise of the Diseases of the Chest.” He meticulously dissected patients he had previously studied and found that the lungs of people with emphysema were hyperinflated and did not empty well. From 1821 to 2023, it is 202 years of history of chronic obstructive pulmonary disease (COPD)—the albeit disease is older than that. After this, John Hutchinson invented the spirometer (which measures vital lung capacity) in 1846. These two instruments (stethoscope and spirometer) played a major role in the understanding of COPD. Spirometry is still indispensable in COPD diagnosis. Chronic obstructive bronchopulmonary disease, diffuse obstructive pulmonary syndrome, chronic obstructive lung disease, nonspecific chronic pulmonary disease, and chronic airflow obstruction were additional acronyms that were used before the term “COPD” was coined. The term “COPD” is thought to have been coined by William Briscoe at the 9th Aspen Emphysema Conference in June 1965. As a result of this term’s widespread use, we now refer to this emerging health issue as COPD.

The two main traditional clinical diagnoses of COPD are chronic bronchitis (chronic cough with phlegm) and emphysema (small air sacs at the end of the lungs’ airways are destroyed). Due to the overlapping clinical, radiological, and pathological features of the two aforementioned conditions, COPD has come to be widely used to refer to both of them. The various clinical and pathological phenotypes, such as exacerbator, nonexacerbator, frequent exacerbator, emphysema-hyperinflation, asthma-COPD overlap, etc., that have been identified in the general population are advantageous to recognize given recent advancements in our understanding of COPD.

EARLY HISTORY OF COPD
The etiology of COPD is probably not recent. The condition that is currently known as COPD may have been referred to by other names in the past. Theophile Bonet first used the term “voluminous lung” in 1679. After this, Giovanni Morgagni reported 19 cases of “turgid lungs” in 1769. In 1789, Baillie ascribed emphysematous lung. Further, in 1814 Charles Batham identified “chronic bronchitis.” Detailed landmarks of COPD are presented in Figure 1.

DEFINITION OF COPD
The first to define COPD was the CIBA guest symposium in 1959 and the American Thoracic Society (ATS) Committee on Diagnostic Standards (1962). Further, the ATS defined emphysema as “enlarged alveolar spaces and loss of alveolar walls, and chronic bronchitis as a chronic cough lasting at least 3 months for at least 2 years.” Recently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2023 characterizes COPD as “a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, and exacerbations) due to abnormalities of the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive airflow obstruction.”

Burdens of COPD
2023 characterizes COPD as “a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, and exacerbations) due to abnormalities of the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive airflow obstruction.”

Burden of COPD
In 1990, COPD was the sixth dominant cause of death, and in 2002, it became the fourth major contributor to death across the globe. After 30 years (1990–2020), COPD became the top third disease killer worldwide. COPD causes 3.23 million deaths in the year 2019, as per World Health Organization (WHO). In low- and middle-income nations, COPD deaths in people under 70 years of age account for nearly 90% of all deaths. India leads the world in COPD prevalence, ranks second only to China in COPD deaths, and is rapidly catching up. COPD affects approximately 10% of people aged 40 and up, though the prevalence varies by country and increases with age. The global prevalence of COPD is 10.3%. Overall, burden of COPD is increasing across the globe (Fig. 2).

GENDER EQUITY
Chronic obstructive pulmonary disease (COPD) was previously thought to be a male-dominated respiratory disease. However, since 2008, the number of women with COPD has been the same as the number of men with COPD; this is primarily due to the fact that more women worldwide smoke and use biomass fuels.

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History of COPD

The concept of pre-COPD and early-COPD

An entirely new notion, pre-COPD, analogous to prediabetes and prehypertension, may be heralded by the discovery of a marker for the development of COPD. Key areas in clinical research on COPD include the characterization of individuals who are at risk, screening, early diagnosis, and management of the risk. Patients with no airway obstruction (forced expiratory volume (FEV1)/forced vital capacity ≥ 0.7) but a high risk of developing COPD are considered to be in the pre-COPD. Despite not meeting the criteria for COPD, these people may be experiencing early...
met in Brussels, Belgium, in January 1997 to discuss a global COPD plan (which was later considered GOLD). Romain Pauwels (University Hospital of Ghent, Belgium), Claude Lenfant and Suzanne Hurd [National Institutes of Health (NIH)] and Nikolai Khaltava (WHO) were chaired and concurred that a system is needed, and they suggested putting together a group of experts in many different areas of COPD to write a report on how to diagnose, treat, and prevent COPD based on evidence. As a result, GOLD was established in 1997 by the composite effort of the National Heart, Lung, and Blood Institute, NIH, and WHO. The first “GOLD Executive Summary” came out in 2001, and after this, GOLD has been updating the report every year and putting out a major report (revision) every 5 years. So, in 2006, 2011, 2017, and 2022, important reports were released. On the GOLD website, 2017, 2018, 2019, 2020, 2021, 2022, and 2023 guidelines are available.

**World COPD Day**

Since 2002, WCD has been held on the ‘third Wednesday in November’ and is coordinated by GOLD and the WHO. The 21st WCD, with the theme “Your Lungs for Life,” will take place on 16th November 2022. The day is one of the most significant global occasions for COPD awareness and education, with organizers hosting events in >50 nations annually. It is planned in conjunction with medical experts and COPD patient organizations from around the world. Its purpose is to spread knowledge, increase awareness, and discuss solutions to the global COPD problem. GOLD selects a subject for WCD each year and organizes the creation and distribution of information and resources. Healthcare workers, educators, and members of the public who wish to make a difference locally and globally arrange WCD activities in each nation.

**Conclusion**

Empysema and chronic bronchitis research spans centuries. Due to the lack of elastic rebound and increased airflow resistance via the complex conducting system of the lungs, evidence suggests that an attack on the alveoli and both large and small airways might produce chronic and irreversible airflow limitation. For treatment, it is necessary to stop smoking and other risk factors. These methods prevent blood gas homeostasis and premature ventilatory dysfunction. In addition to quitting smoking, symptomatic sickness necessitates the use of bronchodilators and sometimes corticosteroids. Oxygen and pulmonary rehabilitation are beneficial to patients. Lung volume reduction surgery enhances elastic recoil in a subset of patients, improving airflow and perfusion, and reducing dyspnea and gas exchange issues. For some people, lung transplantation is beneficial. In the future, early disease identification and treatment are required. Personalized treatment may be used in COPD due to its complexity and heterogeneity. The main diagnostic tool must be spirometry. Alveolar injury and airway inflammation must be minimized by newer therapies in future. GOLD is doing great job in overall management of COPD in the world. We conclude that the future of COPD research, prevention, and therapy looks bright.

**Acknowledgment**

The Indian Council of Medical Research, Delhi, India, is gratefully acknowledged for providing Senior Research Fellowship to AKP (No. 3/1/2/11/Env-2018-NCD-I, dated 19th December 2018).

**References**


**Combined COPD Assessment: ABE Assessment Tool**

Chronic obstructive pulmonary disease (COPD), a complex and heterogeneous disease, cannot be accurately captured by a single parameter FEV1.12,13 Also, there is a statistically significant connection between the severity of airflow restriction and health status at the population level. However, there is a vast individual variation at the genetic, biological, clinical, as well as environmental levels, which means that a single patient’s FEV1 value cannot be used to predict their overall health. So, the ABCD and now ABE assessment tool is used to figure out how COPD affects each patient by adding the assessment of symptoms with spirometry indices and/or risk of exacerbations.

**Personalized Medicine in COPD**

Precision medicine is a relatively new approach that uses factors such as genetic, biomarker, phenotypic, and psychological features to differentiate between people who otherwise have the same diagnosis. The medical fraternity uses the phrases “personalized,” “precision,” and “individualized” medicine interchangeably.12,13 When together, these pieces of data could help doctors predict disease progression and patient reactions, leading to more accurate treatment predictions and less time spent on ineffective medications.

**Twenty–Seven Years (1997–2023) of the GOLD**

Chronic obstructive pulmonary disease (COPD) specialists from around the world...
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Alternate Biochemical Markers in Organophosphate Poisoning

Austin J Mangaly1*, Chandni Radhakrishnan2

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Abstract
In India, organophosphates are the most widely used pesticides for suicide by poisoning. Early recognition of the diagnosis and its severity will help in achieving a better outcome. In poisoning by organophosphorus compounds, serum acetylcholinesterase (AChE) and pseudocholinesterase are currently widely accepted as biochemical markers for estimating the severity. A wide array of alternate, cheap, and easily available markers are explored in this review and using a combination of these markers may be better in terms of early identification of severe poisoning. In peripheral centers without access to costly investigations, these cheap markers may help in guiding an early referral to higher centers for severely poisoned patients. A comprehensive study comparing all these different markers has not been done so far, thereby emphasizing the need for the same. This review identified various new, cheaper, and easily available biochemical markers as having the potential to act as surrogates for assessing the severity of organophosphate poisoning, and there is a scope for future studies to understand its utility.

Introduction
Poisoning by organophosphates (OP) is recognized as a serious medical problem globally, especially in India, where the majority of the population relies on agriculture for their livelihood.

Global Situation
As per the latest statistics published by the WHO in 2019, around 8 lakh deaths occur each year from suicide, amounting to 1 death every 40 seconds, and it is estimated that deliberate self-harm using pesticides amount to 20% of the total deaths. Suicide is a global phenomenon. A total of 77% of the suicides happened in “low and middle-income countries” in the year 2019.

In India
A total of 318 pesticides have been registered in India as of October 2019. According to the WHO toxicity criteria, 18 belong to class 1a or class 1b (extremely or highly hazardous, respectively) pesticides. In a nationally representative mortality survey published in 2012, about 3% of deaths ≥15 years were by suicide. About half of these suicides were from poisoning, most of which was pesticide. Compared to high-income countries, suicide in India is more due to the consumption of pesticides, related to poverty, and also to psychiatric illness to a lesser extent. All these dangerous pesticides are used in agricultural work and hence easily available for poisoning. A reduction in occupational and suicidal poisoning by pesticides can be achieved by a national ban on these pesticides across India.

As per the latest statistics published in 2019, the highest number of suicides in 2019 occurred in Maharashtra, with Kerala being in the sixth place (Fig. 1). Kerala came in third place after Sikkim and Chhattisgarh with 24.3 per 1 lakh population in 2019 (Fig. 2) when suicide rates were calculated.

When the means of suicide were analyzed, poisoning (26.7%) came in second place only to hanging (51.5%) (Table 1).

The most common poison used for suicide in India from 1999 to 2018 were published in 2021 in a systematic review. It concluded that, after the government regulatory changes in 2001, organophosphates replaced aluminium phosphide as the key lethal poison in India. Medication overdose, hair dye, and plant poisoning caused only a few deaths. Aluminium phosphide contributed to fatality mainly in north India, but deaths due to OP poisoning occurred all over India. In the last 10 years, paraquat poisoning has been recognized as an important health issue. Pesticide poisoning deaths are still very common, emphasizing the need for regulatory interventions to reduce the burden of pesticide poisoning deaths in India.

Overview of Anticholinesterase Poisoning
Pesticides include insecticides, herbicides, and rodenticides. Organophosphates, the focus of this article, belong to the class of insecticides. Other classes of insecticides include carbamates, organochlorines, pyrethrins/pyrethroids, neonicotinoids, and nereistoxin analogs. Organophosphates are irreversible anticholinesterases; that is, they are irreversible inhibitors of the cholinesterase enzyme, whereas carbamates are reversible inhibitors.

The neurotransmitter acetylcholine facilitates communication between a neuron and a target cell (a gland, a muscle cell, or another neuron). When stimulated, acetylcholine is released into the synapse. It binds to receptors on the target cell (a gland, muscle, or neuron). This results in muscle fiber activation if the target cell is a muscle. It can also cause variations in heart rate, glandular secretions or interneuronal communication in the brain or autonomic ganglia. Cholinergic pathways are present ubiquitously in the human body in every organ system. Compounds inhibiting the cholinesterase enzyme can inhibit both sections of the human nervous system (the peripheral nervous system (PNS) and the central nervous system (CNS)), as they both have cholinergic neurons (Fig. 3). The PNS consists of acetylcholine-releasing neurons at the neuromuscular junctions and in the autonomic nervous system (glands, ganglia, smooth muscle, and cardiac muscle). The CNS is the other section, and this section also contains cholinergic neurons. They are present in both the brain and also in the spinal cord in the intermediolateral cell column, which regulates autonomic functions.

The cholinergic receptor distribution in the CNS and the PNS is not the same. For example, the striatum, hippocampus, and cerebral cortex are rich in cholinergic neurons, while other regions like the cerebellum have less of the same. Muscarinic and nicotinic receptors are the two types of cholinergic receptors. Both have many subtypes as well. There are differences in the way they are distributed as well, making their effects even more complex. The synapses of neurons releasing acetylcholine contain an enzyme called acetylcholinesterase (AChE), mainly at...
the neuromuscular and other neuroeffector junctions. It degrades acetylcholine and thereby ends its action in the synapses. Therefore, inhibition of this enzyme can cause acetylcholine to accumulate and hence prolong its action. In the PNS, the accumulation of acetylcholine at nerve endings can produce cholinergic symptoms. This can include abdominal cramps (due to contraction of the smooth muscle around the gut), sweating, muscle spasms and twitching, and even flaccid paralysis at higher concentrations. There may also be effects on behavior and on, memory, and learning in the case of chronic poisoning. Thus, we see that AChE inhibition can cause a lot of adverse effects, and depending on the degree of exposure and half-life of the compound, they may be fatal. These symptoms can be due to action on the CNS or the PNS, as explained already. The compounds vary in their ability to enter the CNS or PNS. This is because these two sections differ in their pharmacokinetic properties. These differences may be due to differences in chemicals, or they may be organism-specific. It can also depend on the pharmacodynamic properties of the drug/poison and the type of enzyme it interacts with. Even though butyrylcholinesterase (BuChE)/pseudocholinesterase is similar to AChE in structure, a different gene is responsible for its production. BuChE is produced mainly in the liver. It is also present in plasma and some other tissues. It is usually differentiated from AChE by the fact that it hydrolyses acetylcholine much slower and also by histochemical techniques. Also, the binding affinity of each anticholinesterase to these two enzymes is different. Both AChE and BuChE are present during the nervous system development, but their relative proportions keep changing with location and time. Even though BuChE was found to have no function in the nervous system, in plasma, it was seen to be catalyzing the breakdown of certain ingested plant esters (like cocaine) as well as synthetic local anesthetics and paralytic agents such as succinylcholine. Similarly, erythrocyte AChE also has no known function. These enzymes are considered surrogate measures of cholinesterase activity. Red blood cells contain AChE but no BuChE, while plasma has both, even though their ratio varies widely among humans and animals. Human plasma contains mainly BuChE, while dogs and rats have both AChE and BuChE in considerable amounts in their plasma. It is still yet to be found out if BuChE helps in the development of the nervous system and, if so, how. Research is being conducted to find out if BuChE has any role in the development of the nervous system or its functioning. It is also yet to be found out whether BuChE, AChE or other esterases have any role in carcinogenesis or cell growth and death.

The muscarinic clinical effects of cholinergic excess secondary to organophosphorus insecticide poisoning can be easily recollected using the mnemonics DUMBELS and SLUDGE.

<table>
<thead>
<tr>
<th>Table 1: Means of suicide adopted</th>
<th>Percentage and number</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. No.</td>
<td>Means adopted</td>
</tr>
<tr>
<td>1</td>
<td>Ingestion of sedative tablets</td>
</tr>
<tr>
<td>2</td>
<td>“Drowning”</td>
</tr>
<tr>
<td>3</td>
<td>Fire/self-immolation</td>
</tr>
<tr>
<td>4</td>
<td>Firearms</td>
</tr>
<tr>
<td>5</td>
<td>By hanging</td>
</tr>
<tr>
<td>6</td>
<td>By poison</td>
</tr>
<tr>
<td>7</td>
<td>Self-imposed injuries</td>
</tr>
<tr>
<td>8</td>
<td>Jumping from heights</td>
</tr>
<tr>
<td>9</td>
<td>Runover by vehicles/trains by jumping into their paths</td>
</tr>
<tr>
<td>10</td>
<td>Electrocuton</td>
</tr>
<tr>
<td>11</td>
<td>Other measures</td>
</tr>
<tr>
<td>12</td>
<td>Total</td>
</tr>
</tbody>
</table>

![Figure 1: Suicide percentages in states and union territories in 2019](image-url)

Bronchorrhea, bradycardia, and bronchospasm are also called the “killer Bs.” The nicotinic effects of cholinesterase inhibitors include muscle fasciculations, cramps, weakness, mydriasis, tachycardia, and hypertension. There are four syndromes related to organophosphate poisoning—acute poisoning comprising of symptoms already described, which can occur in various combinations; chronic toxicity, intermediate syndrome, and organophosphate-induced delayed neuropathy. The intermediate syndrome usually occurs 1–5 days after exposure. It need not occur in every case. It is characterized by paralysis of respiratory muscles, neck flexor muscles, and proximal limb muscles. During this phase, there is usually no other symptom or sign of excess cholinergic activity. Ventilatory support may be needed.
Fig. 2: State/union territory wise suicide rate 2019
Alternate Biochemical Markers in Organophosphate Poisoning

It usually resolves within 7 days. Agricultural laborers who are exposed to these pesticides almost daily are susceptible to chronic toxicity. It presents as a symmetrical sensorimotor axonopathy. It usually starts with leg cramps and progresses to weakness and then paralysis, similar to Guillain-Barre syndrome. Extrapyramidal symptoms, memory loss, mood swings, cognitive impairment, peripheral neuropathy, and autonomic dysfunction are features of organophosphate-induced delayed neuropathy.

**Glycemic Status at Presentation in Organophosphorus Poisoning**

In two previous studies from India, it was found that the blood glucose levels at presentation in acute OP poisoning are a reliable and cost-effective marker to estimate severity and outcome. Plausible reasons for glycemic variability were stated as: (1) pancreatic insufficiency; (2) hyperproduction of proinflammatory cytokines; (3) stress hormones like cortisol; (4) altered hepatic metabolism due to toxins; and (5) prior nutritional status. But studies to understand OP-induced glycemic variability are very few. OP poisoning was also found to increase lipid peroxidation in the study conducted by Panda et al., as evidenced by the rise in plasma malondialdehyde (MDA) levels.

In an observational study conducted by Moon et al. and published in 2014, the association between glycemic status at presentation in nondiabetics presenting with organophosphate poisoning and case fatality was analyzed. They also analyzed whether this association would be affected by the type of OP ingested. The patients were divided into certain groups based on their blood glycemic status at presentation. Group I had blood glucose levels <140 mg/dL (n = 63), group II had levels between 140 and 200 mg/dL (n = 58), group III had levels between 200 and 300 mg/dL (n = 41), and group IV had levels ≥300 mg/dL (n = 22). Group IV had higher mortality compared to groups I (p = 0.003) and II (p = 0.015). Group III also had higher mortality than group I (p = 0.040). They concluded that the risk of mortality increases independently as the blood glucose level at presentation increases in those patients without diabetes mellitus. Furthermore, this association varies depending on the type of OP that was ingested.

Ke et al. studied the effect of various factors on the prognosis of patients presenting with organophosphate poisoning was assessed, and they found that blood glucose was higher in patients in the death group. They also concluded that hyperglycemia was an independent risk factor for poor prognosis.

In another study conducted in Turkey, serum cholinesterase levels and plasma glucose levels were assessed as independent predictors of the organophosphate-induced intermediate syndrome, and it was found that the patients who developed intermediate syndrome had higher plasma glucose levels.

On the contrary, in a study conducted in Taiwan, investigators studied whether diabetes mellitus would affect the mortality of patients presenting with acute large-dose exposure to organophosphates and found that that might not be the case. They also concluded that the risk of developing new-onset diabetes mellitus may also be just minimal in the short term (Table 2).

![Acetylcholine signaling at synapse](image)

**Table 2: Studies correlating glycemic status with the severity of poisoning**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>No. of the study participants</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raghapriya et al. 2018</td>
<td>Prospective analytical study</td>
<td>100</td>
<td>11% of the patients were hyperglycemic, and this group had the highest mortality (63.63%) and highest ventilator requirement (100%). Transient hyperglycemia at the time of presentation showed a significant positive correlation with serum MDA as well as the dose of atropine given for treatment (p &lt; 0.05). The patient group with the highest plasma glucose (≥300 mg/dL) at presentation had the highest case fatality rate. Blood glucose at presentation was higher in the group who died (p &lt; 0.01). Intermediate syndrome occurred in 11 patients, and serum cholinesterase was significantly lower in all of them (p &lt; 0.01). They also had significantly higher levels of plasma glucose at presentation (p = 0.037). The difference in mortality (p = 0.117) between patients with and without diabetes mellitus presenting with OP poisoning was not significant.</td>
</tr>
<tr>
<td>Panda et al. 2015</td>
<td>Prospective analytical study</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Moon et al. 2014</td>
<td>Retrospective observational case series</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Ke et al. 2015</td>
<td>Retrospective analytical study</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Colak et al. 2014</td>
<td>Retrospective analytical study</td>
<td>71 (intensive care unit (ICU))</td>
<td></td>
</tr>
<tr>
<td>Liu et al. 2014</td>
<td>Prospective analytical study</td>
<td>118</td>
<td></td>
</tr>
</tbody>
</table>
ACUTE ORGANOPHOSPHATE POISONING AND CREATINE PHOSPHOKINASE (CPK) LEVELS

It has been concluded in a few studies\textsuperscript{16,17} that plasma CPK levels can be an efficient biochemical marker for acute OP poisoning because it is easily available and also cost-effective. Serial measurement of its levels can help predict prognosis as well.

Serum CPK was evaluated as a predictor of intermediate syndrome, and a weak positive correlation was observed between its levels and poisoning severity. Elevated CPK levels were found in all patients 48 hours after poisoning, but three of them had levels higher than 1500 IU/L. These three developed the intermediate syndrome. Hence early recognition of the intermediate syndrome may be possible by periodic estimation of CPK, and this may help to prevent life-threatening complications.

Aygun et al. in 2007\textsuperscript{19} in their study did not find any significant difference between the patients with severe and mild poisoning in the initial levels of aspartate aminotransferase and creatine kinase. They also could not find any rise of these markers in patients with intermediate syndrome either. It was therefore concluded that the serum levels of muscle enzymes measured in the first 24 hours may not predict whether the patients develop intermediate syndrome subsequently (Table 3).

SERUM AMYLASE AND LIPASE

Sumathi et al.\textsuperscript{20} compared various biochemical markers, including serum lipase, amylase, and CPK, with serum cholinesterase for their prognostic significance in OP poisoning. Serum lipase, amylase, and CPK were found to be negatively correlated with serum cholinesterase, which means that higher levels of these markers were associated with lower levels of plasma cholinesterase (that is, more severe poisoning). Out of these, the negative correlation between serum amylase and serum cholinesterase was statistically significant. Therefore, as expected, serum amylase provided the highest accuracy for estimating poisoning severity, followed by serum CPK and serum lipase. They concluded that hyperamylasemia is commonly associated with organophosphate poisoning and that serum amylase can be used as a prognostic indicator for OP poisoning.

Singh et al.\textsuperscript{21} measured the incidence of hyperamylasemia in organophosphate poisoning and found that mild hyperamylasemia was common in organophosphate poisoning.

Lee et al.\textsuperscript{22} published a study in 1998 looking into the significance of hyperamylasemia in organophosphate poisoning and whether it could be equated to a diagnosis of acute pancreatitis. They found that elevated amylase levels are common in severe organophosphate poisoning. But as we already know, elevated amylase levels alone cannot be used to diagnose pancreatitis, and therefore serum amylase is not reliable enough to diagnose OP-induced pancreatitis because its sensitivity and specificity are low. Serum lipase can be used to diagnose pancreatitis in those patients presenting with hyperamylasemia.

Dungdung et al.\textsuperscript{23} also studied the correlation of serum lipase, amylase, and plasma cholinesterase in acute OP poisoning. They conducted an observational study in a hospital on 100 patients who had acute OP poisoning. All age groups and both genders were taken up. All three of the above-said markers were measured at admission. Based on the serum cholinesterase levels at admission, patients got categorized into three groups. Group I had 20–50% of the normal serum cholinesterase levels. Group II had 10–20%, and group III had <10%. In all of them, serum lipase and amylase had a negative correlation with serum cholinesterase levels. It was also statistically significant. Serum amylase was found to have the highest diagnostic accuracy among them. A total of 10 patients died, and of them, six had <10% of normal plasma cholinesterase activity. Eight of these 10 patients also had hyperamylasemia. They concluded that hyperamylasemia is associated with organophosphate poisoning and that serum lipase and amylase and lipase can be used as prognostic indicators alongside serum cholinesterase. Serum amylase is better than serum lipase in predicting poisoning severity.

In 2021, Zobeiri from Iran also concluded that hyperamylasemia was associated with more severe clinical outcomes and higher fatality.\textsuperscript{24} In 2022, Patil et al. also concluded the same\textsuperscript{25} (Table 4).

LEUCOCYTE COUNT AND ORGANOPHOSPHATE POISONING

Kumar et al. in 2018\textsuperscript{26} concluded that leucocyte count is useful as a prognostic marker in organophosphorus poisoning. Ke et al.\textsuperscript{13} and others concluded that the acute physiology and chronic health evaluation (APACHE) II score, which uses leucocyte count, can be used to assess prognosis. Eizadi-Mood\textsuperscript{27} and others analyzed the prognostic value of each element of the APACHE II score in assessing the outcome of OP poisoning. APACHE II scores for patients who survived without intubation were much lower than those who survived after intubation and those who died. White blood cell (WBC) count in APACHE II was found to be prognostically valuable (Table 5).

SERUM PSEUDOCHELINESTERASE (BuChE)

Biomarkers are highly useful in disease diagnosis. Serum cholinesterase is one such marker which is decreased in OP

| Table 3: Studies correlating serum CPK with the severity of poisoning |
|--------------------|----------------|--------------|----------------|
| Study                | Type of study          | No. of study participants | Outcome                      |
| Madboly et al. 2013\textsuperscript{16} | Prospective analytical study | 60                        | About 15% had severe poisoning. There was a highly significant correlation between CPK levels and poisoning severity. A total of 14 patients had severe poisoning (POP score 8–11), and serum CPK levels, as well as the total dose of atropine, showed a positive correlation with severity. CPK levels showed only a weak positive correlation with poisoning severity ($r = 0.352$). Elevated CPK levels at 48 hours were found in all patients after poisoning, but three of them had levels higher than 1500 IU/L. These three developed the intermediate syndrome. Hence early recognition of the intermediate syndrome may be possible by periodic estimation of CPK, and this may help to prevent life-threatening complications. |
| Bhattacharyya et al.17 2011 | Prospective analytical study | 63                        | Did not find any significant difference between the patients with severe and mild poisoning in the initial levels of aspartate aminotransferase and creatine kinase. They also could not find any rise in these markers in patients with intermediate syndrome. |
| Kumar et al. 2015\textsuperscript{18} | Prospective analytical study | 75                        | Did not find any significant difference between the patients with severe and mild poisoning in the initial levels of aspartate aminotransferase and creatine kinase. They also could not find any rise in these markers in patients with intermediate syndrome. |
| Dursun Aygun et al. 2007\textsuperscript{19} | Prospective analytical study | 47                        | Did not find any significant difference between the patients with severe and mild poisoning in the initial levels of aspartate aminotransferase and creatine kinase. They also could not find any rise in these markers in patients with intermediate syndrome. |
poisoning. Organophosphates inhibit serum cholinesterase, and therefore, the decreased level of this biomarker is used to prognosticate acute poisoning. But is this biomarker dependable to diagnose a case without the usual signs and symptoms? A case report published in 2010 showed that the low levels of serum cholinesterase in a patient were due to pulmonary tuberculosis and hepatitis B with associated malnutrition, even though it was initially thought to be due to organophosphorus poisoning.

Eddleston et al. conducted a study in Sri Lanka to find out whether there was any use in measuring serum BuChE levels at admission, along with plasma organophosphorus concentration, to help predict mortality. A total of 91 patients with dimethoate and 208 with chlorpyrifos poisoning were treated using a standard protocol and studied. They recorded serum BuChE levels, serum OP concentration on admission, and the clinical outcomes. Serum BuChE level <600 mU/mL at admission was found to be very sensitive in predicting mortality in chlorpyrifos poisoning (100%), but it had a specificity of only 17.7%. But in the case of dimethoate poisoning, even though it had good specificity (86.4%), its sensitivity was poor (48%). A high serum OP concentration at admission was associated with worse outcomes, but a clear threshold was only deducible for dimethoate poisoning. They concluded that serum BuChE levels at admission could be useful, but it needs careful interpretation. It may be useful to predict whether the patient would need critical care and to predict death only if the pesticide ingested is known and its sensitivity and specificity for that particular pesticide studied. The serum concentration of some OP pesticides may predict the outcome. So, developing rapid bedside tests for the same may help early assessment of severity.

Serum BuChE measurements are very useful for rapid initial screening of organophosphate exposure and hence can help in protecting humans from overexposure to these pesticides.

A study conducted by Xu et al. published in 2010 attempted to evaluate the diagnostic value of plasma BuChE by comparing it with AChE. When the AChE activity was low, the activity of BuChE also became low correspondingly. The levels of both enzymes changed in a similar manner and coincided with clinical symptoms. They found that when the level of BuChE was 20% of normal, OP poisoning was of moderate severity, and when it reached <10%, the poisoning was severe. Different kinds of OP pesticides were taken into consideration to arrive at this conclusion.

**Newer Markers**

Serum β glucuronidase has also been studied as a marker for OP poisoning severity by Beltagy et al., with higher levels found in more severe poisoning.

**Recent Advances**

Reactivators (oximes) have been used since the 1950s to treat OP poisoning, which helps to revive the AChE enzyme inhibited by OP compounds. But, the effectiveness and toxicity potential of these reactivators are still points of debate. Another new option being explored is enzyme therapy. Organophosphorous hydrolases have recently spiked interest. They are a group of enzymes

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**Table 4: Studies correlating serum amylase and lipase with the severity of poisoning**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>No of study participants</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumathi et al. 2014</td>
<td>Prospective</td>
<td>53</td>
<td>Serum lipase, amylase and CPK were found to be negatively correlated with serum cholinesterase. Out of these, the negative correlation between serum amylase and serum cholinesterase was statistically significant.</td>
</tr>
<tr>
<td>Singh et al. 2007</td>
<td>Prospective</td>
<td>79</td>
<td>A significant increase in serum amylase was only observed with Fenthion. Mild hyperamylasemia was common in organophosphate poisoning.</td>
</tr>
<tr>
<td>Lee et al. 1998</td>
<td>Retrospective</td>
<td>159</td>
<td>Hyperamylasemia was found in 36% of patients and was closely associated with poisoning severity.</td>
</tr>
<tr>
<td>Dungdung et al. 2020</td>
<td>Prospective</td>
<td>100</td>
<td>Serum lipase and amylase had a negative correlation with serum cholinesterase levels. It was also statistically significant. Serum amylase was found to have the highest diagnostic accuracy among them.</td>
</tr>
<tr>
<td>Mehdi Zobeiri et al.</td>
<td>Prospective</td>
<td>332</td>
<td>Average levels of serum amylase in patients with confusion or coma were significantly higher, as were the levels in patients who died or needed ICU admission.</td>
</tr>
<tr>
<td>Patil</td>
<td>Cross-sectional</td>
<td>100</td>
<td>The average level of serum amylase was 335.40 ± 192.45 in patients who were discharged, and it was 843.37 ± 22.60 in those who died. A p-value of 0.0001. Hyperamylasemia was associated with more severe clinical outcomes and higher fatality.</td>
</tr>
</tbody>
</table>

**Table 5: Studies correlating total leucocyte count with the severity of poisoning**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>No of study participants</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al. 2018</td>
<td>Prospective</td>
<td>80</td>
<td>Serum cholinesterase level directly correlated with the poisoning severity (p = 0.0001). A leucocyte count &gt;12000 had 60% sensitivity, 76% specificity and an 85% negative predictive value, and when it was &gt;15000, it had 30% sensitivity, 95% specificity, and 80% negative predictive value.</td>
</tr>
<tr>
<td>Ke et al. 2015</td>
<td>Retrospective</td>
<td>116</td>
<td>The Apache II score, which uses leucocyte count, can be used to assess prognosis.</td>
</tr>
<tr>
<td>Eizadi-Mood et al. 2007</td>
<td>Retrospective</td>
<td>131</td>
<td>APACHE II scores for patients who survived without intubation were much lower than those who survived after intubation and those who died. WBC count in APACHE II was found to be prognostically valuable.</td>
</tr>
</tbody>
</table>
that have shown promise in detoxifying OP compounds. They have shown antitodal effects against some OP compounds in vivo in animal models. Stoichiometric bio scavengers and catalytic bio scavengers are two groups of enzymes studied, with examples, including plasma paraoxonase-1 and OP acid anhydrase.23

An alternative strategy which has been studied is serum BuChE reactivation. Organophosphates stoichiometrically inhibit BuChE without any toxicity. Reactivation of BuChE may allow it to bind to the circulating OP molecules before they can reach the target AChE enzyme.34 Recently, zirconium metal-organic polyhedra have also been studied for treatment.25

Liver markers were also studied for correlation with OP poisoning severity in Sri Lanka, and a positive correlation was found between higher hepatic transaminase levels and the severity of poisoning.36

Discussion
Organophosphates are commonly used for suicide by poisoning in India. Early recognition of the diagnosis and its severity will help in achieving a better outcome. Currently, serum AChE and pseudocholinesterase are widely accepted as biochemical markers to estimate OP poisoning severity. But the possibility of using a wide array of alternate, cheap and easily available markers exists, as evidenced by the studies mentioned above and using a combination of these markers may be better in terms of early identification of severe poisoning. In peripheral centers without access to costly investigations, these cheap markers may help in guiding an early referral to higher centers for severely poisoned patients. A comprehensive study comparing all these different markers has not been done so far, thereby emphasizing the need for such a study.

Conclusion
Various new, cheaper, and easily available biochemical markers have been identified as having the potential to act as surrogates for assessing the severity of organophosphate poisoning, and there is a scope for future studies to understand the utility.

References
Simplifying Type 2 DM Care with Linagliptin: A Position Paper

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ABSTRACT

Introduction: The burden of type 2 diabetes mellitus (T2DM) is raising dramatically both internationally and in India. It is often observed that multiple therapies or combinations of different drugs are usually required to successfully control hyperglycemia in patients with T2DM. To facilitate effective control of glucose levels, many new agents have been developed over the past few years.

Materials and methods: Multiple Advisory Board Meetings were conducted with 87 leading key opinion leaders (KOLs) from diabetes specialty PAN India to understand the simplicity aspect of linagliptin therapy in T2DM patients.

Discussion: Linagliptin is a xanthine-based, non-peptidomimetic, selective dipeptidyl peptidase 4 (DPP-4) inhibitor with a different pharmacological profile when compared to other DPP-4 inhibitors already available in India. It is known to decrease the risk of hypoglycemia compared to sulphonylurea (SU), is weight neutral, and no dose modification is required over a broad range of patient populations. This consensus paper discusses the clinical efficacy of DPP-4 Inhibitors and linagliptin in T2DM. It also highlights the evidence for the safety of linagliptin in T2DM patients with renal impairment (RI), cardiovascular (CV) risk, and heart failure (HF).

Conclusion: Linagliptin therapy is simplifying the management of T2DM with good efficacy and its use across a wide range of patients without any dose modification.

Introduction:

Type 2 diabetes mellitus (T2DM) is one of the prevalent forms of diabetes worldwide, contributing to approximately 90% of all cases. It occurs when the pancreas cannot produce sufficient insulin, and the body is unable to effectively utilize the insulin produced. Diabetes has a global incidence of 10.8% in urban settings and a slightly lower prevalence of 7.2% in rural regions. Over the years, the number of individuals living with diabetes has continuously increased. In 2000, the estimated global count was 151 million, which rose by 88% to 285 million in 2009. As per the International Diabetes Federation (IDF) estimates, in 2021, approximately 537 million adults aged 20–79 years are living with diabetes. Projections indicate that this number will rise to 643 million by 2030 and further to 783 million by 2045. Unfortunately, diabetes and its complexities have a significant impact on mortality rates. In 2021 alone, an estimated 6.7 million deaths were attributed to diabetes-related causes. India is the second leading country in the global diabetes epidemic.1 Based on the epidemiological studies that were conducted in India, the IDF Diabetes Atlas 2021 reported 74.2 million adults (20–79 years) with diabetes.2 From 32.7 million in the year 2000, the number of people with diabetes in the year 2015 had risen to 69.2 million.3

In India, district level household survey data showed a rise to 7.7% in 2016 from 5.5% in 1990 in diabetes prevalence in individuals aged 20 years or more.4 It is predicted that in the year 2040, the prevalence will rise to 123.5 million people.5

First-line therapy in T2DM depends on comorbidities, patient-centered treatment factors, and management needs but will generally include metformin and comprehensive lifestyle modification.6 While metformin therapy offers numerous benefits, it is important to acknowledge that it can be accompanied by gastrointestinal adverse effects. These effects may hinder or restrict its usage in certain patients. Sulphonylurea (SU) has been a preferred second-line glucose-lowering therapy in T2DM patients. SU are commonly used to effectively reduce plasma glucose levels, but they can also lead to varying degrees of hypoglycemia, β-cell death, weight gain, and potentially adverse cardiac outcomes. On the other hand, gliptins are newer incretin-based therapies for treating T2DM. They possess antihyperglycemic properties with a relatively safe adverse effect profile. Gliptins carry a low risk of hypoglycemia and are weight neutral. The selection of pharmacologic agents should be guided by a patient-centered approach, as stated in the 2022 American Diabetes Association guidelines.

They should be evaluated for their effectiveness, risk of hypoglycemia, impact on weight, cardiovascular (CV) and renal comorbidities, cost and accessibility, potential adverse effects, and patient preferences. Pharmacotherapy should be started at the time T2DM is diagnosed unless there are contraindications; for many patients, this will be metformin monotherapy in combination with lifestyle modification.7 However, medication(s) from other antidiabetic classes should be provided for the ones intolerant to or have contraindications to using metformin. Among individuals with T2DM who have established atherosclerotic CV disease or indicators of high CV risk, established kidney disease, or heart failure (HF), a sodium-glucose cotransporter 2 inhibitor (SGLT2i) and/or glucagon-like peptide 1 receptor agonist (GLP-1) with demonstrated CV disease benefit is recommended as part of the glucose-lowering regimen and comprehensive CV risk reduction, independent of A1C and in consideration of patient-specific factors.8 If the A1C levels are above the individualized target and there is a compelling need to reduce hypoglycemia, GLP-1 RA, SGLT2i, dipeptidyl peptidase 4 (DPP-4) inhibitor, or thiazolidinedione class of drugs may be administered. If the A1C levels remain still beyond the target, the patient therapy can be continued in combination with...
the other antidiabetic agents from the category of drugs mentioned. If the glycemic target is still not achieved, SU or basal insulin can be added to the therapy. DPP-4 inhibitors, as a class of antidiabetic agents, are effective in the treatment of diabetes. The most widely used DPP-4 inhibitors are saxagliptin, alogliptin, sitagliptin, vildagliptin, and linagliptin. Linagliptin is a DPP-4 inhibitor that has shown high efficacy by inhibiting ~80–90% of DPP-4 but not all DPP-4 inhibitors are administered as once-daily dosing. DPP-4 inhibitors have an oral route of administration and a mechanism of action based on the inhibition of the DPP-4 enzyme, thus preventing the breakdown of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), thereby prolonging their activity and glucose-stimulated insulin secretion, thereby resulting in a low risk of hypoglycemia. DPP-4 inhibitors are weight neutral with an acceptable safety profile.

The objective of this position paper is to understand the role of linagliptin in simplifying the management of T2DM with good efficacy, robust CV, and renal safety evidence and its use across broad patients without any dose modification.

Materials and Methods
To understand the simplicity aspect of linagliptin therapy in T2DM patients, multiple Advisory Board Meetings were conducted with 87 leading key opinion leaders (KOLs) from diabetes specialty PAN India. For the Advisory Board, 16 statements on simplicity aspects of linagliptin were drafted and supported with data from the scientific literature. These statements were presented to a small group of expert panels for validation. After the validation of these statements by the expert panel, the statements were presented as poll questions to 87 KOLs from the diabetes specialty in five zonal advisory board meetings, which were executed on a virtual platform. During the Advisory board meetings, the opinions of these thought leaders were gathered to determine the areas of agreement, neutrality, and disagreement. The statements were considered valid only if 30% of KOLs had responded during poll questions in the advisory board meetings. The results of the poll questions were collected, analyzed, and presented to a group of seven experts from the diabetes specialty, along with supportive scientific data to a respective statement during the national advisory board meeting to form expert opinions. A >50% agreement on a statement was taken into consideration to form an expert opinion (Fig. 1). The statements are listed in Table 1 and addressed in the sections mentioned below:

- Clinical efficacy of a DPP-4 inhibitor.
- Clinical efficacy of linagliptin in T2DM.
- Cardiovascular (CV) and HF safety evidence of linagliptin from (CV outcome trial) CVOTs.
- Clinical evidence of linagliptin in T2DM with renal impairment (RI).
- Convenience and adherence with linagliptin in T2DM.
- Safety of linagliptin across a broad range of T2DM patients.

Results from the Expert Panel Discussion

Clinical Efficacy of a DPP-4 Inhibitor
Dipeptidyl peptidase 4 (DPP-4) inhibitors possess a unique mode of action by inhibiting the DPP-4 enzyme, which plays a role in the rapid degradation of two important incretin hormones: GLP-1 and GIP. The clinical efficacy of several DPP-4 inhibitors, such as saxagliptin, alogliptin, vildagliptin, linagliptin, and sitagliptin, has been demonstrated in numerous studies. A decrease in hemoglobin A1C (HbA1C) and improvement in parameters like fasting plasma glucose (FPG) and postprandial glucose (PPG) are characteristic changes associated with the DPP-4 inhibitors treatment. Table 2, given below, lists the clinical trials which prove these results. Cradley et al. did a comprehensive study to compare the efficacy of DPP-4 inhibitors in T2DM. The review found no significant differences in the average change from baseline in body weight or glycosylated HbA1C, nor in the proportions of patients achieving HbA1C levels below 7% or experiencing hypoglycemic events among patients using DPP-4 inhibitors (Fig. 2). Thus, the presented evidence suggests that linagliptin is equally efficacious as other DPP-4 inhibitors.

87 opinions of the advisors through the poll questions (16 statements) analyzed
A poll question (statement) considered as valid only if over 30% HCPs have responded to the same
More than 50% agreement on a statement considered for development of an expert opinion
Overall opinions will be analyzed and approved by the experts (n = 7)
Preparation of manuscript—Final approval from the experts (n = 7)

Results of the poll questions were collected, analyzed, and presented to a group of seven experts from the diabetes specialty, along with supportive scientific data to a respective statement during the national advisory board meeting to form expert opinions. A >50% agreement on a statement was taken into consideration to form an expert opinion (Fig. 1). The statements are listed in Table 1 and addressed in the sections mentioned below:

Clinical Efficacy of Linagliptin in T2DM
Efficacy of Linagliptin in Drug Naïve Patients and as an Add-on Therapy to Metformin
As per the experts, achieving good glycemic control with linagliptin is the reason for its growing use in therapy. A reduction in HbA1C and PPG and an improvement in FPG levels make linagliptin a suitable choice of treatment. Mentioned below are some studies which testify to the positive impact of linagliptin on glycemic control. Del Prato et al. conducted a study to assess the safety and efficacy of linagliptin. It demonstrated that linagliptin treatment caused a placebo-corrected change in HbA1C from a baseline of approximately —0.69% (p < 0.0001) after the treatment period of 24 weeks. The adjusted HbA1C reduction in patients with baseline HbA1C of 9.0% was 1.01% (p < 0.0001). Improvements in FPG (p < 0.0001) and PPG (p < 0.0001) were seen, and there were no significant hypoglycemic episodes.

Studies by Taskinen et al. and Groop et al. that were conducted to evaluate the efficacy and safety of linagliptin administered as an add-on therapy to metformin in patients with T2DM with inadequate glycemic control (n = 701), significant reductions were observed from baseline in HbA1C (−0.49 vs 0.15%), FPG (−0.59 vs 0.58 mmol/L), and PPG (−2.7 vs 1.0 mmol/L); p < 0.0001 in linagliptin patients. Hypoglycemic events were also rare (0.6%) in linagliptin-treated patients. No significant
Simplifying Type 2 DM Care with Linagliptin

Table 1: The questionnaire to rate each item using a 9-point scale (1–5, disagreement; 5, neutral; 6–9, agreement)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Question</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The efficacy of linagliptin is comparable to other gliptins (n = 65)</td>
<td>4.60%</td>
<td>3.10%</td>
<td>92.30%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>Linagliptin can be administered as a single agent in drug naïve patients when contra indicated/intolerant to metformin (n = 61)</td>
<td>0.00%</td>
<td>4.90%</td>
<td>95.10%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>Linagliptin can be considered a viable option for second-line treatment after metformin failure (n = 61)</td>
<td>1.60%</td>
<td>4.90%</td>
<td>93.50%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>Linagliptin-metformin FDC as a 1st line shows better efficacy as compared to metformin monotherapy (n = 61)</td>
<td>0.00%</td>
<td>4.90%</td>
<td>95.10%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>Linagliptin has comparable efficacy with relatively better durability and safety compared to SU (n = 65)</td>
<td>7.70%</td>
<td>27.70%</td>
<td>64.60%</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>Linagliptin has better efficacy across the Asian population compared to Caucasians (n = 65)</td>
<td>0.00%</td>
<td>21.50%</td>
<td>78.50%</td>
<td>100%</td>
</tr>
<tr>
<td>7</td>
<td>Linagliptin can be an effective oral antidiabetic drug (OAD) as an add-on to insulin (n = 64)</td>
<td>0.00%</td>
<td>14.10%</td>
<td>85.90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Due to variations in study design, methodology, and populations, comparison of studies should be evaluated cautiously.40–43

<table>
<thead>
<tr>
<th>Condition</th>
<th>SAVOR TIMI 53 (saxagliptin)</th>
<th>TECOS (sitagliptin)</th>
<th>CARMELINA (linagliptin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHF</td>
<td>HR 1.27† (95% CI 1.07–1.51)</td>
<td>HR 1.00† (95% CI 0.83–1.20)</td>
<td>HR 0.90† (95% CI 0.74–1.08)</td>
</tr>
<tr>
<td>CV death</td>
<td>HR 1.03 (95% CI 0.87–1.22)</td>
<td>HR 1.03 (95% CI 0.89–1.19)</td>
<td>HR 0.96 (95% CI 0.81–1.14)</td>
</tr>
<tr>
<td>3P-MACE</td>
<td>HR 1.00† (95% CI 0.89–1.12)</td>
<td>HR 0.99† (95% CI 0.89–1.10)</td>
<td>HR 1.02† (95% CI 0.89–1.17)</td>
</tr>
</tbody>
</table>

†Testing for superiority for 3P-MACE was the primary endpoint (4P-MACE for sitagliptin); †exploratory outcome; 3P-MACE, 3-point major adverse CV events; CI, confidence interval; HR, hazard ratio

change in body weight was observed in both groups.10

Lv et al. investigated the possibility that the initial combination therapy with metformin and linagliptin could offer better glycemic control (HbA1C ≤ 6.5%) than metformin alone without aggravating hypoglycemia. In comparison to metformin alone, combination therapy increased the proportion of patients who achieved HbA1C ≤ 6.5%, both for metformin doses of 1000 mg (49.5 vs 35.4%, respectively) and 500 mg (40.1 vs 22.9%, respectively). Early combination therapy with metformin and linagliptin increases the likelihood of obtaining tight glycemic control (HbA1C of ≤6.5%) without raising the risk of hypoglycemia or other side effects.11

Efficacy of Linagliptin vs Sulfonylureas (SU) in T2DM

The usage of SU is linked to a higher risk of weight gain and hypoglycemia. SU has reliable efficacy, particularly in patients with recently diagnosed diabetes.12 They are the most extensively used antihyperglycemic medications that act by lowering glucose levels by exhibiting their effect on β-cells and inducing an insulinotropic response.13 Outpatients suffering from T2DM to HbA1C readings of 6.5–10.0% participated in a 2-year parallel-group, noninferiority double-blind experiment conducted by Gallwitz et al. in 2012. Then, these patients were randomly assigned to receive either oral linagliptin (5 mg) or oral glimepiride (1–4 mg) once
daily. In the linagliptin [−0.16% (standard error 0.03)] and glimepiride [−0.36% (0.03)] groups, comparable patterns of declines in adjusted mean HbA1C were observed (difference 0.20%; 95.5% confidence interval (CI): 0.09–0.30). Consequently, the trial’s predetermined noninferiority threshold of 0.35% was achieved. When compared to the glimepiride group, the incidence of hypoglycemia and severe hypoglycemia was lower in the linagliptin group (one (1%) vs 12 (2%) patients). When compared to the glimepiride group, the linagliptin group’s patients reported considerably fewer CV events (12 vs 26 patients). According to the study’s findings, linagliptin is noninferior to glimepiride in terms of efficacy and has a reduced risk of adverse events than glimepiride.14

Efficacy of Linagliptin in Asians with T2DM
In a study conducted by Sarashina et al., the impact of race on the pharmacodynamics, pharmacokinetics, safety and efficacy of linagliptin monotherapy was assessed in patients with T2DM. It consisted of two studies: study 1 consisted of Japanese patients exclusively, and study 2 enrolled both White and Asian patients. The results showed that linagliptin effectively inhibited DPP-4 activity in plasma, with concentrations more than half-maximal inhibitory concentration and DPP-4 inhibition of >80% at the trough. This inhibition was consistent in study 1 and study 2, indicating similar pharmacokinetics and pharmacodynamics across the different racial groups. Furthermore, the reduction in FPG concentrations was similar in magnitude across all groups. However, there was a greater decrease in HbA1C levels observed in study 1 (Japanese) and the Asian (non-Japanese) patients in study 2. The safety profile of linagliptin was favorable in each racial group, indicating the medication can be safely used in patients of different races. Based on these findings, the study concluded that a daily dose of 5 mg of linagliptin is appropriate for use in various racial groups.15

Efficacy of Linagliptin as an Add-on to Insulin in T2DM
A 24-week, double-blind, placebo-controlled, phase III trial conducted by Yang et al. assessed the safety and efficacy of linagliptin in 206 Chinese patients with inadequately controlled T2DM having HbA1C values between 7.5–10.0%, receiving metformin and insulin (basal or premixed). The cohort was randomized to receive a placebo or 5 mg linagliptin. With linagliptin, the drop in HbA1C from baseline was higher than with placebo (p = 0.0016). Significantly better improvements in 2-hour PPG (p < 0.001) were observed with linagliptin, and numerical reductions in FPG (p = 0.2241) versus placebo were also noted. A higher percentage of patients on linagliptin achieved an HbA1C reduction of ≥0.5% vs those on placebo (odds ratio 2.293, p < 0.01). Hypoglycemic events identified by the investigators were reported, but none were severe (linagliptin: 17.3%; placebo: 12.7%). Linagliptin as an add-on to insulin in Chinese patients with T2DM improved glycemic control and was well tolerated.16

Opinions from experts on the efficacy of linagliptin in T2DM
Linagliptin can be used as monotherapy in drug naïve patients when contraindicated/ intolerant to metformin (95.1%). Linagliptin can be considered a second-line therapy after metformin failure (93.3%). Linagliptin-metformin fixed dose combination (FDC) as a 1st line shows better efficacy as compared to metformin monotherapy (95.1%).

Cardiovascular (CV) and HF Safety Evidence of Linagliptin from CVOTS
As various glucose-lowering medications are associated with many CV safety issues, CV disease is the primary cause of mortality among diabetic individuals. The effects of linagliptin on CV safety have been examined in significant, large landmark trials like CAROLINA and CARMELINA. Participants with T2DM who were at high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] 30 mg/gm) and high renal risk were examined for their reactions to linagliptin in the CARMELINA randomized clinical investigation performed by Rosenstock et al., Randomly assigned patients were given linagliptin (n = 3494) or a placebo (n = 3485). Major adverse CV events (MACE) with a 3-point outcome occurred in 434 of 3,494 subjects (12.4%) receiving linagliptin and 420 of 3,485 subjects (12.1%) receiving a placebo (hazard ratio (HR), 1.02; 95% CI, 0.89–1.17; p < 0.001 for noninferiority; p < 0.74 for superiority). Hospitalization for HF (hHF) was noted in 209 (6.0%) linagliptin patients compared to 226 (6.5%) placebo patients. Linagliptin did not increase the probability of a composite CV outcome over a median of 2.2 years compared to placebo in T2DM patients with high CV and/or renal risk when added to usual therapy.17

Similarly, patients with relatively early T2DM and risk factors for established evidence of atherosclerotic CV disease were included in the CAROLINA study to compare the linagliptin (n = 3,203) and glimepiride (n = 3,010) CV outcomes. In the linagliptin group, 356 out of 3,023 participants (11.8%) and, in the glimepiride group, 362 out of 3,010 (12.0%) experienced the primary endpoint, 3-point MACE. The noninferiority requirement (p < 0.001 for noninferiority) was therefore satisfied, but not the superiority criterion (p = 0.76).18

The European Society of Cardiology: European Association for the Study of Diabetes guideline 2019 also states that among the available DPP-4 inhibitor, linagliptin and sitagliptin have neutral effects on the risk of hHF and may be considered for T2DM treatment in patients with HF.19

Opinions from experts on linagliptin—CV and HF safety evidence from CVOTS
Linagliptin has a reassuring safety profile with robust evidence across the cardiac and renal comorbidities with CARMELINA (97.1%). Linagliptin has a neutral effect on hHF and may be considered in T2DM with a risk of HF (82.6%).
Simplifying Type 2 DM Care with Linagliptin

Linagliptin has the best renal safety evidence among the gliptins (84.3%).

Linagliptin has proven safety and effectiveness across the spectrum of chronic kidney disease (CKD) in T2DM (94.3%).

Convenience and Adherence with Linagliptin in T2DM

Inappropriate Renal Dose Adjustment of DPP-4 Inhibitor is Associated with Poor Clinical Outcomes in T2DM

Gliptins have similar efficacy profiles but distinct pharmacokinetic characteristics. Patients with T2DM and CKD were studied in a retrospective observational cohort study (N = 82,332). The cohort was separated based on the prescription of DPP-4 inhibitor (with or without dosage modifying them based on eGFR). The suitable or incorrect dosage of DPP-4 inhibitors was determined based on the daily dose of DPP-4 inhibitor, the patient’s eGFR, and the manufacturer’s guidelines. Between 2009 and 2012, over 40% of patients with T2DM and CKD received incorrect DPP-4 inhibitor dosages, which decreased to 24.4% in 2015. In individuals with T2DM and CKD stage 3 or 4, inappropriate DPP-4 inhibitor dosing was associated with a 15% higher risk of death from any cause, a 7.6% higher risk of emergency department visits, and a 19.9% higher risk of serious hypoglycemia compared to individuals given an appropriate dose.

In the case of mild RI, sitagliptin, saxagliptin, and vildagliptin are given in the following doses: 100 mg once a day (OD), 5 mg OD and 50 mg twice a day, respectively. However, for moderate to severe RI, dosage adjustment is clinically necessary. Saxagliptin is adjusted at 2.5 mg OD dosage for moderate/severe RI, whereas vildagliptin is changed at 50 mg OD dose. In the case of sitagliptin, 50 mg OD is prescribed for moderate RI and 25 mg OD for severe RI. Linagliptin, on the other hand, does not require dosage change in RI. Instances of a necessity to modify the DPP-4 inhibitor dosage for diabetic patients suffering from RI have been reported for therapies that involve the use of sitagliptin, vildagliptin, saxagliptin, and teneligliptin. Tmax of linagliptin occurred approximately 1.5 hours after oral administration of a 5 mg OD dosage to healthy participants; the mean plasma area under the curve (AUC) was 139 nmol.hour/L, and Cmax was 8.9 nmol/L. Following oral treatment, the bulk of linagliptin (about 90%) is excreted unaltered, showing that metabolism is a minor elimination mechanism. Renal clearance at a steady state was approximately 70 mL/minute. Treatment with 5 mg OD linagliptin has shown efficacy and safety in all stages of RI, including hemodialysis. The adjustment of dose can be a major challenge in diabetic patients with RI, and therefore linagliptin may be an ideal choice of treatment in such instances. Hence, a single 5 mg OD dosing without dose adjustment with linagliptin is convenient for the management of T2DM and increases patient adherence to the dosing regimen across the broad patient profiles, as per the experts’ opinion.

Safety of Linagliptin across a Broad Range of T2DM Patients

Linagliptin’s clinical safety has been evaluated in more than 14,000 T2DM patients.

Among the DDP-4 inhibitors available in the market, linagliptin has some data which demonstrate that dose modification is not essential for any mild/moderate, or severe hepatic impairment. Graefe-Mody et al. investigated the effect of hepatic impairment on the pharmacodynamics, pharmacokinetics, and tolerability of linagliptin. An open-label, parallel-group, single-center study was conducted that enrolled healthy subjects (n = 8) and patients with severe (n = 8), moderate (n = 9), and mild (n = 8) hepatic impairment. Renal excretion of unaltered linagliptin (≤7%) and accumulation determined by AUC or Cmax were comparable between groups. At steady-state trough levels, median plasma DPP-4 inhibition was similar in healthy (91%), mild (90%), and moderate (89%) hepatic impairment patients, as well as in patients with severe hepatic impairment receiving a single dosage 24 hours later (84%). Since linagliptin was well tolerated, the patient
with liver impairment does not require dose adjustment for linagliptin.32 A pooled analysis was conducted by Inagaki et al. in 2016 to assess the effectiveness of linagliptin in patients with T2DM and hepatic difficulties. Between participants with and without baseline hepatic problems, there was no discernible difference in HbA1C reduction (p = 0.4042).33 In patients taking linagliptin, acute pancreatitis and biliary pemphigoid have been reported. In the CARMELINA experiment, adjudicated acute pancreatitis was recorded in 0.3% of linagliptin-treated patients and 0.1% of placebo-treated patients, while biliary pemphigoid was documented in 0.2% of linagliptin-treated patients, but not in any placebo-treated patients. In such cases, linagliptin should be discontinued.20

Hypoglycemia in patients with T2DM often results in a series of physiologic effects that may lead to cardiac arrhythmias and can cause oxidative stress. These consequences could result in ischemic cerebral damage and may cause sudden cardiac death. Thus acute and chronic episodes of hypoglycemia may initiate several potential mechanisms that raise the possibility of CV complications.34 A study conducted by Greco et al. concluded that, among elderly T2DM patients, severe hypoglycemia is a significant and frequent metabolic emergency.35 The glucose-lowering mechanisms of many pharmacological agents also contribute directly to weight gain.36 The CAROLINA study found that across all specified hypoglycemia severity categories, the incidence of hypoglycemic episodes (as assessed by the investigator) was lower in the linagliptin group than in the glimepiride group. Lower hypoglycemia risk in the analyzed subgroups was consistently observed in the linagliptin group vs the glimepiride group.37

A study by Barnett et al. assessed the safety and efficacy of linagliptin in elderly patients. HbA1C was −0.61 vs −0.04%, placebo, p < 0.0001. A 0.64% placebo-corrected reduction was observed. Both the linagliptin and placebo groups had roughly comparable levels of overall safety and tolerability; 75.9% of patients in each group experienced a negative side effect (placebo n = 60, linagliptin n = 123). There was no mortality. The study drug was not deemed to be responsible for any of the severe adverse events that occurred, but it did impact 6.3% (five) of the patients in the placebo group and 8.6% (14) of patients in the linagliptin group. The most frequent adverse event was hypoglycemia, which occurred in both groups but at similar rates, 16.5% (13) in the placebo group and [24% (39) in the linagliptin group; odds ratio 1.58, 95% CI: 0.78–3.78, p = 0 2083]. Therefore, it can be suggested that linagliptin is effective in lowering glucose with a safety profile similar to a placebo.38 Espeland et al. conducted a study to compare the CV safety of linagliptin with glimepiride in older and younger participants in the CAROLINA trial. Moderate-to-severe hypoglycemia was markedly reduced with linagliptin, with no differences among age groups (p = 0.23). The mean weight was −1.54 kg (95% CI: −1.80−1.28), lower for linagliptin versus glimepiride. A relative risk reduction of 83% in hypoglycemia was reported in older patients over 75 years with linagliptin. Weight neutrality across age groups was a vital observation with linagliptin.39 Linagliptin-based insulin regimens are also an effective alternative to intensive basal-bolus insulin in very old T2DM patients.39 In the CARMELINA study, it was concluded that treatment based on linagliptin does not elevate the risk of cardio renal events in older patients.17

Opinions from experts on the safety of linagliptin across a broad range of T2DM patients

Linagliptin can be safely used in T2DM patients with mild to moderate liver dysfunction (86.9%).
Linagliptin can be safely considered in broad patient profiles, including elderly patients with T2DM (98.3%).
Linagliptin, with a lower risk of hypoglycemia and weight neutrality as compared to glimepiride, alleviates the fear of hypoglycemia and weight gain in T2DM (96.7%).

CONCLUSION

The current position paper has been developed based on expert opinions, experience, and common therapy practices in India while providing relevant clinical evidence to support the guidance that has been developed for the use of linagliptin. To effectively treat a patient with T2DM, healthcare professionals must take into account a number of factors when choosing a regimen for drug treatment, including the patient’s preferences, age, reduction of CV risk, individualized glycemic targets, avoidance of hypoglycemia, renal protection, comorbidities, cost, weight gain, and other side effects of the medication. The expert opinions documented in this paper help justify the clinical role of linagliptin in managing T2DM. It is an efficacious and well-tolerated drug for the management of T2DM. It reduces the risk of hypoglycemia, is weight neutral, and does not require dose adjustment across the broad patient profile regardless of hepatic or renal status. It can be utilized as a single agent for drug naïve patients when metformin is contraindicated/patients who are intolerant to metformin or as second-line therapy after metformin failure, or as an effective OAD add-on to insulin.

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Ambrish Mittal has received honoraria as speaker and advisor from AstraZeneca, Abbott, Boehringer Ingelheim, Cipla, Dr Reddy’s, Eli Lilly, Glenmark, GlaxoSmithKline, Ipca, Janssen, Lupin, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi, Serdia Servier, Sun Pharma, Torrent, Wockhardt and Zyus Nutrition. Ambady Ramachandran has received honoraria as an advisory board member from Boehringer Ingelheim India, AstraZeneca; as a speaker from Boehringer Ingelheim India, Bayer, Novo Nordisk, Eli Lilly, Sanofi, and grant from Novartis, Sanofi, and AstraZeneca. Arpande Bhattacharya has no share in pharmaceutical companies. Manoj Chadha has received d honorarium as a speaker and advisory board member from Boehringer Ingelheim India, AstraZeneca, Janssen, Novo Nordisk, Eli Lilly, MSD, Wockhardt, Alkem, USV and Sanofi-Aventis. Mala Dharmalingam has received honoraria as a speaker from Abbott, Boehringer Ingelheim, Cipla, Eli Lilly, Glenmark, Ipca, Janssen, Lupin, Novartis, Novo Nordisk, Sanofi, and Sun Pharma. Anirban Majumder has received honoraria as a speaker and advisory board member from AstraZeneca, Abbott, Boehringer Ingelheim, Cipla, Dr Reddy’s, El I Lilly, GlaxoSmithKline, Janssen, Lupin, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Jansen, Serdia Servier, Wockhardt and Zyus Nutrition. Debmalya Sanyal has received an honorarium as an advisory board member from Boehringer (Fig. 2) Ingelheim, India.

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Show Me the Money: Finance for the Physician

Rohit Bansal*

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E ach one of us became a doctor with passion and fire in our hearts, with an aim to excel in one’s chosen field, bring a meaningful change in a patient’s life, and ultimately fulfill one’s dreams. A majority of us who were raised in hinterlands wish to own a house in a metro city, end up taking loans, or utilize a major chunk of precious savings. This satisfies most of us. But don’t we deserve better? Have we not flipped and mugged tomes for more than a decade when everyone around us had already started earning and leading financially independent lives? Are we earning at par with our counterparts in the western world. The fact is that most of us are just living an average lifestyle. Not the one that we actually aspire to or deserve. The top of the lot who are working in the private and corporate sectors, are burning the midnight oil in pursuit of fame and name, and maybe jet-setting across hospitals and conferences. But are they able to spare enough time for themselves and their families? Why is there a financial ceiling for a doctor who sincerely wishes to maintain a work-life balance?

The answer and the secret lie in how we manage our hard-earned money. With our little financial knowledge and learning, most of us park it in savings accounts, and when a substantial corpus is built, we do a bank or company fixed deposit (FD) and renew it on maturity. Some of us make a bank recurring deposit or take a multi-option deposit (MOD) scheme. A MOD scheme allows the auto-transfer of funds over and above a minimum limit from a savings account into the MOD at a higher rate of interest. We also regularly invest in Public Provident Fund to a maximum of 1.5 lakhs a year, which gives a decent 7.1% tax-free return. Investment policies by life insurance companies are another option that we explore. Property as an investment and asset class has its own charm. Either one buys and then rents out the property or invests in an upcoming project with potential. Some of us have even tried and burnt our fingers by investing directly in the stock market, thereby developing a lifelong apprehension.

This is how we have seen people investing around us; this is what we do with our own savings as well. This is all we have time for, to understand, and invest with ease.

Given the current financial situation of overvalued equities, better debt returns in recent times, and global uncertainty, these options seem to be dependable, especially for those who are nearing superannuation and are rather settled in life. Any form of risk at this stage is unacceptable. But for those of us who still have greenhorns, is this the right strategy? Does this always beat inflation? Does the property provide liquidity in times of dire need, and does it always adequately appreciate in value, per our expectations?

The truth is that we lack the requisite financial knowledge. The mere mention of other ways to manage money gives us jitters. Teaching that was imparted to us in our alma mater was good enough to make money. But how to manage it was never taught. Personal finance was never a part of our curriculum.

The silver lining is that one need not have a very deep knowledge of the financial sector or devote significant hours digging out information from business channels and newspapers. Just a basic but sound knowledge of the right investment instrument, discipline, temperance, and patience would do. Learning and knowing about mutual funds, is the way forward.

National Pension System (NPS) is a good option for everyone. It is not exclusive to government employees. Activating tier-2 in NPS account is a simple process on the NPS portal: enps.nsl.com. One must have a tier-1 NPS account to activate tier-2. NPS tier-2 is easy and works just like mutual funds, with no exit load and no additional maintenance expenses. One needs to choose a pension-fund-management company from the choices given. Either HDFC, ICICI, or SBI, the largest financial institutions in the country, is a good choice. It is then required to fix a desired percentage allotment in equity, corporate bonds, and government securities to a total of 100, as per one’s risk appetite. The equity portion (E), majorly invested in large-cap companies, gives growth. Corporate bonds (C) and government securities (G), covering the debt portion, provide stability from market volatility. A simple formula that may be followed is to keep the portion in debt equal to one’s age and allot the rest as equity, under active choice. For example, if one is 40 years of age, then one may opt as:

- Scheme C + G: 40% (may be divided equally between two)
- Scheme E: 60%

Investing directly in stocks is a process of buying and selling shares of stocks or companies listed on the stock exchange, and mutual funds do the same. The only difference is that here a group of financial experts (fund managers) do it on your behalf, and they, in turn, charge their professional fees in terms of the total expense ratio of the respective mutual fund. Investing directly in stocks can be risky and require constant know-how of changing market scenarios and company dynamics, with a sound knowledge of when to buy and, more importantly, when to sell. It’s an art that is not easy to master. Investment in mutual funds is more diversified, and if done in a systematic manner (systematic investment plan), it mitigates the risk considerably over a period of more than 10 years. Here the money may remain invested for as long as one wants without a fixed term or tenure, unlike an FD. Only on redemption one has to give tax on the capital gains accrued. One can go for a combination of better performing and rated flexi cap, large-cap index, and aggressive hybrid funds if one is a moderately aggressive investor. Multi-asset and balanced advantage funds hold good for conservative investors. Investment in mutual funds can be made through an investment agency (expenses are more)

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or directly by registering a folio with the respective asset management company. Performance tracking and transactions can be done through Computer Age Management Services (CAMS) and KFin Technologies, which are mutual fund transfer agencies. After building an emergency corpus in the form of fixed deposit or debt mutual fund to cover expenses of 2-3 years, one should save and invest regularly in equity through mutual fund, to bring forth the magic of compounding. This way, the troika of liquidity of money when needed, returns beating inflation over the longer term, and tax efficiency on long-term capital gains is achieved. After all, it is never too late, and a good doctor can be a great wealth manager too. One may have started late, but there are still enough laps left to sprint and win.
Brucellosis in a Sickle Cell Patient with Hyposplenia

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Abstract
Sickle cell disease patients are prone to infection and overwhelming sepsis because an immune-deficient state arises from asplenia (autosplenectomy/surgical splenectomy) and functional hyposplenism. The common pathogen encountered in sepsis with asplenic/hyposplenism patients is encapsulated organism, gram-negative bacilli, but in developing countries like India, there are many possibilities of infection by an uncommon organism that make it difficult to diagnose. Here, we have described a case of sickle cell disease presented with persistent fever and later, found to have an atrophic spleen with involvement of respiratory system and osteoarticular system. After extensive workup, he was diagnosed to be brucellosis. So, unusual infectious causes be kept as a differential diagnosis in a susceptible host while dealing with persistent symptoms. Uncommon infections like Brucella need to be studied in hyposplenism patients as data are lacking.

Introduction
Sickle cell anemia is a genetically transmitted disease in which infection is a significant cause of mortality apart from other complications like vaso-occlusive crisis and acute chest syndrome. Sickle cell disease patients are susceptible to infection because of autosplenectomy, surgical splenectomy, or hyposplenism.1,2 Brucellosis is an underreported zoonotic disease across the world, including in India. The clinical manifestation ranges from mild flu-like febrile illness to severe life-threatening organ involvement.3 Brucellosis is a very uncommon infection in sickle cell disease patients with or without hyposplenism. There are very few studies of brucellosis in India.

Case Description
A 22-year-old young male patient presented to us with complaints of intermittent high-grade fever, back pain, shoulder pain, and pain in the bilateral lower chest for 2 weeks. He did not give any history of cough, dysuria, skin lesion, gastrointestinal symptom, or joint swelling. He had similar episodes of fever 1 month back that resolved with a short course of antibiotics. The patient was a known case of sickle cell disease with a history of blood transfusion a few years back, and he was on hydroxyurea for 3 years. He had a history of cat bites over the dorsum of his right hand 1 year back without any sequelae.

There was only pallor on examination, and the rest of the general physical examination was unremarkable. Pulse rate—112/minute, blood pressure—108/66 mm Hg, respiratory rate—20/minute, temperature—101°F. Systemic examination revealed hepatomegaly.

Routine investigation showed hemoglobin—9.5 gm/dL, leucocytosis (16000/cumm), monocytosis (14%, 2350/cumm), indirect hyperbilirubinemia (1.49 mg/dL), transaminitis (aspartate transaminase—166 U/L, alanine aminotransferase—154 U/L). The kidney function test was normal. Routine urine microscopy was normal. ESR (90 mm at 1 hour) and C-reactive protein (CRP) (104.2 mg/dL) were high.

X-ray showed right lower zone increased bronchovascular marking with subtle haziness. He was managed empirically with piperacillin/tazobactam, vancomycin, azithromycin, and other supportive treatment. Serology for malaria, dengue, scrub typhus, hepatitis (A, B, C, and E), and human immunodeficiency virus were negative. COVID-19 reverse transcription polymerase chain reaction was negative. Later blood serology for leptospira—immunoglobulin (Ig) M and IgG (immunochromatography) came positive. Blood and urine cultures were sterile. Peripheral smear showed toxic granules with leukocytosis. Serum procalcitonin was normal. Antibiotics were changed to meropenem and doxycycline on day 6th as he was still symptomatic.

On further workup, the whole abdomen sonography revealed hepatomegaly (20 cm) and an atrophic spleen (6.6 cm). High-resolution computed tomography (HRCT) chest showed bilateral basal opacification predominantly in the right with ill-defined lytic-sclerotic lesions in D5, D6, and D8 vertebrae (Fig. 1). Bronchoalveolar lavage (BAL) was done and the sample was negative for gram stain, fungal KPotassium hydroxide test, Acid-Fast Bacilli Smear, and Cartridge based nucleic acid amplification test. BAL sample showed no growth for bacteria, fungi, or mycobacteria (liquid culture). Toxoplasma serology (IgM, IgG) was negative. Serum galactomannan and Mantoux tests were negative. He was still febrile even after day 15 of antibiotics. Repeated blood cultures did not show any growth. Gentamycin was added considering the organism associated with asplenia/functional hyposplenism.

Later, Brucella IgM (13.8 U/mL) by enzyme-linked immunosorbent assay, normal <12 U/mL came positive whereas Brucella IgG was 0.63 U/mL (negative, normal <12 U/mL). So, the diagnosis was finalized as sickle cell disease with functional hyposplenism with brucellosis (pneumonia and vertebral osteomyelitis). After 8 days, the patient became afebrile and was later discharged. On follow-up, the patient was afebrile with complete normalization of blood parameters, including inflammatory markers (ESR, CRP) except anemia.

Discussion
Brucellosis is a major underdiagnosed and underreported disease of livestock as well as humans and is endemic in Asia. The prevalence of brucellosis varies from <0.01 to >200 per 100,000 across the world. In India also, the prevalence varies from 0.8 to 26.6%.4 The average prevalence of high-risk groups, for example, veterinarians, meat handlers, and abattoir workers, is around 11%. The prevalence of brucellosis in India is encapsulated organism, gram-negative bacilli, but in developing countries like India, there are many possibilities of infection by an uncommon organism that make it difficult to diagnose. Here, we have described a case of sickle cell disease presented with persistent fever and later, found to have an atrophic spleen with involvement of respiratory system and osteoarticular system. After extensive workup, he was diagnosed to be brucellosis. So, unusual infectious causes be kept as a differential diagnosis in a susceptible host while dealing with persistent symptoms. Uncommon infections like Brucella need to be studied in hyposplenism patients as data are lacking.
prevalence in clinically suspected hospitalized patients was 7%. Causative agents of brucellosis are Brucella abortus (cattle), Brucella melitensis (small ruminant), Brucella suis (swine), Brucella canis (dogs), and Brucella ovis (sheep). Transmission is mainly by direct/indirect contact with infected animals or through the consumption of animal products (cattle, sheep, pigs, and dogs). However, transmission by a cat is unclear. In developing countries, contact and exposure to livestock are obscurely high. In our case, the cat might be a suspect of disease transmission.

Clinical features of brucellosis range from undifferentiated febrile illness to life-threatening organ involvement lasting a few days to 1 year. Nonspecific symptoms may be muscle pain, sweating, and arthralgia. Common complications reported are hepatitis (45%), osteoarthritis (22%), respiratory involvement mainly pneumonia (13%), cardiovascular system (9%), central nervous system (5%), and orchitis/epididymitis (9%). Our case had persistent fever involving the respiratory system, hepatobiliary, and osteoarticular system.

Abnormal laboratory parameters reported in the literature are leucocytosis (24.1%), anemia (23.9%), thrombocytopenia (15.8%), and pancytopenia (13.2%). The gold standard test for diagnosis is blood culture, but it only has a sensitivity of 48.3%. So, where blood culture is negative with a high index of suspicion, the serological test may be applied for early disease detection.

Hyposplenism is an acquired disorder of functional impairment of the spleen seen in hematological disease, hemoglobinopathies, and immunological diseases. The encapsulated organism like Streptococcus, Neisseria, and H. influenzae are major pathogens for bloodstream infection in these patients. Other less common pathogens are gram-negative bacilli, Capnocytophaga, Bartonella, malaria, and Babesia. The work-up for all tropical infection, including tuberculosis, were negative in our case. However, leptospiral serology was positive, which may be fortuitously positive as our country is endemic. Again, the prolonged fever with pneumonia, skeletal involvement with serological evidence, and response to doxycycline plus aminoglycosides, all favor the diagnosis of brucellosis.

**Conclusion**

Brucellosis in sickle cell disease with altered splenic function has not been reported in the literature. Are sickle cell diseases with/without functional spleen more prone to brucellosis? Also, is hydroxyurea responsible for increased predisposition to infection? So further research is required to address these questions. The unusual cause of febrile illness should be kept in the etiological checklist while dealing with undifferentiated prolonged febrile patients.

**Declaration**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

**References**

Kidney Biopsy: The Key to Diagnosis of a Systemic Illness

Georgi Abraham1*, Praveen S Raj2, Gopinathan Mathiyazhagan3, Milly Mathew4

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A 16-year-old Sudanese boy presented with fever, bone pain, and Acute Kidney Injury (AKI) for 2 months. He had tenderness in both knees, ankles, and chest wall. Serum creatinine—2.4 mg/dL, hemoglobin—10.6 gm/dL, white blood cells—8000 cells/mm³, platelets—190000/mm³, lactate dehydrogenase (LDH)—2755 U/L, serum uric acid—3.8 mg/dL, and urine analysis was unremarkable. Marrow aspirate and biopsy done from the posterior superior iliac spine in view of bone pains, Pyrexia of Unknown Origin, and raised LDH were unremarkable. A positron emission tomography (PET) scan showed increased uptake in both knees (Fig. 1), but a bone biopsy from the left distal end of the femur was not yielding. As he had AKI, a right-sided kidney biopsy was performed, a bedside touch imprint of the tissue showed large cells with multiple vacuoles within the cytoplasm and an enlarged nucleus with two–three inconspicuous nucleoli which was suggestive of infiltration with a high-grade neoplasm (Fig. 2). Histopathology revealed scattered glomeruli and tubules with an infiltration of sheets of small cells with scanty eosinophilic cytoplasm, enlarged hyperchromatic nuclei with inconspicuous nucleoli (Fig. 3). Immunohistochemistry of the renal biopsy was suggestive of a B cell neoplasm with a Ki-67 index of 95% and positivity for cellular Myelocytomatosis (proto-oncogene). He was subtyped as Burkitt lymphoma and was started on Lymphoma Malignancy B - 89 protocol protocol, with a chemotherapy backbone of cyclophosphamide, vincristine, and prednisolone. He had severe Tumor Lysis Syndrome which was medically managed. Creatinine came down to 0.6 mg/dL post-Cyclophosphamide, Vincristine, Prednisolone prephase, thus permitting us to initiate a full dose of Rituximab - Cyclophosphamide, Oncovin (Vincristine), Prednisolone, Adriamycin (Doxorubicin), Methotrexate Phase 1 Induction regimen chemotherapy, which was uneventful.

This highlights the value of kidney biopsy in making the diagnosis of a systemic illness when other measures were unsatisfactory.

Fig. 1: 18F-fluorodeoxyglucose-PET showing diffuse increased uptake

Fig. 2: Touch imprint showing large leukemic cells with multiple vacuoles (A)

Fig. 3: Renal biopsy showing infiltration of the tubulointerstitium with leukemic cells (B) and normal glomerulus (C). Hematoxylin and eosin stain under 45x magnification
A 65-year male, known diabetic, presented to casualty with dyspnea for the last 4 days. The patient had undergone debridement of the right foot 1 month back which revealed *Staphylococcus aureus* (methicillin-resistant). He was started on oral linezolid (600 mg). He was conscious oriented, had tachycardia and required oxygen support. On systemic examination, he had basal crepts. On examination of the tongue, the patient had blackish-brown discoloration involving the posterior two-thirds, sparing tip, sides, and buccal mucosa, (Fig. 1A) which could not be wiped off. He denied a history of smoking or excessive consumption of coffee, colored beverages, and tobacco. A swab culture was sent which was sterile. Linezolid was stopped. He was given chlorhexidine mouthwash for frequent use. Discoloration partially cleared on day 5 at the time of discharge (Fig. 1B). On discharge, he was advised to maintain good oral hygiene.

Linezolid-induced black discoloration of the tongue is a rare and benign disorder, which can be associated with multiple causative factors such as drugs (anticholinergics, antihypertensives, and antidepressants), smoking, drinking alcohol, chewing tobacco, poor oral hygiene, radiation therapy, etc. The exact method by which linezolid causes a black hairy tongue remains unknown, however, it has been studied that defect in the desquamation of the keratinized layer of the tongue causes overgrown as well as thickened papillae leading to a collection of microorganisms. The median period from initiating linezolid to the diagnosis of discoloration in reported cases is 2 weeks. In a study done by Hau in 2002, it was seen that the incidence of patients developing black hairy tongues as a result of receiving linezolid was as low as 0.2%. Once diagnosed, discontinuation of the drug and good oral hygiene resolves most of the problem.

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The **Big picture** of diabetes management across a broad patient population

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Avior
Paul Berg born (1926) an American biochemist, graduated from Pennsylvania State University in 1948 and earned his doctorate from Western Reserve University in 1952.

Paul Berg pursued further studies at the Institute of Cytophysiology in Copenhagen and at Washington University in St. Louis, United States of America, where he remained as assistant professor of microbiology until 1959. From 1959 he was associated with the medical school of Stanford University, serving as chairman of the Biochemistry Department and ultimately becoming director of the Center for Molecular and Genetic Medicine (1970).

During the 1950s, Paul Berg tackled the problem of how amino acids, the building blocks of proteins, are linked together by an RNA template as per the decoded form of DNA called messenger RNA. Paul Berg held that the amino acids did not directly interact with RNA but were linked together in a chain by special molecules he called adapters and are now known as transfer RNAs (tRNA). In 1956, Paul Berg demonstrated just such a molecule, which was specific to the amino acid methionine. Each of the 20 amino acids has its own such tRNA.

DNA is a large molecule that cannot be cleaved in a reproducible manner. Paul Berg began his experiment by cutting the mouse tumor virus the simian vacuolating virus 40 (SV40), DNA into pieces using restriction endonuclease, which had been discovered several years before by other researchers. These enzymes let him choose the exact sites to cut each strand of the double helix. Paul Berg decided to combine the DNA of the SV40 mice tumor virus into the common intestinal bacteria Escherichia coli and reconstructed the SV40 section of DNA. The foreign DNA incorporated into the host caused the synthesis of proteins that were not ordinarily found there. This new technique was named recombinant DNA. It offered the means to put genes into rapidly multiplying cells, such as bacteria, which would then produce the genes to make the corresponding protein in large amounts. Researchers then made use of simple organisms like bacteria and mammalian cells to grow valuable substances like hormones such as insulin, pharmaceuticals, and agricultural products.

Paul Berg understood the darker side of this technology as well. He knew that this method could offer a potential danger of creating a novel pathogen by accident or otherwise. He was influential in warning the scientific community of the problem.

Paul Berg was awarded the Nobel Prize in chemistry in 1980, for his studies of nucleic acid biochemistry with particular regard to recombinant DNA technology along with Walter Gilbert and Frederick Sanger who determined the base sequence of nucleic acids.

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Probiotics: An Armament for Vaginal Healthcare

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Sir,

Vaginitis, inflammation, or infection of the vagina, is common in women during the reproductive years and could be symptomatic or asymptomatic. Since the first report by Gardner and Dukes in 1955, researchers have been unable to establish the etiologic cause of vaginitis. Vaginitis is caused by a variety of infectious agents. These infections could lead to sexually transmitted diseases, endometritis, pelvic inflammatory disease, infertility, and cancer, and during pregnancy, increase the possibility of adverse pregnancy complications. As per a recent report, the global prevalence of bacterial vaginal infections in the general population ranges from 23 to 29%, where South Asia accounts for the highest incidence (29%).1 Further, a significant proportion (35.3%) of bacterial vaginosis (BV) was reported in Pakistan.1 Among pregnant women, the prevalence of BV was 37 and 39% in Bangladesh3 and Nepal,4 respectively, and was also associated with premature deliveries and a higher risk of late miscarriage.

The actual incidence of vaginal infection in India is not known, but it is assumed to be greater due to social behaviors, cultural behaviors, and the stigma women experience, which prevents them from acquiring knowledge, testing, and seeking treatment for vaginitis. In addition, poor menstrual hygiene practices are also strongly associated with an increased prevalence of vaginal infections.2 Douching is a prevalent technique among rural women for personal hygiene and to prevent pregnancy. Douching alters the vaginal microenvironment, increasing susceptibility to vaginal infections and cervical cancer. Besides, the low availability of female physicians in rural India decreases the access of women to reproductive healthcare.

Vaginitis has an increased incidence (48%) among women in developing countries with poor access to reproductive healthcare. Vaginitis could be more disadvantageous to women in India as breastfeeding and menstruation are a global threat, and newer strategies to combat antibiotic resistance (AMR) of pathogens and chronic recurrent infections are a global threat, and newer strategies to combat AMR are required.

Probiotics for vaginal health could improve the quality of life in women where antibiotics are ineffective in curing infection. However, there have been debates regarding the success of probiotic therapy in improving the vaginal microbiota, which could be due to the compositional quality of the probiotic formulations. Choosing appropriate probiotics with good viability and optimal functionality remains a global challenge with particular concern in developing countries such as India and Pakistan. Herein, considering the ethnicity variation in women in the indigenous beneficial microbes inhabiting the vagina could be more advantageous to ward off infections. The probiotics and their constituents could be used as oral or vaginal capsules/tablets or incorporated in hygienic materials with prebiotics to promote the growth of probiotics. This challenge can be achieved in collaboration with regulatory authorities, research groups, and relevant industries.

Increased awareness and improvement in menstrual health have been successfully implemented in India under Menstrual Hygiene Management scheme, which was established under the National Health Mission program in 2011. The scheme could be expanded further to women of reproductive age to encourage and facilitate regular screening for vaginal infections. Primary health care workers and physicians play an important role in providing service at the ground level and should be empowered with adequate knowledge about the diagnosis of vaginal infections and the usage of probiotics to treat these infections. In addition, an increase in resources directed toward public health policy can help to develop public interest and awareness about the impact of probiotics on women’s health.

Remdesivir in the Management of COVID-19!

Is there a Way Out of the Predicament?

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Dear Editor,

We came across the original article on the study of the efficacy of injection remdesivir in patients of coronavirus disease 2019 (COVID-19) by Chaudhry et al.1 In the index study, authors have tried to elucidate...
the beneficial effects of injection remdesivir by highlighting the significant reduction in days of hospital stay and change in the inflammatory marker levels. Since the beginning of the COVID-19 pandemic and the landmark ACTT-1 trial, it has been a roller-coaster ride for remdesivir. We would like to share certain experiences and viewpoints on the subject.

At the outset, COVID-19 has three main phases: viral phase, inflammatory phase, and long-COVID-19 phase. Pulmonary involvement, which is the leading cause of mortality, is an outcome of the inflammatory phase, and that is why corticosteroids have been found to reduce mortality. However, remdesivir has been shown to have no impact on mortality among COVID-19 patients with pulmonary involvement, which, in itself, is a case of exceeding expectations from an antiviral drug. The supportive evidence comes from the PINETREE trial, where remdesivir was used in the first week of illness (corresponding to the viral phase). The study demonstrated that just a 3-day course of early remdesivir prevented progression to hospitalization or death in 87% of nonhospitalized COVID-19 patients. This matches our unpublished results of using remdesivir on 10 unvaccinated high-risk subjects presenting in the early/viral phase of illness. We concur with the findings of Chaudhary et al. that remdesivir may be associated with a reduction in hospitalization duration. However, we have reservations regarding the timing of remdesivir, which could have been analyzed and presented.

Additionally, different durations of remdesivir courses have been analyzed from 10 to 5 to 3 days. Considering the noninferiority of a 5-day remdesivir course, the availability of similar data from the index study could have added value to the current evidence. The data regarding the ideal duration of remdesivir use among Indian subjects is still missing. Similarly, the timing of the treatment initiation by reporting the illness’s duration at the time of presentation could have made the readers wiser. Finally, the dose of steroids and other immunomodulatory agents like tocilizumab and tofacitinib could have been analyzed, given that these agents were commonly used during the mentioned time period.

In contrast to the current evidence, All India Institute of Medical Sciences/Indian Council of Medical Research national task force on COVID-19, in their latest version, recommend the use of remdesivir in moderate to severe cases. Evidence exists for the contrary, which supports the use of remdesivir in the early phases of viral illness. Similarly, the duration as well is recommended for 5 days, whereas the only study demonstrating mortality benefit with remdesivir has used it for only 3 days.

In conclusion, we would like to highlight that, in support of evidence-based medicine, remdesivir use should be restricted to cases who are at high risk and for 3 days only. Judicious and timely use of remdesivir will improve equity in availability and reduction in futile use of remdesivir.

**Contributorship Statement**

The conception was done by PKS and OK. PKS and OK wrote the manuscript. Proofreading was done by DC. PKS is the overall content guarantor.

**Manuscript Approval Statement**

The final submitted manuscript has been read and approved by all authors.

**References**

ESC 2021 & AHA/ACC/HFSA 2022 Guidelines recommend the early & concurrent use of

4 Pillars in management of HFpEF\(^1,2\)

- Beta-blocker
- ARNI
- MRA
- SGLT2i

In HF, Initiate Early for Improved Outcomes

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