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EDITORIAL

Need for Pandemic Preparedness Teaching during the Medical Curriculum

Vikram Londhey*

When we talk about 20-20 it goes without saying that we are talking about Indian Premier League matches. But when we talk about 2020, we get goosebumps even remembering the memories of the coronavirus disease 2019 (COVID-19) pandemic! It was just about that time when the National Medical Commission (NMC) rolled out the Competency-based Medical Education (CBME) curriculum for the first Bachelor of Medicine, Bachelor of Surgery (MBBS) batch admitted in the 2019–2020 academic year. Who knew that the timetable so well planned would go for a toss due to the global pandemic? It was indeed a learning lesson for all. The word pandemic is derived from the Greek words pan = all and demos = people. An epidemic that affects large geographic areas across the entire world at the same time is called a pandemic. Most of the pandemics are caused by viruses, for example, influenza, acquired immune deficiency syndrome, and now COVID-19. Susceptible individuals get affected, they transmit the organism to many individuals in a short time. International travel spreads the disease globally in a short time and a pandemic is declared. Hence, it is the need of the hour to sensitize the medical students by incorporating the pandemic preparedness module in the medical curriculum.

The definition of the Indian Medical Graduate (IMG) described in the CBME curriculum mentions lifelong learner as one of the roles of IMG; which turned out to be true for the entire medical fraternity and more so for the medical teachers in clinical branches who had to fight on different fronts managing patients with the new attire of PPE kits, training residents and students, answering to phone calls (24 × 7), attending online meetings and webinars for updating the knowledge, and keeping oneself fit. It was no less than walking on a thin-edged rope balancing the body without falling. One of the desirable outcomes of the CBME is to enable the IMG to be prepared for the unknown and to be able to understand, investigate, treat and prevent new, and emerging diseases as a clinician and a community leader. The emergence of COVID-19 and its rapid spread across the globe has further underlined the need to develop the skills of undergraduate students who form the young working force when they become interns and residents. Knowledge of the history of pandemics can help the students to learn about the causative agents, their route of transmission, incubation period, protective measures to be taken to prevent the transmission, understanding what are the precipitating factors, successful strategies and steps, and time taken to control it in future. What are the various trends in pandemics from the past; lessons learnt! What are the existing infection control practices? What is the role of the Hospital Infection Control Committee? What are the theories of emerging and reemerging infectious diseases? What are the diagnostic tools available to make the diagnosis? Is there a vaccine already available for the disease or it needs to be developed? The next step is to find out what treatment options are available for treating the disease. What are the signs and symptoms to identify the disease severity and how it is classified? The students should be made aware of the role of national and international bodies like Indian Council of Medical Research and the World Health Organization (WHO), respectively in handling the pandemics and the opportunities that can be available in these sectors in future for their career. The guidelines are prepared by the State and the Central government while handling such pandemics. Outbreak management which includes managing quarantine, isolation, contact tracing and reporting, and active surveillance so that measures to curtail the outbreak can be planned. The signs of an unusual increase in the number of cases during a given time at a particular place or clustering of deaths of individuals with similar signs and symptoms are a warning of a likely outbreak of an epidemic. In the era of social media, there are rumors and fake news which cause scare and havoc in the minds of the common man about any disease outbreak. Any loose talks or general comments in an open public forum should be avoided which can cause panic. Hence, confirmation of the outbreak by public health authorities is necessary to verify the diagnosis and confirm a pandemic. Dissemination of this new knowledge by appropriate and rational use of mass media without producing any scare among the people is essential. The news can be authentic when released by the official spokesperson of the Public Health Department.

The Public Health Administrative authorities take interdisciplinary measures by establishing rapid response teams. The Epidemic Act of 1897 has been referred to for formulating guidelines during the COVID-19 pandemic. Any pandemic is likely to cause the death of individuals on a large scale. The disposal of dead bodies with dignity is another issue in the health sector which has to be handled in a sensitive way and has to be told to the medical trainees. Data management and statistics are another important aspect of the pandemic and reporting of new cases, as well as how many have recovered from the disease and how many deaths have occurred needs to be maintained meticulously. This data is useful in finding out the incidence, prevalence, case fatality rate, and comorbidities in affected individuals. Settlement of the life insurance of the deceased is one more aspect in which a medical graduate should be sensitized and educated, which is not routinely taught in the curriculum.

The pandemic has other facets to be addressed like the restriction of global travel to curb the transmission of the disease and the impact on production in industries that can affect the health sector, for example, the import or export of raw materials in drug production and medical machinery production. What is the impact on health, economics and society as a whole due to the pandemic? This holistic approach is necessary without which the pandemic module will seem to be incomplete. Preparedness for a pandemic is a necessary step to successfully handle minimal loss of life, economic, and social disruption. This needs

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proper planning and coordination between the government and private health sector with the involvement of individuals, families, and the community. Activities that lead to capacity building; like training of trainers at the International, National, and local levels are essential to disseminating this knowledge about the pandemic module. Collaboration with WHO, the World Bank, the United Nations International Children’s Emergency Fund, and the World Food Program is necessary to deliver universal health coverage and basic health services. Teams have to be set up to look after essential supplies of life-saving medicines, personal protection equipment and mass vaccination programs once vaccine is available.

Considering the above facts, the pandemic module has been designed by NMC to ensure that the MBBS student acquires competencies in handling not only the illness; but also the social, legal, and other issues arising from such disease outbreaks. Roles of the IMG viz clinician, communicator, leader, member of the healthcare team, professional, lifelong learner, committed to excellence is ethical, responsive, and accountable to patients as described by NMC are very aptly needed during the pandemic. The pandemic module will also help the IMG in serving the people as a doctor, leader, and healer during the times of pandemic. The module has been very well prepared by the Academic Cell and Expert Group in a very short duration and will serve as a ready reference for the medical colleges and educational institutes that are actively involved in medical education and patient care. The skills needed to be acquired by the IMG in a phased-out manner include the history of the pandemic, infection control, diagnosis, disease management, epidemic management and research, communication skills, various stakeholders involved, how to access and utilize the resources available, coordination between government agencies, Nongovernmental Organizations, and community leaders.

Any module once prepared and released has to be evaluated as regards who are its stakeholders, what's are its implications to the various stakeholders and the impact it has created on a short as well as long-term basis. Thus there is certainly a need for teaching pandemic preparedness in the current medical curriculum and a positive step has been taken in this direction by NMC. However, wishful thinking would always say “Yeh, Wakt (pandemic) Fir Na Aye Dobara!”

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A Study on QT Dispersion before and after Thrombolysis in Acute Myocardial Infarction and its Prognostic Implications: A before and after Comparison Study

Apoorva M¹, Harshwardhan Khandait², Chinmay Guralwar³, Vinod Khandait⁴, Rashi Mahajan⁵, Chandrashekhar Atkar⁶

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ABSTRACT

Introduction: Acute myocardial infarction (AMI) stands as one of the most catastrophic occurrences in the progression of coronary artery disease. Measuring QT dispersion (QTd) is a fairly straightforward and noninvasive technique for predicting mortality in patients at high risk following a myocardial infarction (MI).

Objective: To measure the QT, corrected QT interval (QTc), QTd, and corrected QT dispersion (QTcd) intervals before and after thrombolysis in patients with AMI and to determine prognostic implications of QTd in AMI.

Materials and methods: This was a before and after comparison study conducted in the intensive care unit (ICU) of a tertiary care center in Central India. It was carried out in patients with AMI (ST-elevation myocardial infarction (STEMI)) who underwent thrombolysis in ICU. A total of 160 participants were enrolled over the time period of 24 months using the convenience sampling technique.

Results: The most prevalent (68 patients) risk factor among MI patients was hypertension (HTN). QT parameters such as QT, QTd, and QTcd showed significant statistical validation of p-value < 0.0001 when compared at admission and after thrombolysis. No significant difference (p > 0.05) in QT parameters at admission (QTd, QTc, and QTd) between anterior and inferior wall MI except for QT interval (p = 0.0010). Among the 33 patients who experienced arrhythmia, ventricular tachycardia was the most prevalent arrhythmia in 22 patients (13.75%). There was a significant statistical correlation between the arrhythmic event and the outcome of the patient (p < 0.0001). Patients who died had higher QT parameter values at admission, and these remained on the higher side even after thrombolysis, whereas those who got discharged had lower QT parameter values at admission, and their values decreased after thrombolysis.

Conclusion: Successful thrombolysis significantly decreases the QTd and thereby the arrhythmogenic potential, and thus can also be used as a reliable predictor of arrhythmia in patients with MI.

INTRODUCTION

Acute myocardial infarction (AMI) stands as one of the most catastrophic occurrences in the progression of coronary artery disease (CAD). It is the most common diagnosis in hospitalized patients in developed countries. Roughly 50% of AMI-related deaths occur before the patient arrives at the hospital.¹

Despite notable recent improvements in AMI treatment, its occurrence is linked to substantial early and late mortality. Early (both out and in-hospital) mortality is attributed to arrhythmic events, mainly ventricular tachycardia (VT) and ventricular fibrillation (VF).²

In an electrocardiogram (ECG), the QT interval represents the electrical activity of the ventricles during systole. Ventricular systole comprises two phases, including depolarization and repolarization. Repolarization time and, subsequently, the QT interval can be altered by any change in cardiac electrophysiology, autonomic tone, pharmacological characteristics, or electrolyte imbalance. Variable cells in distinct areas of the left ventricle have variable ventricular repolarization times, resulting in regional heterogeneity of repolarization time, which in turn results in QT interval dispersion in different ECG leads. Therefore, QT dispersion (QTd) shows typical desynchronization of distinct myocardial regions with variable excitability recovery periods.³

Increased dispersion of ventricular recovery time is thought to create a foundation that facilitates the occurrence of severe ventricular arrhythmias. The presence of ventricular tachyarrhythmia can lead to critical clinical manifestations and trigger instances of sudden cardiac death. Patients experiencing arrhythmias display notably higher QTd compared to similar patients who do not experience such occurrences.⁴

Materials and Methods

This was a before and after comparison study conducted in the intensive care unit (ICU) of a tertiary care center in Central India. It was

Measuring QTd is a fairly straightforward and noninvasive technique for predicting mortality in patients at high risk following a myocardial infarction (MI). Resting QTd fluctuates between 30 and 60 milliseconds in healthy subjects, but between 60 and 80 milliseconds in patients with CAD.³ QTd stands as a crucial indicator that mirrors fluctuations in ventricular repolarization and the potential for developing arrhythmias. Patients who have had successful thrombolysis have shown a decreased incidence of early and late mortality and higher left ventricular ejection fraction compared to individuals receiving conventional care. Additionally, studies have shown that in-hospital and long-term thrombolysis benefits are tightly connected to early reestablishment and maintenance of coronary blood flow. Besides having an impact on mechanical function, the effects of reperfusion therapy on electrical stability are a topic of curiosity.⁵

The present study was designed—(1) to measure the QT, corrected QT interval (QTc), QTd, and corrected QT dispersion (QTcd) intervals before and after thrombolysis in patients with AMI and (2) to determine prognostic implications of QTd in AMI.

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carried out in patients with AMI (ST-elevation myocardial infarction [STEMI]) who underwent thrombolysis in ICU. A total of 160 participants were enrolled over the time period of 24 months using the convenience sampling technique. The inclusion criteria were as follows:

- Patients with AMI (STEMI).
- Treatment with a thrombolytic agent (streptokinase).

The exclusion criteria were as follows:

- Drugs affecting QT interval.
- Prior coronary bypass surgery.
- Atrial fibrillation.
- Serum potassium <3.5 mmol/L or >5.0 mmol/L.
- Hypertrophic cardiomyopathy.
- Bundle branch blocks.
- Congenital long QT syndromes.

**Operational Definitions**

- AMI (STEMI) 5
  Detection of a rise and/or fall in cardiac biomarker values (preferably cardiac troponin), with at least one value above the 99th percentile upper reference limit (URL) IHD, ischemic heart disease. and with at least one of the following:
  - Symptoms of ischemia.
  - New ST-elevation at the J point in two contiguous leads with the following cut points:
    - Around ≥0.1 mV in all leads (except V2–V3).
    - In leads V2–V3, the following cut points apply:
      - Around ≥0.2 mV in men ≥40 years.
      - Around ≥0.25 mV in men <40 years.
      - Around ≥0.15 mV in women.
  - Development of pathologic Q waves on the ECG imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - QT interval: onset of QRS complex to the end of T wave.
  - Corrected QT interval (QTc): computed using Bazett’s formula for each lead:
    - QTc = QT/√RR. The typical QTc range falls between 0.35 and 0.43 seconds.
  - QT interval dispersion (QTd): difference between maximum and minimum QT interval.
  - Corrected QTc dispersion (QTcd): difference between maximum and minimum QTc interval.

**Collection of Data**

This study included patients with AMI, admitted to a tertiary care institution and hospital in Central India, who underwent thrombolysis with streptokinase (thrombolytic agent) (1.5 million units in 50 mL of 5% dextrose in water given intravenous [IV] over 1 hour). Details of the patients were collected using a predesigned proforma after taking well-informed written consent. The research was carried out after receiving approval from the institutional ethics committee.

All of the study participants’ 12-lead ECGs were captured at the time of admission, and a follow-up ECG 1 hour after thrombolysis was performed. ECG was recorded at a 25 mm/second paper speed. The QT interval was manually determined from the start of the QRS complex till the conclusion of the T wave. The T wave’s end was regarded as the location where it returned to the isoelectric line. If U waves were present, then the QT interval was measured from the onset of the QRS complex to the lowest point between T and U waves. The hospitalized patients were monitored for at least 5 days during their stay at the hospital for evaluation. The occurrence of abrupt death, VF, or poorly sustained VT was seen as an arrhythmic event.

**Statistical Analysis**

We inputted the collected data into a Microsoft Excel spreadsheet. To create tables and charts, we utilized Microsoft Word and Excel software on a Windows 7 operating system. The QTd was compared before and after thrombolysis in the study group by performing paired t-test for normalized data. For nonnormalized data, the Wilcoxon signed-rank test was used. p < 0.05 was taken as statistical significance. The statistical analysis was carried out using Statistics and Data Analysis Software version 14.0 software.

**Results**

A total of 160 patients were studied after considering the inclusion and exclusion criteria. Data on their demography, type of MI, QTd, and other relevant parameters were compiled and statistically analyzed. The following observations and results were obtained.

In the present study, as shown in Table 1, the mean age was 50.09 ± 12.76 years. There were 121 (75.63%) male subjects and 39 (24.37%) female subjects in our study. The mean age in male patients was 49.09 ± 13.29 years, and in female patients, it was 53.20 ± 10.47 years. There was no significant statistical correlation between age and gender of the study subjects (p = 0.08). The most prevalent (68 patients) risk factor among MI patients was hypertension (HTN) (42.50%), followed by diabetes mellitus (DM) in 57 patients (35.63%). A total of 106 patients suffered from anterior wall MI (66.25%), and 54 patients suffered from inferior wall MI (33.75%). For the sake of convenience, subtypes of anterior wall MI, such as anteroseptal and anterolateral, were considered under the heading of anterior wall MI, and the same was done for inferior wall MI.

In this study, as per Table 2, QT parameters such as QT, QTd, and QTcd showed significant

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At admission (in seconds)</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>After thrombolysis (in seconds)</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>0.37</td>
<td>0.06</td>
<td></td>
<td>0.34</td>
<td>0.06</td>
<td></td>
<td>&lt;0.0001, highly significant</td>
</tr>
<tr>
<td>QTd</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
<td>0.01</td>
<td>0.02</td>
<td></td>
<td>&lt;0.0001, highly significant</td>
</tr>
<tr>
<td>QTc</td>
<td>0.41</td>
<td>0.05</td>
<td></td>
<td>0.40</td>
<td>0.08</td>
<td></td>
<td>0.1180, highly significant</td>
</tr>
<tr>
<td>QTcd</td>
<td>0.04</td>
<td>0.04</td>
<td></td>
<td>0.02</td>
<td>0.03</td>
<td></td>
<td>&lt;0.0001, highly significant</td>
</tr>
</tbody>
</table>
A Study on QTd Before and After Thrombolysis

Statistical variation of p-value < 0.0001 when compared at admission and after thrombolysis. Thus, thrombolysis significantly decreased QT interval, QTd, and QTcd, but not QTc in our study.

As indicated in Table 3, no significant difference (p > 0.05) was seen in QT parameters at admission (QTd, QTc, and QTcd) between anterior and inferior wall MI, except for QT interval (p = 0.0010).

In our study, out of 160 study subjects, 127 of them did not have any arrhythmic episodes (79.38%). Among the 33 patients who experienced arrhythmia, VT was the most prevalent arrhythmia in 22 patients (13.75%), followed by ventricular premature capture beats in eight patients (5%) and only three patients suffered from VF (1.88%).

In our study, as per Table 4, for predicting the occurrence of arrhythmia, QT parameters such as QT interval, QTd, and QTcd showed significant statistical variation before and after thrombolysis (p < 0.05).

Out of the 33 patients who experienced an arrhythmic event, 16 patients (48.48%) were discharged, and 17 patients (51.52%) expired during their hospital course. Out of the 127 patients who did not experience any arrhythmic event, 119 patients (93.70%) were discharged, and eight patients (6.30%) expired during their hospital course, probably due to an arrhythmic event which could not be documented. A significant statistical correlation was seen between the occurrence of arrhythmic events and the patient’s outcome (p < 0.0001) (Fig. 1).

As shown in Figure 2, out of 160 study subjects, majority (135 patients) of the patients were discharged from the hospital (84.38%), and 25 patients expired during the hospital stay (15.63%).

As per Table 5, patients who died had higher QT parameter values at admission, and these remained on the higher side even after thrombolysis, whereas those who got

Table 3: Correlation of anterior wall MI and inferior wall MI and change in QT, QTd, QTc, and QTcd after thrombolysis

<table>
<thead>
<tr>
<th>Parameter at admission (in seconds)</th>
<th>After thrombolysis (in seconds)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>0.36</td>
<td>0.06</td>
</tr>
<tr>
<td>QTd</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>QTc</td>
<td>0.41</td>
<td>0.05</td>
</tr>
<tr>
<td>QTcd</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 4: Correlation of presence of arrhythmia with values of QT, QTd, QTc, and QTcd on admission and after thrombolysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arrhythmia</th>
<th>Admission (in seconds)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>Yes</td>
<td>0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>QTd</td>
<td>Yes</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>QTc</td>
<td>Yes</td>
<td>0.43</td>
<td>0.04</td>
</tr>
<tr>
<td>QTcd</td>
<td>Yes</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>QT</td>
<td>No</td>
<td>0.36</td>
<td>0.05</td>
</tr>
<tr>
<td>QTd</td>
<td>No</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>QTc</td>
<td>No</td>
<td>0.40</td>
<td>0.06</td>
</tr>
<tr>
<td>QTcd</td>
<td>No</td>
<td>0.04</td>
<td>0.03</td>
</tr>
</tbody>
</table>
A Study on QTd Before and After Thrombolysis

discharged had lower QT parameter values at admission, and their values decreased after thrombolysis.

Only QTcd showed significant statistical correlation after thrombolysis in predicting the outcome of MI patients (p = 0.0120) with the median [interquartile range (IQR)] QTcd of 0.01 (0–0.09) in discharged patients and 0 (−0.09–0.03) in patients who expired.

**DISCUSSION**

In this study, QTd is measured before and after thrombolysis in individuals with AMI at a tertiary care facility in Central India from November 2018 to October 2020. In total, 160 patients were enrolled during the study period based on inclusion and exclusion criteria.

The mean age of the participants in our study was 50.09 ± 12.76 years. The results of our study were comparable with the study carried out by Wahab et al., where the mean age was 58.95 ± 7.65 years. In our study, HTN was the most prevalent risk factor found in 68 patients (42.50%). While in the study conducted by Rahimi Darabad et al., who studied 160 MI patients, 53 patients had HTN (33.13%).

In the present study, majority of the patients suffered from anterior wall MI (106 patients, 66.25%), followed by 54 patients who suffered from inferior wall MI (33.75%). For the sake of convenience, subtypes of anterior wall MI, such as anteroseptal and anterolateral, were considered under the heading of anterior wall MI, and the same was done for inferior wall MI.

The results of our study were comparable with the study conducted by Wahab et al., which included 124 patients; among them 82 patients suffered from anterior wall MI (66.12%), and 42 patients suffered from inferior wall MI (33.87%).

There was no significant statistical correlation between site of infarction and type of risk factor present in our study (p > 0.05).

The standard of care for treating patients with CAD is typically percutaneous coronary intervention (PCI). However, due to the unavailability of PCI at our center, all patients in our study were administered thrombolytic therapy. The establishment and maintenance of coronary artery patency is the primary objective of thrombolytic therapy in AMI. This aims to improve left ventricular function and reduce mortality rates.

Our study found that thrombolysis decreased the QT interval, QTd, and QTcd, but not QTc. The results of our study were comparable with the study conducted by Agrawal et al. and Ornek et al., where decreases in the QTd and QTcd were observed due to thrombolytic therapy. Whereas the study conducted by Oni Heris et al. found that the difference was not statistically significant. When Moreno et al. evaluated 244 AMI patients who were given streptokinase, they also found that the dispersion parameters lowered. Their findings indicated that improved reperfusion status correlates with reduced QTd. The impact of IV streptokinase on QT and JT dispersions was evaluated by Lörincz et al. According to Nikiforos et al., effective thrombolysis following an AMI was linked to a notable reduction in QTd on the standard 12-lead ECG. Furthermore, Karagounis et al. and Fukushima et al. found that successful thrombolysis and successful recanalization respectively were associated with lower QTd. Hence, thrombolytic therapy helps normalize the electrophysiological environment, which is disturbed after AMI. Promptly reestablishing patency of vessels may potentially be associated with a lower incidence of arrhythmic events or mortality related to cardiac causes. Since patients are generally at a higher risk of dying from arrhythmias after MI, a measure of ventricular repolarization in these patients through reperfusion could have important clinical consequences.

In the present study, there was no statistically significant difference (p > 0.05) in QT parameters at admission (QTd, QTc, and QTcd) between anterior and inferior wall MI, except for QT interval (p = 0.0010). Thus, the type of vessel affected in MI does not affect QT parameters. The results were similar to the study conducted by Oni Heris et al., whereas the studies conducted by Moreno et al. and Ornek et al. found no significant difference in QTd between anterior and inferior infarcts. Similarly, the study by Tikiz et al. also denied the impact of the type of vessel involved and the QTd. There was a significant statistical correlation between arrhythmic events and the outcome of the patient (p < 0.0001) in our study. Therefore, patients of AMI with unusually high value of QTd upon presentation to the hospital and that remaining on the higher side post thrombolysis may be helpful to recognize patients with a heightened risk of arrythmias. In patients of AMI, QT parameters such as QT interval, QTd, and QTcd can be used to predict the occurrence of arrhythmic events.

In the present study, out of 160 study subjects, 25 patients expired during the hospital stay (15.63%). Patients who died had higher QT parameter values at admission, and these remained on the higher side even after thrombolysis. The above results align with the result of the study by Wahab et al., where QTcd showed significant statistical variation before and after thrombolysis in our study (p = 0.0120) and can be used as a prognostic marker in AMI patients.

**Study Limitations**

- Since the QT parameter measurement was done manually and the readings were subjective, this is a nonstandardized way, and that would preclude the use of this QT parameter commonly.
- It is largely unclear if QTd adds any additional information relative to other prognostic markers and to quantify that information even if it adds any.
- Lastly, the outcomes in the longer term were not studied in this study. Therefore, further research studies need to be done to confirm the clinical consequence of reduced QTd after thrombolysis.

**CONCLUSION**

The results of the present study show that successful thrombolysis is associated with lesser QTd on ECG in patients of AMI. Our data support the hypothesis that QTd after MI depends on reperfusion status. Reduction in QTd may be a mechanism of benefit of thrombolytic therapy. The predictive significance of prolonged QTd is still a subject of debate. Based on the existing data, it can be explained by the effect of scarred myocardium on future arrhythmogenicity, which is reflected in the amount of QTd. Thus, at the very least, it can be an indicator of increased risk of death after AMI.

**REFERENCES**


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**Table 5: QTcd and outcome in study population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Outcome</th>
<th>At admission (in seconds)</th>
<th>After thrombolysis (in seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcd</td>
<td>Mortality</td>
<td>Mean</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>QTcd</td>
<td>Discharge</td>
<td>Mean</td>
<td>Standard deviation</td>
</tr>
</tbody>
</table>

| QTcd Mortality | 0.08 | 0.07 | 0.08 | 0.03 |
| QTcd Discharge | 0.04 | 0.03 | 0.01 | 0.01 |
A Study on QTd Before and After Thrombolysis

Comparing the Knowledge, Attitude, and Practices on Oral Fluids, Electrolytes, and Energy Management in Non-diarrheal Illnesses across Different Physician Specialties in India

Prachee Sathe¹, Pavitra Chakravarty², Christian Tesado³, Priti Thakor⁴, Harshad Malve⁵

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ABSTRACT

Background: The management of non-diarrheal illnesses requires careful attention to maintaining the proper balance of fluids, electrolytes, and energy (FEE). Nevertheless, there is a limited amount of information accessible regarding the utilization of oral FEE formulations in the treatment of these conditions.

Objective: The objective of this study was to assess and contrast the levels of knowledge, attitude, and practices (KAP) among various medical specialties in India when it comes to addressing FEE imbalances in non-diarrheal illnesses through the use of oral FEE formulations, as well as to examine how these approaches influence perceived patient outcomes. We also present a subgroup analysis of KAP in healthcare personnel (HCPs) whose practices include 25% or more diabetic or geriatric patients.

Materials and methods: A cross-sectional online assessment was created and conducted among physicians (n = 494) representing different medical specialties in India, which include general practitioners (GPs) (n = 128), MD physicians (n = 121), gynecologists (n = 122), and pediatricians (n = 123).

Results: A total of 494 physicians across specialties, including GPs, MDs (MD internal medicine physicians), obstetrics and gynecologists (OB-GYN), and pediatricians, participated in the online assessment from September to October 2021. Knowledge scores were moderate across specialties, and there was no significant difference in knowledge level across specialties. More pediatricians and GPs than other HCPs consider FEE deficit to have a high impact on recovery. Further, pediatrician prescribers consider FEE management to be of high importance compared to other specialties. A significantly higher percentage of pediatricians assess all their patients (100%) for hydration levels, and significantly more gynecologists spend >5 minutes providing hydration advice to their patients. Among all specialties, MD and gynecologist prescribers are more likely to recommend oral FEE for patient recovery. HCPs with diabetes practice agrees slightly more than HCPs with geriatric practices that oral FEE management recommendations facilitate the speed of the recovery process from non-diarrheal illnesses in their patients. However, only approximately 30% of them recommend FEE to 70% of their eligible patients, of which approximately 70% of these HCPs give formal (written/electronic) prescriptions of ready-to-drink (RTD) fluids to their patients.

Conclusion: Enhancing the understanding of physicians across diverse specialties in India regarding oral FEE management and formulating recommendations for the utilization of oral FEE formulations in non-diarrheal conditions could lead to better outcomes. While knowledge and awareness of oral FEE management are similar across specialties, their practice behaviors vary. Additional research into this disparity and the assessment of the clinical advantages of oral FEE formulations in non-diarrheal illnesses among various specialties should be conducted.

INTRODUCTION

Dehydration is a prevalent nutritional state that can be potentially life-threatening and hampers the normal functioning of the body due to a reduction in total body water (TBW) content.¹ ² Water balance is well regulated in healthy adults, but there is an increased risk of imbalance in young infants and elderly people.³ Multiple factors predispose to dehydration in the elderly, including restricted access to fluid intake because of physical disability or polypharmacy, as well as usage of diuretics in addition to other drugs. Also, some elderly patients suffer from urinary incontinence. To save the embarrassment, they may restrict their oral fluid intake. Hence, this demographic is more prone to dehydration and imbalances in electrolytes, rendering them more vulnerable to related health complications and increased risk of associated morbidity and mortality.⁴ ⁵ Furthermore, individuals with prevalent chronic conditions like diabetes might also experience heightened susceptibility to deficits in fluids, electrolytes, and energy (FEE) due to metabolic alterations.

Dehydration can have a major impact, leading to impaired consciousness, weakness of extremities, orthostatic hypotension, and even tachycardia.⁶ Fluid and electrolyte therapy is the key to managing dehydration. The scenarios demanding such treatment vary widely, encompassing urgent instances of circulatory failure to less critical situations of slight dehydration stemming from gastroenteritis.⁷ Identification of dehydration is linked to the existence of other comorbidities, extended hospitalization periods, increased likelihood of future hospital stays, and elevated mortality rates.⁸ Dehydration in children caused by diarrhea is prevalent and has established recommendations/guidelines.

Nevertheless, prevalent conditions such as fever, nausea, vomiting, heat-related exhaustion, viral infections, upper respiratory tract ailments, as well as tropical diseases like dengue, malaria, typhoid, and urinary tract infections, can similarly result in overt or subclinical dehydration, triggering imbalances in FEE among both adults and children.⁹ ¹⁰

Metabolic alterations occurring in prevalent chronic conditions like diabetes, as well as hypermetabolic conditions like fever resulting from diseases such as dengue, malaria, and typhoid, along with infections like viral illnesses, upper respiratory tract infections, urinary tract infections, and heat-related ailments among adults, can also heighten individuals’ vulnerability to imbalances in FEE deficits.¹¹ ¹⁴ These

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circumstances can be further aggravated in older individuals or children due to their distinct physiological characteristics. The disruption in fluid and electrolyte equilibrium can result in indications like malaise, vomiting, and cognitive disarray. The sudden-onset can result in indications like malaise, vomiting, disruption in fluid and electrolyte equilibrium. Management strategies.

The sudden-onset can result in indications like malaise, vomiting, disruption in fluid and electrolyte equilibrium. As a result, extending the use of ORS to non-diarrheal conditions may not be fully sufficient. An ORS solution that is highly concentrated can substantially diverge. Typically, healthcare professionals possess a well-established understanding of the significance of fluid and electrolytes in diarrheal cases. However, within non-diarrheal illnesses, the need to treat and prevent dehydration, alongside energy management and its influence on the speed of recovery, remains incomplete.

Currently, there is a deficiency of comprehensive guidelines concerning the utilization of oral FEE solutions for non-diarrheal conditions in the Indian population. This study will, therefore, be the first to research the knowledge, attitude, and practices (KAP) of healthcare personnel (HCPs) around the usage of oral FEE formulations in non-diarrheal ailments. The aim was to contrast the KAP among various medical specialties regarding the management of FEE imbalances in patients with non-diarrheal ailments. The study also investigated how physicians from different specialties perceive the effect of FEE management on the rate of patients’ recovery. We also present here a subgroup analysis of KAP of HCPs practicing Diabetes and Geriatrics.

**Materials and Methods**

A cross-sectional online survey questionnaire was designed to evaluate the KAP of physicians across different specialties in India, focusing on their approach to the treatment of FEE deficit in patients with non-diarrheal illnesses. The comprehensive methodology can be found in the primary manuscript published earlier. “Prescribers” were defined as physicians who provide formal written or electronic prescriptions for oral FEE formulations to over 50% of their eligible patients for managing FEE deficits. Conversely, “nonprescribers” were defined as those who do not offer formal (written or electronic) prescriptions of ready-to-drink (RTD) fluids to eligible patients for managing oral FEE deficits. KAP and physician-perceived patient outcomes among different specialties of physicians were assessed.

General practitioners (GPs) and internal medicine physicians with >25% diabetic patients in their overall patient pool were considered to have diabetes practices (n = 190), while GPs and internal medicine physicians whose practices include 25% or more geriatric patients were considered to have geriatric practices (n = 180). This is done to seek specific data points from the physicians regarding the FEE needs in diabetic and geriatric patients.

**Statistical Analysis**

The total knowledge scores, with a maximum possible score of 6, were computed. A two-sample t-test was employed to examine differences in knowledge scores between prescribers and nonprescribers. The distinction in attitudes between prescribers and nonprescribers was assessed using Pearson’s Chi-squared test, and the outcomes were presented as proportions. Statistical analyses were conducted using Statistical Package for the Social Sciences 25, and all hypothesis tests were carried out with a two-tailed significance level (α) set at 0.05.

**Table 1: Demographics of participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (n = 494)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of practice years, mean (standard deviation)</td>
<td>17.8 (6.6)</td>
</tr>
<tr>
<td>Specialty, n (%)</td>
<td>Prescriber (n)</td>
</tr>
<tr>
<td>GP</td>
<td>128 (25.9)</td>
</tr>
<tr>
<td>• GP (diabetes)</td>
<td>128 (25.9)</td>
</tr>
<tr>
<td>• GP (geriatrics)</td>
<td>121 (24.5)</td>
</tr>
<tr>
<td>• MD physician</td>
<td>121 (24.5)</td>
</tr>
<tr>
<td>• MD (diabetes)</td>
<td>62 (12.5)</td>
</tr>
<tr>
<td>• MD (geriatrics)</td>
<td>59 (11.9)</td>
</tr>
<tr>
<td>• Pediatrician</td>
<td>123 (24.9)</td>
</tr>
<tr>
<td>• OB-GYN</td>
<td>122 (24.7)</td>
</tr>
<tr>
<td>Prescriber status, n (%)</td>
<td>248 (50.2)</td>
</tr>
<tr>
<td>• Prescriber</td>
<td>252 (51.0)</td>
</tr>
</tbody>
</table>

*Metro cities in India are major cities like Mumbai, Delhi, Chennai, and Kolkata*
Comparing the KAP on FEE Non-diarrheal Illnesses

**Results**

**Demographics**

The demographic characteristics of the participants are outlined in Table 1. The distribution of participants was evenly spread among different clinical specialties, prescriber statuses, and practice areas.

**Knowledge**

The average knowledge score assessing physicians’ understanding of dehydration and FEE management was moderate [mean: 3.28 (±1.36) out of 6]. There was no significant difference in knowledge level across specialties. Across different specialties, there was no significant difference observed in the understanding of the definition of dehydration, though FEE prescribers generally had a better understanding, with a significant

<table>
<thead>
<tr>
<th>Table 2: Knowledge, attitude, and practices (KAP) across specialties</th>
<th>All</th>
<th>GP</th>
<th>MD</th>
<th>Ped</th>
<th>OB-GYN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge (all prescribers and nonprescribers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average knowledge score</td>
<td>3.3</td>
<td>3.4</td>
<td>3.3</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Understanding of broad clinical definition of dehydration (%)</td>
<td>52</td>
<td>51</td>
<td>52</td>
<td>59</td>
<td>48</td>
</tr>
<tr>
<td>Perception of high prevalence of dehydration among outpatients and inpatients (%)</td>
<td>56</td>
<td>56</td>
<td>41</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Attitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The perceived high importance of FEE management awareness and application in non-diarrheal illness (%)</td>
<td>53</td>
<td>52</td>
<td>55</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>The perceived high importance of FEE management for patient health during recovery from non-diarrheal illness (%)</td>
<td>48</td>
<td>45</td>
<td>45</td>
<td>48</td>
<td>56</td>
</tr>
<tr>
<td>Perceived high level of impact of chronic undetected dehydration on health (%)</td>
<td>51</td>
<td>54</td>
<td>55</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>Practice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess patients for hydration level (%)</td>
<td>66</td>
<td>60</td>
<td>61</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>Recommend oral FEE to &gt;70% patients (%)</td>
<td>30</td>
<td>31</td>
<td>30</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Time spent providing hydration advice &gt; 5 minutes (%)</td>
<td>35</td>
<td>27</td>
<td>30</td>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>Give formal (written/electronic) prescriptions of RTD fluids (%)</td>
<td>71</td>
<td>68</td>
<td>72</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Perceived patient outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aid in improving the speed of recovery (%)</td>
<td>87</td>
<td>88</td>
<td>82</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Recovery duration is shortened (%)</td>
<td>98</td>
<td>98</td>
<td>97</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>Mean estimated days of shortened recovery duration via written prescription vs verbal advice</td>
<td>3.83</td>
<td>3.87</td>
<td>3.09*, 3.73**</td>
<td>3.6</td>
<td>4.4</td>
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</tbody>
</table>

*MD physicians with diabetes practice; **MD physicians with geriatric practice

<table>
<thead>
<tr>
<th>Table 3: Knowledge, attitude, and practices (KAP) across HCPs with diabetes and geriatric practices</th>
<th>HCPs with diabetes practice</th>
<th>HCPs with geriatric practice</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>GPs</td>
<td>MD physicians</td>
</tr>
<tr>
<td>Knowledge</td>
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<tr>
<td>Average knowledge score</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Understanding of broad clinical definition of dehydration (%)</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>Perception of the high prevalence of dehydration among outpatients and inpatients (%)</td>
<td>56</td>
<td>42</td>
</tr>
<tr>
<td>Attitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The perceived high importance of FEE management awareness and application in non-diarrheal illness (%)</td>
<td>52</td>
<td>58</td>
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<tr>
<td>High level of importance to FEE management for patient health during recovery from non-diarrheal illnesses (%)</td>
<td>45</td>
<td>47</td>
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<tr>
<td>Perceived high level of impact of chronic undetected dehydration on health (%)</td>
<td>51</td>
<td>54</td>
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<tr>
<td>Practice</td>
<td></td>
<td></td>
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<tr>
<td>Assess patients for hydration level (%)</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>Recommend oral FEE to &gt;70% patients (%)</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Time spent providing hydration advice &gt; 5 minutes (%)</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Give formal (written/electronic) prescriptions of RTD fluids (%)</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Perceived patient outcome</td>
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<td></td>
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<tr>
<td>Aid in improving the speed of recovery (%)</td>
<td>88</td>
<td>87</td>
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<td>Recovery duration is shortened (%)</td>
<td>98</td>
<td>93</td>
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<tr>
<td>Mean estimated days of shortened recovery duration via written prescription vs verbal advice</td>
<td>3.87</td>
<td>3.09</td>
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</table>
Comparing the KAP on FEE Non-diarrheal Illnesses

Across different specialties, the prescribers generally had a better understanding of fluids and electrolyte deficits, with significant differences among pediatrician prescribers vs nonprescribers (Fig. 2). Unlike other specialties, MD physicians were significantly more likely to perceive low prevalence vs a significant prevalence of dehydration in both outpatients and inpatients (Fig. 3).

Knowledge among HCPs with Diabetes and Geriatric Practice

While an understanding of the broad clinical definition of dehydration is similar across GPs and MD physicians (51 and 55%, respectively), a significantly higher number of MD physicians, as compared to GPs with diabetic practices, perceive nonspecific clinical presentation as a major clinical challenge in the assessment of dehydration (Table 3 and Fig. 4). Knowledge about dehydration was observed to be similar among GPs and MD physicians with geriatric practices with almost half of them understanding the clinical definition of dehydration (Table 3 and Fig. 4).

A significantly higher percentage of MD physicians, as compared to GPs with diabetic practices, perceive a low prevalence of dehydration among their patients (68 vs 52%, respectively). Also, though the perception of a high prevalence of dehydration was low (41%), it was similar among GPs and MD physicians with a geriatric practice (Table 3 and Fig. 5). Similar percentages (64–77%) of MD physicians and GPs with diabetic and geriatric practices think poorer outcomes are linked with dehydration among patients admitted to hospitals and care homes, that is, increased morbidity and mortality (Table 3 and Fig. 5).

Significantly more MD physicians, as compared to GPs with diabetic practices, perceive headache (82 vs 64%) and decreased skin turgor (58 vs 52%) as presenting symptoms and signs of dehydration (Fig. 6). Occurrence of thirst (88%) and dry mucous membranes (81 and 86%) were reported as the most common physical signs and symptoms of dehydration by the GPs and MD physicians with geriatric practices, respectively (Fig. 6).

Similar percentages (55–63%) of MD physicians and GPs with diabetic and geriatric practices perceived that mild to moderate dehydration can impair performance on tasks such as short-term memory, arithmetic ability, psychomotor skills, and concentration/attention, indicating awareness to be at par across diabetes and geriatric practice (Fig. 7).

Attitude

Physicians across specialties perceived FEE management awareness and application in non-diarrheal ails as highly important (Table 2). However, a slightly higher percentage of pediatricians considered FEE management to be of high importance as compared to other specialties (Table 2). In general, significantly more prescribers vs nonprescribers agreed that FEE management is highly important and aimed at patient health throughout recovery from non-diarrheal ailment, and this was consistent across specialties (Fig. 8). Across all the specialties, prescribing physicians reported a higher impact of chronic undetected dehydration on health vs nonprescribers; however, the differences only met statistical significance for MD physicians and gynecologists (Fig. 9).

Practice

On average, 66% of the HCPs assess all their patients (100%) for hydration levels, with a significantly higher rate in pediatricians vs MD physicians and GPs (Fig. 12). HCPs were likely to recommend oral FEE for patient recovery similarly across specialties (Table 2). On average, HCPs were most likely to recommend oral FEE for conditions like general weakness; however, gynecologists recommended it slightly more for upper respiratory tract infection (Fig. 13). The HCPs, across specialties, have similar patterns of practice with only approximately 30% of them recommending FEE to a high percentage (>70%) of their patients (Table 2). Generally, most physicians who recommend RTD fluids with FEE do so for increased compliance, taste, and convenience (Fig. 14). In general, most
Comparing the KAP on FEE Non-diarrheal Illnesses

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Similar percentages (60–61%) of GPs and MD physicians with diabetes and geriatric practice spend 0–5 minutes providing hydration advice to eligible patients. Significantly more gynecologists spend >5 minutes providing hydration advice compared to GPs and MDs (Table 2). In general, as per HCP’s opinion, more patients opt for powder/RTD WHO-ORS and RTD FEE compared to other types of oral fluids; significantly fewer pediatric patients opt for RTD FE compared to obstetrics and gynecologists (OB-GYN) or GP patients (Fig. 15).

**Fig. 2:** Physicians’ perception of reasons for FEE deficits in illness

**Fig. 3:** Healthcare personnel’s (HCP’s) perception of dehydration prevalence in a healthcare setting

**Fig. 4:** Understanding of the definition of dehydration by HCPs with diabetes and geriatric practice
Comparing the KAP on FEE Non-diarrheal Illnesses

Fig. 5: Perceived prevalence of dehydration by HCPs with diabetes and geriatric practice

Fig. 6: Physical signs and symptoms of dehydration reported by HCPs with diabetes and geriatric practice

Fig. 7: Impairment of tasks due to dehydration reported by HCPs with diabetes and geriatric practice
Comparing the KAP on FEE Non-diarrheal Illnesses

There were no significant differences in the time spent providing hydration advice between diabetic and geriatric GPs and MD physicians. However, only 25% of GPs and 35% of MD physicians with diabetes practice and 29% GPs and 25% of MD physicians with geriatric practice spend >5 minutes providing hydration advice to their eligible patients, with prescribers giving more time than nonprescribers in both categories (Table 3 and Fig. 16). However, approximately only 30% of them recommend FEE to 70% of their eligible patients of which approximately 70% of HCPs give formal (written/electronic) prescriptions of RTD fluids to their patients (Table 3).

There was no difference observed in the practice of GPs and MD physicians with diabetes and geriatric practices about conditions in which they prescribed FEE, though both the categories most commonly prescribe oral FEE for general weakness followed by upper respiratory tract infection (Fig. 17).

Taste/palatability, convenience, and compliance were cited as the reasons for recommending RTD for FEE in patients by both MD physicians and GPs with diabetes and geriatric practices (Fig. 18).

In general, as per the opinion of HCPs with diabetes and geriatric practices, more patients opt for powder/RTD World Health Organization-ORS and RTD FEE compared to other types of oral fluids (Fig. 19).

**Physicians Perceived Patient Outcomes across Specialties**

The majority of physicians (87%) concurred that recommendations for FEE management would enhance the speed of recovery (Fig. 20). This agreement was uniform across different medical specialties and 29% of MD physicians with geriatric practice spend >5 minutes providing hydration advice to their eligible patients, with prescribers giving more time than nonprescribers in both categories (Table 3 and Fig. 16). However, approximately only 30% of them recommend FEE to 70% of their eligible patients of which approximately 70% of HCPs give formal (written/electronic) prescriptions of RTD fluids to their patients (Table 3).

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In general, as per the opinion of HCPs with diabetes and geriatric practices, more patients opt for powder/RTD World Health Organization-ORS and RTD FEE compared to other types of oral fluids (Fig. 19).

**Fig. 8:** Impact of FEE management on patient health throughout recovery from non-diarrheal illness across specialties

**Fig. 9:** Impact of chronic undetected dehydration on health across specialties

**Fig. 10:** Perception of the level of importance of FEE management for patient health during recovery from non-diarrheal among physicians with diabetes and geriatric practice
specialties, with a considerable proportion of healthcare professionals (HCPs) expressing consensus that RTD FEE formulations prove more efficacious in hastening recovery time, and patients recover faster when provided with written prescriptions of RTD FEE formulations as compared to verbal guidance alone (Table 2). Among approximately 40% of physicians across specialties who were able to provide an estimate, gynecologists perceived the greatest reduction in recovery duration with the provision of written prescriptions vs verbal advice (averaging 4.4 days), closely followed by GPs (averaging 3.8 days) (Table 2).

**Perceived Patient Outcome among HCPs with Diabetes and Geriatric Practice**

Healthcare personnel (HCPs) with diabetes and geriatric practices agree that oral FEE management recommendations aid in improving the speed of patient recovery from non-diarrheal illnesses (Fig. 21).

Healthcare personnel (HCPs) with diabetes and geriatric practices agreed that recovery duration is shortened in patients taking RTD format (Table 3). The perceived mean estimated decrease in time required for recovery when a prescription is given in written format vs verbal advice ranged from 3.09 to 3.87 days. (Table 3).

**Discussion**

Dehydration, a highly prevalent condition, is often under-recognized and inadequately managed both in the outpatient department and inpatient department setting.

A decrease in total body water by as little as 2% due to dehydration can lead to noteworthy declines in physical, visuomotor, psychomotor, and cognitive capabilities.
Additionally, the research highlighted a 17% mortality rate within 30 days among older adults whose primary diagnosis as per the International Classification of Diseases was dehydration, with the 1-year mortality rate reaching nearly 50%. Although dehydration is frequently associated with an increased risk of hospitalization and mortality, there is a lack of comprehensive recommendations on the role of oral FEE in non-diarrheal illnesses in Indian patients. Due to varying presenting signs and symptoms in non-diarrheal illnesses, diagnosing dehydration in such patients is even more challenging.

The treatment of acute illnesses can be time-sensitive, and therefore, timely FEE management plays a key role in their treatment. An Indian expert panel concluded in their discussion that nutrition and hydration are central to recovery from acute illnesses, and oral FEE should be recommended as part of the core treatment from day 1 of non-diarrheal illness for improved patient outcomes. Commercially available appropriately formulated oral formulations based on individual taste preferences with the right balance of FEE were preferred by the panel.

This research provides valuable insights into current KAP among different specialties of physicians in India regarding their treatment of FEE deficits in patients with non-diarrheal illnesses.
Comparing the KAP on FEE Non-diarrheal Illnesses

It was observed that knowledge scores across different physician specialties are only "moderate," suggesting a potential knowledge deficiency regarding FEE management among physicians across specialties. Overall, prescribers of FEE formulations generally had a better understanding of fluid and electrolyte deficits compared to nonprescribers. The reason for this difference may have been their hands-on experience with prescribing FEE formulations. A significant difference was observed among pediatrician prescribers vs nonprescribers and other specialties in the perceived level of importance of FEE management for outpatients in common non-diarrheal illnesses. This could have been because fluid, electrolyte, and caloric needs can be different in children with non-diarrheal dehydration as compared to adults. A group of experts suggested that physicians...
Comparing the KAP on FEE Non-diarrheal Illnesses

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should recommend and oversee dehydration therapies for every patient with equivalent diligence as they would for conditions involving diarrhea, and the suggestion is to advocate for early oral FEE replacement at the onset of the illness (during the patient’s visit or on the first day of illness).1,2 Furthermore, the panel concluded that RTD formats and premixed ORS are desirable because of their known concentration of electrolytes and palatable taste to increase compliance in children vs the variable homemade solutions, which may have errors in preparation.1,7 Among various specialties, significantly more pediatricians assessed their patients for hydration levels, and gynecologists spent more time on hydration advice for patients. However, across specialties, the surveyed HCPs had similar patterns of practice regarding the recommendation of FEE; only 30% of the HCPs recommend FEE to a high percentage (>70%) of their patients.

Intervention to enhance understanding of dehydration and FEE management in non-diarrheal conditions could potentially lead to improved disease outcomes in real-world scenarios. This is supported by the observation that higher knowledge scores correlated with a more proactive approach to prescription and a perceived enhancement in patient outcomes. With the growing body of evidence underscoring the advantages of hydration, future panels responsible for formulating guidelines should contemplate the inclusion of dehydration evaluation and a recommended minimum allocation of time for hydration advice as part of the standard care protocol for patients with non-diarrheal illnesses.

However, the survey of knowledge and prescription behavior had an interesting observation. While pediatricians and GPs perceived the high impact of FEE deficits on the recovery of patients, MD physicians and gynecologists appeared to be numerically more likely to recommend FEE formulations for patient recovery.

An additional important observation is that GPs and gynecologists in India exhibited a stronger perception compared to other medical specialties that the utilization of RTD solutions and written prescriptions, in contrast to verbal guidance, contributed to a decrease in recovery time. This implies that these physicians may hold the belief that patients are more likely to adhere to the consumption of such FEE formulations when provided in RTD form and that written prescriptions reinforce their significance in the recovery process.

Further, the study demonstrated an overall lack of knowledge among diabetes practitioners as <50% of these practitioners perceived a high level of importance to FEE management for patient health during recovery. This is further seen translating into their clinical practice, with only 31% of them recommending FEE formulations to 70% of their eligible patients. Among the diabetic practitioners who recommend FEE formulations, a very high percentage prefer giving a formal written prescription. Interestingly, while the knowledge and the clinical practice are suboptimal, a high number of HCPs with a diabetes practice perceive that oral FEE management aids in improving the speed of recovery and shortens the recovery duration from nondiarrhoeal illnesses in patients.

The study showed a similar pattern in HCPs with a geriatric practice. Overall knowledge and understanding of dehydration of physicians treating an elderly population was suboptimal, with only half of the physicians having a clear understanding of the definition of dehydration. While the awareness was low, understanding of various aspects like symptoms, risk factors, and impact of dehydration in patients was quite similar among GPs and MD physicians with geriatric practices. Physicians with geriatric practices agree on the impact of oral FEE management in recovery from non-diarrheal illnesses; however, they spend limited time on hydration advice. While the majority agree that FEE formulations speed up recovery and shorten the recovery time, only approximately 30% of HCPs with geriatric practices are likely to recommend FEE therapy to 70% of their eligible patients. These observations highlight the opportunity for educating physician regarding the importance of screening and proactively managing their elderly patients with non-diarrheal illnesses for dehydration. It also opens avenues for more patient education, helping create awareness of the

![Fig. 20: Physician's perception of whether FEE recommendation aids in improving the speed of patient recovery](image)

![Fig. 21: Perception of HCPs with diabetes and geriatric practice on whether FEE recommendation aids in improving the speed of patient recovery](image)
Comparing the KAP on FEE Non-diarrheal Illnesses

significance of FEE formulations in managing these conditions.

The results of this survey indicate the need to create more awareness of the importance of managing nondiarrhoeal dehydration among different patient populations. This warrants educating physicians at all levels, including the primary care level, to screen and treat FEE deficits. Moreover, education that helps patients and caregivers identify early signs of dehydration, especially in more vulnerable populations like the elderly, diabetics, and children, may also help in implementing better FEE management.

Hence, future guidelines should take into account these preliminary results, and additional investigations should be undertaken to assess the practical disparities in recovery time associated with different formats of FEE formulations and types of prescriptions.

This research had several limitations. Though the overall study sample size is large, the sample size across individual specialties might be inadequate to reach definitive conclusions. A larger sample size for each specialty may be needed to draw more definitive conclusions. When categorizing participants into prescribers or non-prescribers, the prescriber criteria were established based on consensus among key opinion leaders (KOLs). Using an alternative definition could potentially have led to dissimilar outcomes. Additionally, the reliance on self-reported data through the questionnaire may have introduced biases in the responses. It’s important to acknowledge these limitations while interpreting the results.

However, given that this is the initial study assessing KAP about FEE management and the application of FEE formulations in non-diarrheal illnesses in India. Additional real-world investigations targeting specific conditions within non-diarrhoeal illnesses across diverse medical specialties might be necessary to verify and examine the reduction in illness duration when FEE formulations are appropriately prescribed and adhered to. This potential can enhance patients’ quality of life and potentially decrease the utilization of healthcare resources, thereby alleviating the burden on both patients and healthcare systems.

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REFERENCES
Critical Appraisal on the Role of Warfarin in the Current Era

Tiny Nair*

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ORIGINAL ARTICLE

ABSTRACT

Warfarin has been the most extensively used oral anticoagulant (OAC) in medical settings for over 60 years. Its uses, potential adverse effects, and methods for reversing its effects have been firmly established, rendering it a routine medication in medical settings where most professionals feel at ease employing it. Compared to other vitamin K antagonists (VKAs), such as acenocoumarol, warfarin offers benefits like diminished prothrombin time (PT) assays leading to enhanced oral anticoagulation. Observations over the past few years have seen the inclusion of novel/direct OACs (NOACs/DOACs) in the anticoagulant armamentarium. Although DOACs have several advantages, warfarin still has an important role in subsets of patients where DOACs are contraindicated, not well-tolerated, or cannot afford DOACs due to higher costs. Moreover, there are patient profiles where warfarin is still considered a superior choice compared to DOACs, such as age group of >75 years, kidney failure with creatinine clearance (CrCl) below 30 mL/minute, and prosthetic mechanical valve replacement. Precise management of the international normalized ratio (INR) is crucial for the effectiveness of warfarin treatment. INR monitoring is the major concern in the Indian context due to the lack of laboratories for standardized measurement. Adopting strategies such as point-of-care INR monitoring devices and anticoagulation clinics can help to improve clinical outcomes with warfarin therapy. The present review provides a critical overview of the role of warfarin therapy in the current OAC arsenal and strategies for improving therapeutic control and patient adherence.

INTRODUCTION

Since its discovery in 1933, warfarin has become the prominent choice for oral anticoagulant (OAC) use in the management and prophylaxis of thromboembolic disorders.1-3

The nomenclature “warfarin” is constructed from the abbreviation WARF (Wisconsin Alumni Research Foundation) combined with the suffix “-arin,” which is derived from the term “coumarin.” In Wisconsin, Karl Link and Harold Campbell inferred that the anticoagulant present in sweet clover was responsible for an outbreak of cattle death in the Northern United States of America (USA), which is 3,3’-methylenebis(4-hydroxy coumarin). Warfarin, synthesized in 1948, was originally authorized for use as a rodenticide in the USA and later for human use in 1954.4

Warfarin is widely employed to treat and prevent blood clot formation. The approved clinical applications for warfarin by the Food and Drug Administration (FDA) encompass the following:5

- Prophylaxis and management of venous thrombosis (VT) and pulmonary embolisms (PE).
- Prevention and treatment of thromboembolic complications arising from atrial fibrillation (AF) or cardiac valve replacement.
- Decrease in mortality rate, recurrence of myocardial infarction, and thromboembolic incidents subsequent to a myocardial infarction.

WARFARIN VS OTHER VKAS

Molecular as well as Pharmacokinetic Differences

Oral anticoagulants (OAC) are a part of the 4-hydroxycoumarins group, acting by suppression of vitamin K epoxide reductase complex subunit 1 (VKORC1) in a noncompetitive manner (Fig. 1).6,7 Following oral administration, VKAs are readily absorbed through the gastrointestinal tract, displaying full oral bioavailability. However, S-acenocoumarol experiences substantial first-pass metabolism. Peak plasma concentrations are attained within a short duration. Despite showing an affinity for protein binding in human plasma (approximately 98%), these compounds also showcase variations in their volumetric distribution. In overextended therapeutic durations, the plasma levels of acenocoumarol are notably diminished in comparison to those of warfarin or phenprocoumon.6,7

Phenprocoumon, acenocoumarol, and warfarin exhibit distinct elimination half-lives (t1/2) spanning 110–130, 1.8–6.6, and 24–58 hours, respectively. Warfarin’s metabolic clearance predominantly involves hydroxylation and reduction, with 80% excreted through urine and 20% through feces. S-warfarin metabolism primarily relies on the enzymatic activity of CYP2C9, while hydroxylation of the R-enantiomer is mediated by CYP1A2, CYP2C8, CYP2C19, and CYP3A4. Conversely, CYP2C9 is responsible for the hydroxylation of the S-form of acenocoumarol and about 60% of the R-enantiomer. In the case of phenprocoumon, its metabolism is chiefly governed by CYP2C9 and CYP3A4, acting as the primary enzymes.7

Clinical Evidence on Outcomes of Warfarin vs Other VKAs

Only a few studies are available comparing the effectiveness and safety of warfarin and acenocoumarol.6 Acenocoumarol, due to its brief half-life (6–8 hours), may induce routine variations in factor VII levels. These variations may affect prothrombin time (PT) and alterations in the levels of oral anticoagulation.6 Acenocoumarol is associated with a twofold increased risk of causing instability in the anticoagulation process compared to warfarin.9

A comparative study between acenocoumarol and warfarin later showed fewer PT assays and enhanced oral anticoagulation stability. Warfarin was associated with significantly better quality of treatment (72 vs 67%, p < 0.001, respectively) and a higher proportion of patients within the assay range (warfarin 50.7% compared to acenocoumarol 34.5%, p < 0.05).10

A study assessing the therapeutic stability of acenocoumarol and warfarin in AF patients showed that within the acenocoumarol group, there were 0.3 visits per patient per year where the international normalized ratio (INR) was ≥6, as opposed to 0.07 visits in the warfarin group (p = 0.003), suggesting that anticoagulation stability of acenocoumarol is lower than warfarin.11 Another study demonstrated that warfarin was more stable...
Role of Warfarin in the Current Era

Apixaban, edoxaban, and rivaroxaban, along with the direct thrombin inhibitor dabigatran, are collectively referred to as NOACs/DOACs and have been approved. DOACs have several advantages, such as the absence of routine anticoagulation monitoring, anticipated pharmacokinetic profile, and lesser food-drug and drug–drug interplay. However, warfarin still has an important role in a specific subset of patients where DOACs are contraindicated, not well tolerated, or the subject cannot afford the high cost of therapy with DOACs.¹⁴

A Well-controlled “Time-in-therapeutic Range (TTR)” Patient on Warfarin is no Different from DOAC

The multinational DOAC randomized controlled trials (RCTs) have shown parallel outcomes.

In the Randomized Evaluation of Long-term Anticoagulation Therapy trial, dabigatran exhibited an efficacy rate of 64%. The Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism trial in Atrial Fibrillation trial reported an efficacy rate of 55% for rivaroxaban. Similarly, the Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation trial showed an efficacy rate of 62% for apixaban.¹⁵ This translates to the fact that warfarin with a good TTR is equivalent to DOACs in safety and efficacy.

The initial meta-analysis conducted by Carmo et al. marked the pioneering effort to assess the relative effectiveness and safety of all available DOACs in contrast to warfarin across distinct center-specific TTR (cTTR) thresholds for the prevention of stroke in patients with AF. This comprehensive analysis included four substudies pertaining to TTR, encompassing a cumulative cohort of 71,222 patients. The results unveiled a distinct advantage associated with DOACs over warfarin in terms of diminishing the risk of stroke and systemic embolism (SSE), notably prominent among patients with a cTTR below 60% [hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.68–0.90] and those within the range of 60–70% (0.82, 0.71–0.95). However, this beneficial effect was not sustained for patients exceeding a cTTR threshold of 70% (1.00, 0.82–1.23), with a statistically significant interaction emerging between cTTR subgroups of <70 and ≥70% (p = 0.042). Furthermore, the assessment of major or nonmajor clinically relevant (NMCR) bleeding risk exhibited a notable reduction in patients receiving DOACs compared to that administered warfarin across all cTTR subgroups, except for patients with a cTTR ≥70% (HR 0.84, 0.64–1.11). The interaction analysis for cTTR <70 vs ≥70% did not reach statistical significance (p = 0.271). The study’s findings collectively demonstrated that the superiority of DOACs over warfarin for the prevention of stroke diminishes beyond a cTTR threshold of approximately 70%.¹⁶

Direct OACs (DOACs)

Contraindicated in Patients with Mechanical Prosthetic Valves

Dabigatran has been demonstrated to be a potent substitute for warfarin in patients with AF. However, a study conducted by Eikelboom et al. revealed that the utilization of dabigatran among patients with mechanical heart valves demonstrated elevated occurrences of both thromboembolic events and bleeding complications when compared with warfarin. Among the dabigatran-receiving group, nine patients (5%) experienced an ischemic or unspecified stroke, while no such incidents were recorded in the warfarin-treated group. Moreover, the occurrence of major bleeding events was observed in seven patients (4%) treated with dabigatran, in contrast to two patients (2%) within the warfarin group.¹⁷

Benefits of DOACs in mechanical prosthetic valve remains unproven.¹⁸ Currently, DOACs are not advised for use in cases of moderate to severe mitral stenosis and among patients with mechanical heart valves.¹⁹

Warfarin vs DOACs in Specific Situations

Left Ventricular (LV) Thrombi

A multicentric, retrospective cohort study compared the results associated with DOACs and warfarin in 514 eligible patients with LV thrombi, confirmed by echocardiography (n = 300 received warfarin and n = 185 received a DOAC) over a median follow-up duration of 351 days; DOAC therapy vs warfarin use (HR, 2.71; 95% CI, 1.31–5.57; p = 0.01), and initial stroke or systemic embolism (SSE) (HR, 2.13; 95% CI, 1.22–3.72; p = 0.01) were associated with SSE. In a multivariable analysis, the utilization of anticoagulants involving DOACs relative to warfarin (HR = 2.64; 95% CI = 1.28–5.43; p = 0.01) and the presence of previous systemic embolism (prior SSE) (HR = 2.07; 95% CI = 1.17–3.66; p = 0.01) retained significant associations with SSE. Despite adjusting for additional influencing variables, treatment with DOACs demonstrated an elevated propensity for SSE in comparison to warfarin. These findings present a challenge to the conventional assumption of therapeutic equivalence between DOACs and warfarin concerning the management of LV thrombi.²⁰

Warfarin vs Novel/Direct OACs (NOAC/DOAC)

In the recent past, four recently developed drugs, namely the direct factor Xa inhibitors...
Role of Warfarin in the Current Era

Postcoronary Artery Bypass Grafting (CABG)

While direct OACs (DOACs) have gained widespread approval and utilization for venous thromboembolism prevention and nonvalvular AF treatment, their application in postoperative patients remains limited in available information. A retrospective analysis investigated the occurrence of postoperative effusions in 246 patients who received anticoagulation with either warfarin (n = 182) or DOACs (n = 64) following CABG. Among patients treated with DOACs after surgery, 26.6% necessitated invasive interventions to address effusions, contrasting with 13.2% in those receiving warfarin (p < 0.014). This dataset bears significance and should guide the selection of an appropriate anticoagulation strategy for postoperative CABG patients.

Complications Associated with PE

Chronic thromboembolic pulmonary hypertension (CTEPH) represents an infrequent clinical setback to acute pulmonary emboli, requiring prolonged use of anticoagulant therapies. A retrospective analysis was conducted to assess outcomes and complication incidences in CTEPH cases of postpulmonary endarterectomy (PEA), comparing individuals receiving VKAs (n = 794) or DOACs (n = 206). Warfarin remains consistent among the VKA (99%), while rivaroxaban is consistent among DOACs (77%). Both VKA and DOAC cohorts exhibited substantial enhancements in hemodynamic and functional status post-PEA (p < 0.001). Comparable rates of major hemorrhagic events were observed between VKA-treated (0.67%/person-year) and DOAC-treated (0.68%/person-year) patients. However, DOACs exhibited a relatively higher recurrence rate of venous thromboembolism (VTE) (4.62%/person-year) in contrast to VKAs (0.76%/person-year), although overall survival did not exhibit variance.

Antiphospholipid Syndrome (APS)

In APS, the suitable duration of warfarin treatment for secondary prevention of recurrent VT following an initial event remains a subject of debate. The recommended standard of care currently advocates for an indefinite, prolonged course of warfarin treatment. The cessation of anticoagulation in individuals with AP antibodies lacks a solid foundation in empirical evidence and should only be contemplated in exceptionally chosen patients subsequent to thorough counseling and a comprehensive evaluation of risk factors. No data, apart from anecdotal reports, are available on DOACs in this disease.

Poor Adherence to Therapy with DOACs

Data from RCTs have provided evidence that patients struggle to maintain anticoagulation with DOACs over the long term and that a large proportion of those discontinue DOACs even before the end of treatment. In a clinical trial encompassing 18,113 individuals with AF, the discontinuation rates for dabigatran at doses of 110 and 150 mg, as well as warfarin, were observed as 14.5, 15.5, and 10.2%, respectively, at the end of the 1st year. These figures increased to 20.7, 21.2, and 16.6% at the end of the 2nd year.

A study showcased at the Heart Rhythm Society’s (HRS’s) 39th Annual Scientific Sessions reported that lower DOAC use was associated with more thromboembolic events than warfarin when adherence was low. Within the study, the cohort encompassed 52,365 patients who were prescribed warfarin and 67,686 patients who were prescribed any of the four DOACs. Notably, thromboembolic events were found to be 69% more probable in individuals with lower adherence to DOACs (p < 0.001) and 48% more likely in those with lower adherence to warfarin (p < 0.001).

Dose Adjustment of DOACs Based on the Kidney Function and CrCl Values

Chronic kidney disease (CKD) represents a significant global public health concern due to its proximal association with cardiovascular disease. Approximately 28% of patients diagnosed with acute coronary syndrome exhibit moderate CKD with an eGFR ranging from 59 to 30 mL/minute/1.73 m², whereas 5.5% of patients have an eGFR below 30 mL/minute/1.73 m². CKD is linked with an elevated risk of thromboembolism, which necessitates anticoagulation therapy. However, the increased incidences of hemorrhage are quite challenging.

DOACs are preferred in CKD stages 1–3, while warfarin remains consistent as the first choice of treatment in patients with end-stage renal disease (ESRD). Due to the variable degree of renal clearance, dosage adjustment is mandatory in CKD patients treated with DOACs (Table 1).

Data from a meta-analysis also favored the efficacy and safety of warfarin in nonend-stage CKD. In a landmark meta-analysis by Dahal et al., the utilization of warfarin among patients with nonend-stage CKD yielded a reduced risk of ischemic stroke or thromboembolism (HR: 0.70; 95% CI: 0.54–0.89; p = 0.004) and mortality (HR: 0.65; 95% CI: 0.59–0.72; p < 0.00001), while exhibiting no discernible impact on major bleeding (HR: 1.15; 95% CI: 0.88–1.49; p = 0.31).

Warfarin Therapeutic Monitoring and Measures to Improve Therapeutic Control

International normalized ratio (INR) monitoring is the key to a safe and effective warfarin therapy. The following advances have made an assessment of INR and maintenance to obtain the highest TTR.

Point-of-care Device

The utilization of point-of-care INR testing confers several benefits: the user-friendly nature, the rapid outcomes from capillary blood testing, and improved decentralization of management. Various point-of-care INR testing methods have been explored in clinical studies, such as the CoaguChek XS (Roche Diagnostics, Basel, Switzerland), which employs electrochemical detection of thrombin activity, the INRatio 2 (Alere Inc., San Diego, California, USA) utilizing electrochemical detection of impedance changes, the ProTime Micro coagulation system (International Technidyne).
Table 1: Titration of DOAC dosages based on the degree of CKD severity in individuals afflicted with AF or venous thromboembolism

<table>
<thead>
<tr>
<th>Recommended OAC</th>
<th>CrCl (mL/minute) estimated using the Cockroft-Gault equation</th>
<th>End-stage renal disease on dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥50</td>
<td>30–49</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Preferable to adjust the dose function of time in the therapeutic range, optimal ≥70%</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 and 110 mg twice daily for ≥80 years, or associated with P-glycoprotein Inhibitors, or high risk of hemorrhage</td>
<td>Same</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg once daily</td>
<td>15 mg once daily (dose used by landmark trials recommended by small pharmacokinetic studies)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 and 2.5 mg twice daily if any ≥2 of the following: age ≥80 years, body weight ≤60 kg, and creatinine ≥1.5 mg/dL</td>
<td>Same</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 and 30 mg once daily when ≥2 of the following criteria are met—body weight ≤60 kg, CrCl 30–50 mL/minute, and therapy with verapamil, dronedarelone, or quinidine is associated with FDA black box warning for CrCl &gt;95 mL/minute</td>
<td>30 mg once daily</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; DOAC, direct oral anticoagulants; FDA, Food and Drug Administration

Pharmacogenetic Testing for Warfarin Dosage

Repetitive investigations through candidate gene studies have consistently revealed that the genetic makeup of VKORC1 and CYP2C9 plays a significant role in shaping individual responses among patients. This has been confirmed by several genome-wide association studies (GWAS).38–40 Following the identification of the CYP2C9 and VKORC1 genes, their correlation with the necessary warfarin dosage has been investigated in multiple research studies.41

The International Warfarin Pharmacogenetics Consortium (IWPC) investigated involving 4,000 patients to assess the relationship between pharmacogenetic factors, clinical variables, and warfarin dosage. The study revealed that incorporating genetic data into the dosage prediction significantly improved its proximity to the required dosage, surpassing estimations from a clinical algorithm or a fixed-dose strategy (8.5 vs 9.9 vs 13.0%, respectively). This predictive accuracy was particularly notable among patients necessitating high dosages (e.g., the 49 mg/week group), constituting 46% of the study cohort.42

The Swedish Warfarin Genetics (WARG) study showcased that a multi-regression...
Role of Warfarin in the Current Era

INDIA-SPECIFIC CHALLENGES IN ANTICOAGULATION

Differences in Prevalence of Rheumatic Heart Disease (RHD) in India, Compared to the West, where Trials are Done

Heart failure (HF) has a higher prevalence in India because of increasing vascular disease and the persistence of pretransitional diseases such as RHD. The India Ukier Study conducted to determine the HF incidence in remote populations along with other comprehensive healthcare institutions conducted in North India reported that RHD (52%) constituted the primary prevalent factor, succeeded by ischemic heart disease (17%). According to the Acute Failure Registry Study, RHD accounted for 10.8% of the instances succeeded by ischemic heart disease (17%).

Adherence to Therapy: Skipping of Dose is more Harmful with DOAC than Warfarin

Direct OACs (DOACs) are shorter-acting compared to warfarin. When a dose of warfarin is inadvertently skipped, the patient’s blood might remain sufficiently anticoagulated for over 24 hours. This extended effect is attributable to the gradual waning of warfarin’s anticoagulant impact over several days. In contrast, the anticoagulant effect of a DOAC diminishes rapidly upon missing a dose due to its brief half-life.

Cost of Therapy: Warfarin vs Acenocoumarol and DOACs

Currently, VKA drugs like warfarin remain the number one agent of choice for oral anticoagulation in India based on physician comfort due to years of usage and the prohibitive cost of dabigatran. The cost-benefit favors DOACs in the US since medical benefits associated with PT/INR testing are high. In India, a PT/INR costs around US $5, which favors enormous economic savings favoring warfarin. In India, warfarin is the most cost-effective OAC therapy as compared to acenocoumarol and DOACs. A point-of-care device helps reduce the cost, further favoring warfarin compared to DOACs.

CONCLUSION

When prescribing OACs in India, it is essential to consider factors such as cost, patient adherence, and dietary habits. The utilization of newer OACs is accompanied by a set of challenges that encompass higher cost, suboptimal adherence, limited monitoring infrastructure, absence of dedicated countermeasures, and an elevated risk of severe bleeding incidents among patients with renal impairment and those aged >80 years. Warfarin has been the mainstay of OAC treatment in India for >60 years. Attributed to its distinctive pharmacokinetic properties, amenability to monitoring, cost considerations, and other defining attributes, warfarin stands as the favored anticoagulant option for a specific subset of patients. Proficiently managed and carefully monitored warfarin therapy further diminishes the likelihood of unfavorable occurrences such as recurrent VTE and bleeding events, consequently curbing the financial burden associated with VTE treatment.

Consistent INR monitoring plays a pivotal role in detecting instances of suboptimal medication adherence during warfarin treatment. Recent advancements like point-of-care INR testing devices, anticoagulation clinics, and pharmacogenetic testing can be an effective strategy for improving INR monitoring and patient adherence to warfarin.

REFERENCES


Effectiveness of Rabeprazole and Other Proton Pump Inhibitors in Managing GERD with Varying Severity: A Retrospective, Real-world EMR-based Study (POWER GERD Study)

Parimal Lawate1, Nikhil Jilawar2, Kaushal Vyas3, Kranti Kiran Pebbili6, Shashank Desai5*, Rahul Rathod6, Bhavesh Kotak7, Akhila Paspulate8

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ABSTRACT

Purpose: To evaluate the effectiveness of rabeprazole and other proton pump inhibitors (PPIs) in providing symptomatic relief in patients with varying severity of gastroesophageal reflux disease (GERD).

Methods: In this multicenter retrospective study, electronic medical records (EMRs) of GERD patients prescribed with PPIs at two Indian clinics/hospitals were reviewed (2016–2020). Rabeprazole’s effectiveness was assessed at different follow-up visits and compared with other PPIs.

Results: Overall, 269 patients (moderate and severe GERD: 84.39%) were included in three groups, viz rabeprazole, pantoprazole, and esomeprazole groups. A significant proportion of patients experienced quick and complete symptomatic relief at visit 1 with rabeprazole compared to the baseline visit, which gradually increased till visit 4 for both daytime (viz heartburn (38.78–93.88%; p < 0.001)) and nocturnal symptoms (viz sleep disturbances (62.92–97.75%; p < 0.001)). Rabeprazole provided quick relief at visit 1 when compared with pantoprazole for daytime heartburn (38.78 vs 5.56%; p = 0.01), daytime epigastric pain (66.04 vs 12.12%; p = 0.049), and nocturnal water brash (60.71 vs 16.13%; p = 0.015), and when compared with esomeprazole for nocturnal nausea (82.61 vs 20.00%; p = 0.013). Further, the proportion of patients exhibiting complete treatment response was relatively higher in the rabeprazole group (83.33%) than in the pantoprazole (62.07%) and esomeprazole (65.67%) groups at visit 4.

Conclusion: Rabeprazole was effective in providing quick and sustained relief for both daytime and nocturnal GERD symptoms in patients with moderate and severe GERD. Rabeprazole also demonstrated greater effectiveness when compared with pantoprazole and esomeprazole in reducing the severity of multiple GERD symptoms.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal diseases, characterized by the recurrent return of gastric contents back into the esophagus.1 It affects millions of people worldwide, with a reported global pooled prevalence of 13.9% in the year 2020.2 A meta-analysis and meta-regression study estimated the prevalence of GERD to be 15.6% in the Indian population.3 GERD is caused by different mechanisms that can be intrinsic, structural, or both, and entails the impairment of the anti-reflux barrier (lower esophageal sphincter and the crural diaphragm) at the esophagogastric junction, resulting in exposure of the esophagus to acidic gastric contents.4 The severity of the disease is highly pH-dependent and directly correlates with the degree and duration of esophageal acid exposure. Patients may manifest both classical (heartburn, regurgitation) and atypical symptoms, including chest pain, epigastric pain, nausea, vomiting, belching, bloating, early satiety, and pain in swallowing. Most of these symptoms are experienced by the patients both during daytime and nighttime (nocturnal). Sleep disturbances (nocturnal awakening/early awakening) are other major nocturnal symptoms of GERD.5,6 Apart from anatomical factors, several other factors like age ≥50 years, low socioeconomic status, tobacco use, excessive alcohol consumption, connective tissue disorders, pregnancy, and usage of certain drugs (like benzodiazepines, nonsteroidal anti-inflammatory drugs, and aspirin) play a major role in causing GERD.7 Since GERD adversely affects patients’ quality of life (QoL), its management is intended to restate the QoL and reduce the socioeconomic burden of the disease.8 The goals of GERD treatment include symptom control, prevention of symptom relapse, and diminishing the severity of GERD-associated complications like dysphagia, bleeding, strictures, etc.9

Proton pump inhibitors (PPIs) are considered the most effective medical therapy for GERD due to their profound and prolonged acid suppression.9 The acid inhibition by PPIs is mediated through the irreversible binding of the protonated molecule to the hydrogen-potassium ATPase (H+/K+-ATPase) pumps, which are present in the gastric parietal cells and are responsible for the secretion of hydrochloric acid into the gastric lumen. Though all the available PPIs share the same antisecretory mechanism, the degree of acid suppression is closely related to variation in their pharmacokinetic parameters. All PPIs, except rabeprazole, are metabolized primarily by the hepatic cytochrome (CYP) P450 enzyme system, and the genetic polymorphisms of the CYP2C19 iso-enzyme affect their clearance and bio-availability.10 Unlike other PPIs, rabeprazole is metabolized to rabeprazole thioether, mainly through a nonenzymatic pathway, and to a much lesser extent by the CYP P450 isoenzymes (like CYP2C19 and CYP3A4).11 Hence, rabeprazole’s antisecretory activity is not affected by the genotypes of the CYP2C19 and is more predictable as compared to other PPIs. Moreover, owing to its high pKa value (~5.0, the pH at which a drug becomes 50% protonated), it can be activated at higher pH levels much faster than other PPIs and, thus, displays a slightly more rapid onset of acid inhibition.11 Hence, the effectiveness of rabeprazole may be different from other PPIs in the real world, and therefore, the present study aimed to evaluate the real-world effectiveness of rabeprazole in providing symptomatic relief and to assess the treatment response in patients...
with GERD of varying severity. The outcomes were also compared with other PPIs, such as pantoprazole and esomeprazole.

**METHODS**

**Study Design, Data Sources, and Study Population**

This retrospective, observational study was conducted by collecting the data from electronic medical records (EMRs) of patients with GERD of varying severity and visiting Indian clinics/hospitals (n = 2) between 2016 and 2020 (5 years). The study included patients >18 years old with a clinical diagnosis of GERD and who had been treated with PPIs (rabeprazole, pantoprazole, and esomeprazole) for 4–8 weeks to manage GERD. Additionally, patients who had been treated with these three PPIs for an additional 8 weeks to heal erosive or ulcerative GERD, when not healed during the initial 8 weeks of therapy, were also included. However, patients with other acid peptic diseases (esophageal ulcer, gastritis, peptic ulcer disease, Zollinger–Ellison syndrome, and Meckel’s diverticulum ulcer), history of surgical management of GERD, and incomplete records for medical management of GERD were excluded from the study. The severity of symptoms was assessed using a three-grade Likert scale as mild (awareness of symptoms but easily tolerated), moderate (discomforting symptoms sufficient to cause interference with normal activities, including sleep), and severe (incapacitating symptoms, with the inability to perform normal activities, including sleep). The patients were divided into three groups based on the prescribed PPIs: rabeprazole, pantoprazole, and esomeprazole groups.

**Study Outcomes**

The study outcomes were evaluated during 4 weeks (1–7 and 8–30 days after baseline visit) and after 4–8 weeks (31–60 and 61–90 days after baseline visit) of treatment. The primary outcome of the study was to evaluate the effectiveness of rabeprazole based on symptomatic relief from daytime to nocturnal symptoms. The relief of each symptom was evaluated as either complete relief (resolution of that symptom during therapy), satisfactory relief (reduction in symptom severity), or no relief (no change in symptom severity), as defined by Robinson et al. The secondary outcomes of the study were to compare the effectiveness of rabeprazole with other PPIs (pantoprazole and esomeprazole) in terms of providing symptomatic relief from both daytime and nocturnal symptoms and to evaluate the treatment response among patients during and after 4 weeks of treatment. The patient’s response to a standard dose of PPI was evaluated as complete response (no heartburn during PPI treatment), partial response (heartburn of any intensity at a lower frequency during PPI treatment compared to baseline), and nonresponse (same or higher frequency of heartburn during PPI treatment compared to baseline) as defined by Bytzer et al.

**Statistical Analysis**

Data was analyzed using R Studio 3.5.3 and managed using Microsoft 365. The descriptive analysis of the study data, including baseline characteristics, clinical symptoms, treatment details, etc., was presented using descriptive statistics. All the continuous variables (e.g., age) were presented as mean ± standard deviation (SD), and the categorical variables (e.g., gender) were presented as frequency (or proportions). The effectiveness of rabeprazole in terms of providing symptomatic relief, along with the comparative analysis of rabeprazole with other PPIs and further treatment response at different visits, were evaluated by applying the Chi-squared tests. Statistical significance was considered at p < 0.05.

**RESULTS**

**Baseline Characteristics**

A total of 269 GERD patients, fulfilling the selection criteria, were included in the study. More than half of the patients (58.74%) were found to be males, and the mean age of the patients was observed to be 43.77 ± 16.98, 47.56 ± 13.38, and 45.08 ± 15.45 years in rabeprazole, pantoprazole, and esomeprazole groups, respectively. Overall, 15.61, 75.84, and 8.55% of patients had mild, moderate, and severe GERD, respectively. Cumulatively, 84.39% of patients had moderate and severe GERD. All the patients complained of both daytime and nocturnal GERD. At baseline, the most frequently reported symptoms were heartburn (88.85%), regurgitation (83.27%), water brash (57.99%), epigastric pain (54.65%), and bloating (33.83%). Similarly, among nocturnal symptoms, heartburn (76.58%), sleep disturbances (71.38%), regurgitation (65.80%), epigastric pain (63.57%), and water brash (50.93%) were most frequently reported. Several patients had multiple comorbidities, with psychological disorders being the most frequently reported comorbidity, by 44.24% of patients. Among psychological disorders, stress was reported as the most common disorder by 99.15% of patients.

**Treatment Details**

At baseline, the oral formulations of rabeprazole (20–40 mg), pantoprazole (40 mg), and esomeprazole (10–60 mg) were prescribed in the respective groups for 4–12 weeks. The dose of the drug in the esomeprazole group was found to be increased to 20–60 mg for 32.05% of patients at visit 3 (day 31–60) and 40–60 mg for 5.13% of patients at visit 4 (day 61–90) from 10–60 mg at visits 1 (day 1–7) and visit 2 (day 8–30), which might be attributed to partial or nonresponse of the patients to the drug. The doses remained the same in the rabeprazole and pantoprazole groups. The number of patients receiving once a day (OD) dose compared to twice a day (BD) dose was found to be relatively more in the rabeprazole group (58.33 vs 41.67%) and esomeprazole group (57.69 vs 42.31%) as compared to the pantoprazole group (45.07 vs 54.93%) at visit 1 (day 1–7) and visit 2 (8–30 days) (Table 2).

The patients received various concomitant drugs along with PPI treatment, of which rifaximin, sucralfate, and domperidone were prescribed most frequently (Table S1).

**Effectiveness of Rabeprazole**

Rabeprazole demonstrated its potential effectiveness in providing complete relief for both daytime and nocturnal symptoms across varying severity of GERD (Table S2). The effectiveness of rabeprazole in providing complete relief from the three major daytime and nocturnal symptoms, that is, heartburn, regurgitation, epigastric pain, and sleep disturbances, among patients with varying severity of GERD has been presented in Figure 1.

A quick resolution of daytime and nocturnal symptoms was reported, as a significant proportion of patients with moderate and severe GERD experienced relief at visit 1 (days 1–7) as compared to the baseline, and this proportion of patients reporting complete relief was found to be gradually increased till visit 4 (day 61–90) (Table 3). Similar trends for symptom resolution were observed in the subcategory of mild, moderate, and severe GERD (Table S2).

**Comparative Effectiveness of Rabeprazole vs Other PPIs**

All the PPIs demonstrated improvement in both daytime and nocturnal symptoms, though it was not statistically significant in all the patients with varying severity of GERD (Tables S3 and S4). When the comparative analysis was carried out, Rabeprazole was found to be more effective than pantoprazole and esomeprazole in providing complete relief with quick onset from multiple symptoms (like heartburn, epigastric pain, water brash, and nausea), observed at visit 1 (day 1–7). A significantly greater percentage of patients...
with moderate and severe GERD reported complete relief in the rabeprazole group as compared to the pantoprazole group for daytime heartburn (38.78 vs 5.56%; \( p = 0.01 \)), daytime epigastric pain (66.04 vs 12.12%; \( p = 0.049 \)), and nocturnal water brash (60.71 vs 16.13%; \( p = 0.015 \)) at visit 1 (day 1–7). Also, a higher percentage of patients reported complete relief in the rabeprazole group as compared to the esomeprazole group (82.61 vs 20.00%; \( p = 0.013 \)) at visit 1 (day 1–7) (Table 4). Similar trends were observed in the subcategory of mild, moderate, and severe GERD patients (Tables S3 and S4).

### Variable Treatment Response to Different PPIs (Complete/Partial/Nonresponse to Heartburn)

A complete resolution of reflux symptoms is experienced by most of the patients with GERD receiving PPIs. However, some patients respond partially to the treatment, and heartburn tends to occur more frequently in partial responders. In the present study, all the patients with varying severity of GERD were observed to respond effectively to the PPI therapies (Fig. 2A). However, a greater percentage of patients with moderate to severe GERD in the rabeprazole group (83.33%) were found to exhibit complete response to heartburn than in pantoprazole (62.07%) and esomeprazole group (65.67%).
Effectiveness of Rabeprazole and Other Proton Pump Inhibitors

Researchers, wherein the prevalence of the disease is reported to increase with age (>40 years),\(^{18,19}\) and men were reported to suffer more frequently from GERD than women.\(^{20}\) Further, all patients with GERD were reported to experience both daytime and nocturnal symptoms. These symptoms were in accordance with the typical (heartburn and regurgitation) and atypical symptoms (dyspepsia, epigastric pain, nausea, bloating, and belching) as mentioned in the guidelines by the American College of Gastroenterology (ACG) for the diagnosis and management of GERD.\(^{21}\)

GERD impairs the patients’ health-associated QoL, daily and social functioning, and physical and emotional activities. Thus, it has a negative influence on patients’ psychological well-being. In a cross-sectional study carried out by Zhang et al. 2017, approximately 60% of GERD patients...
reported worsening of the symptoms during stress. In concordance, 44.24% of patients included in the present study reported having psychological disorders, of which stress was the most reported complaint.

**GERD Treatment**
According to the Association of Physicians of India, the treatment algorithm for GERD includes the initial standard of care with PPIs given OD for 4 weeks in standard doses (rabeprazole 20 mg, pantoprazole 40 mg, and esomeprazole 40 mg). If there is partial or nonresponse to OD PPI, then augmentation of the dose of the same PPI (given BD) or switching to another PPI is considered. If the patient does not respond to the optimal dose of PPI until 8 weeks (i.e., refractory GERD), a further diagnostic evaluation is recommended. An almost analogous treatment approach was observed in the current study, wherein the therapy was initiated with rabeprazole 20–40 mg, pantoprazole 40 mg, and esomeprazole 10–60 mg in rabeprazole, pantoprazole, and esomeprazole groups, respectively, and the dose of the drug was increased in esomeprazole group at days 31–60 (nearly after 4 weeks), while it remained same in rabeprazole and pantoprazole groups.

**Effectiveness of Rabeprazole**
Assuring an early relief of symptoms is the key treatment goal in patients with GERD. The findings of the present study demonstrated that a significant proportion of patients with moderate and severe GERD receiving rabeprazole achieved complete relief with rapid onset at visit 1 (day 1–7), and this proportion was observed to be increased till visit 4 (day 61–90) for both daytime [e.g., heartburn (38.78–93.88%)] and nocturnal symptoms [e.g., sleep disturbances (62.92–97.75%)]. These findings were similar to those reported in other studies, wherein a marked improvement in patients’ global evaluations (including symptoms like heartburn, regurgitation, belching, bloating, satiety, nausea, and vomiting) was observed in patients who had received rabeprazole 10 mg (52.4%) and 20 mg (51.6%). Further, an open-label, multicenter study evidenced that rabeprazole 20 mg/day prescribed for 8 weeks markedly decreased both daytime and nocturnal heartburn severity, regurgitation, and belching.
Effectiveness of Rabeprazole and Other Proton Pump Inhibitors

Table 3: Effectiveness assessment of rabeprazole based on symptomatic relief from daytime to nocturnal symptoms among patients with moderate and severe GERD (n = 102)

<table>
<thead>
<tr>
<th>GERD symptoms</th>
<th>Baseline visit (n)</th>
<th>Visit 1 (day 1–7) n (%)</th>
<th>Visit 2 (day 8–30) n (%)</th>
<th>Visit 3 (day 31–60) n (%)</th>
<th>Visit 4 (day 61–90) n (%)</th>
<th>p-value (baseline-visit 1)</th>
<th>p-value (baseline-visit 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn</td>
<td>98</td>
<td>38 (38.78%)</td>
<td>72 (73.47%)</td>
<td>92 (93.88%)</td>
<td>92 (93.88%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>90</td>
<td>40 (44.44%)</td>
<td>63 (70%)</td>
<td>75 (83.33%)</td>
<td>76 (84.44%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>53</td>
<td>35 (66.04%)</td>
<td>47 (88.88%)</td>
<td>48 (90.57%)</td>
<td>48 (90.57%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain</td>
<td>23</td>
<td>11 (47.83%)</td>
<td>13 (56.52%)</td>
<td>19 (82.61%)</td>
<td>20 (86.96%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Water brash</td>
<td>63</td>
<td>39 (61.9%)</td>
<td>58 (92.06%)</td>
<td>59 (93.65%)</td>
<td>59 (93.65%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Belching</td>
<td>17</td>
<td>11 (64.71%)</td>
<td>16 (94.12%)</td>
<td>17 (100%)</td>
<td>17 (100%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bloating</td>
<td>25</td>
<td>14 (56%)</td>
<td>21 (84%)</td>
<td>23 (92%)</td>
<td>23 (92%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early satiety</td>
<td>19</td>
<td>10 (52.63%)</td>
<td>17 (89.47%)</td>
<td>17 (89.47%)</td>
<td>18 (94.74%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>15 (51.72%)</td>
<td>22 (75.86%)</td>
<td>24 (82.76%)</td>
<td>25 (86.21%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24</td>
<td>17 (70.83%)</td>
<td>22 (91.67%)</td>
<td>22 (91.67%)</td>
<td>23 (95.83%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain in swallowing</td>
<td>24</td>
<td>19 (79.17%)</td>
<td>22 (91.67%)</td>
<td>22 (91.67%)</td>
<td>23 (95.83%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Sleep disturbances are frequently confronted in nearly 25% of GERD patients, likely due to nocturnal gastroesophageal reflux.25 The consequences of nocturnal GERD are reported to be more severe than daytime GERD in terms of clinical complications such as the enhanced risk of esophageal lesions, respiratory conditions (like asthma, bronchitis), as well as issues of health-related QoL, sleep and work productivity.26 The present study demonstrated the potential effectiveness of rabeprazole in improving nocturnal symptoms, including heartburn, regurgitation, epigastric pain, sleep disturbances, etc., as the number of patients who exhibited these symptoms decreased significantly at visit one as compared to baseline, till visit 4. The efficacy of rabeprazole in improving nocturnal symptoms may be attributed to its ability to significantly reduce the duration of nocturnal acid breakthrough (NAB) by enhancing the pH of nocturnal alkaline amplitude (NAKA) (an abrupt rise in intragastric pH to above 4–6 after sleeping) as well as by prolonging the persisting time of NAKA.27 This is in concurrence with a study conducted by Luo et al. 2003, which has reported that a single dose of rabeprazole increased the pH of NAB to a significantly greater extent (1.84 vs 1.15 and 1.10 for rabeprazole vs omeprazole and pantoprazole, respectively; p < 0.01) and prolonged the time of NAKA (4.65 hours vs 3.22 hours and 3.22 hours for rabeprazole vs omeprazole and pantoprazole, respectively) as compared to other PPIs.28

**Comparative Effectiveness of Rabeprazole vs Other PPIs**

On performing the comparative analysis, rabeprazole was found to be more effective than pantoprazole in providing complete relief from symptoms like daytime epigastric pain, nocturnal regurgitation, water brash, and sleep disturbances in patients with moderate and severe GERD. Similar findings have been reported by a single-center, investigator-blinded, cross-over study that compared the effects of rabeprazole 20 mg and pantoprazole 40 mg on 24-hour intragastric acidity in patients with GERD. The study observations demonstrated that a greater number of patients experienced a higher degree of acid suppression after taking rabeprazole (78.0%) than pantoprazole (22.0%).29 Furthermore, rabeprazole also showed complete relief from nocturnal water brash in a greater number of patients with moderate and severe GERD as compared to esomeprazole. This is in concurrence with a comparative study conducted to assess the efficacy of rabeprazole and esomeprazole in providing symptom relief in patients with mild to moderate GERD, which observed greater improvement in overall symptom score in the rabeprazole group (37.8%) as compared to the esomeprazole group (25%).30 The greater effectiveness of rabeprazole as compared to other PPIs can be attributed to its acid stability and distinct pharmacokinetic properties. Rabeprazole undergoes rapid activation over a wider pH range (due to its high pKa value), and the subsequent doses can continue to bind and inhibit the H⁺/K⁺-ATPase pump at higher pH levels, resulting in early as well as sustained acid suppression.31

Further, in the present study, the number of patients receiving OD dose as compared to BD dose was comparatively higher in the rabeprazole and esomeprazole groups but not in the pantoprazole group at visits 1 and 2. This indicates OD dose as the preferred dose for rabeprazole and esomeprazole, which can be attributed to their higher effectiveness than pantoprazole as reported by other studies.32,33 In a study carried out by Miner et al. 2010, single dose of rabeprazole (20 mg) was found to be significantly more effective than pantoprazole (40 mg) as it increased the mean percentage time with intragastric pH
Variable Treatment Response to Different PPIs

Usually, a complete resolution of reflux symptoms is experienced by most patients with GERD receiving PPIs. However, in some patients, PPI therapy provides only partial symptom relief. This may be ascribed to the different genotypes of CYP2C19 [i.e., rapid, extensive metabolizer (RM), intermediate metabolizer (IM), and poor metabolizer (PM)], wherein both the pharmacokinetics and pharmacodynamics of PPIs depend on CYP2C19 genotype status. The drug plasma levels and intragastric pH during PPI therapy are lowest in the RM group, those in the IM group come next, and highest in the PM group, resulting in high interpatient variability to the PPI therapy. However, since the metabolism of rabeprazole is least dependent on CYP2C19, it is least affected by genetic polymorphism of the enzyme, which results in more consistent inhibition of gastric acid secretion and more predictable treatment outcomes with rabeprazole compared to other PPIs. In concurrence, the present study has shown that a complete response was observed to be relatively higher among those receiving rabeprazole than pantoprazole and esomeprazole. In fact, the following statement from the latest ACG Clinical Guideline for the Diagnosis and Management of GERD also supports rabeprazole’s predictable treatment outcomes compared to other PPIs.

“Studies suggest that genetic differences in CYP2C19 metabolism affect PPI response. If one is considering a PPI switch, changing to a PPI that does not rely on CYP2C19 for primary metabolism (rabeprazole) might be considered.”

Strengths and Limitations

The present study included EMRs of patients with varying severity of GERD to evaluate the real-world effectiveness of rabeprazole in managing GERD-related symptoms. The outcomes were compared to other PPIs (like pantoprazole and esomeprazole) for the resolution of GERD symptoms, with a greater proportion of patients having moderate and severe GERD. However, due to its retrospective nature, the scope of the present study was limited to the information available in existing electronic database records.

Conclusion

The present study demonstrates the effectiveness of rabeprazole in providing rapid onset and sustained relief for both daytime and nocturnal symptoms associated with GERD. Sleep disturbances were significantly improved after rabeprazole therapy. Further, rabeprazole reduced the severity of multiple GERD symptoms more effectively than pantoprazole and esomeprazole. This study

Table 4: Comparative analysis of rabeprazole versus other PPIs in providing complete symptomatic relief at visit 1 (day 1–7)

<table>
<thead>
<tr>
<th>GERD symptoms</th>
<th>Rabeprazole</th>
<th>Pantoprazole</th>
<th>Esomeprazole</th>
<th>p-value (rabeprazole vs pantoprazole)</th>
<th>p-value (rabeprazole vs esomeprazole)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 120)</td>
<td>(n = 71)</td>
<td>(n = 78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn</td>
<td>38 (38.78%)</td>
<td>3 (5.56%)</td>
<td>6 (9.38%)</td>
<td>0.01</td>
<td>0.354</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>35 (66.04%)</td>
<td>4 (12.12%)</td>
<td>9 (27.27%)</td>
<td>0.049</td>
<td>0.628</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water brash</td>
<td>34 (60.71%)</td>
<td>5 (16.13%)</td>
<td>6 (16.67%)</td>
<td>0.015</td>
<td>0.269</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (82.61%)</td>
<td>6 (75%)</td>
<td>2 (20%)</td>
<td>–</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Figs 2A and B: (A) Treatment response to PPIs at visit 4 (day 61–90); (B) Dosage exploratory effectiveness analysis at visit 1 (day 1–7) of patients with moderate and severe GERD receiving OD dosage of PPIs

>4 (44.0 vs 32.8%; p < 0.001) for the 24-hour postdose administration.

Variable Treatment Response to Different PPIs

...
also showed that the number of patients exhibiting complete response was relatively higher in the rabeprazole group compared to other PPI groups.

**Ethical Statement**

Patients’ confidentiality was maintained using anonymized and deidentified data at the source level. The data collection was performed as per the protocol and applicable ethical and regulatory guidelines, including the Declaration of Helsinki, Indian Good Clinical Practices (GCP), and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use–GCP. The study was approved by the Royal Pune Independent Ethics Committee (RPIEC), Pune, India (Ethics Approval Number: RPIEC230821; dated: 25th Aug 2021).

**Acknowledgments**

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**Authors Declaration**

Supplementary tables are available with corresponding author and can be provided whenever required.

**References**


Prevalence of Hyperuricemia in Indian Population with Hypertension


Received: 03 March 2023; Revised: 23 May 2023; Accepted: 23 May 2023

ABSTRACT

Background and objective: The prevalence rate of hyperuricemia (HU) is comparatively higher in Asian countries than in the Western regions. Patients with coexisting HU and hypertension (HTN) are at greater risk of uncontrolled HTN, metabolic syndrome, and complications. This study aims to determine the prevalence of HU in individuals with HTN from the major geographical regions across India.

Materials and methods: A cross-sectional, multicentric, observational study conducted in primary and secondary care centers from urban areas across different regions in India. Primary inclusion criteria were either a history of HTN or blood pressure systolic blood pressure (SBP) ≥140 and diastolic blood pressure (DBP) ≥ 90 mm Hg. A structured Google form was circulated among the participating healthcare practitioners from various participating centers to record the demographic, clinical, and biochemical parameters of patients visiting the respective centers. The data was consolidated and analyzed using Microsoft Excel. Screening for HU among individuals with HTN was based on two criteria—(1) self-reported diagnosed history of HU or (2) based on serum uric acid (SUA) levels > 7 and > 6 mg/dL for men and women, respectively. The data were analyzed and represented using GraphPad Prism version 9.

Results: Among the study population from 12 participating centers across different regions in India, 1,528 individuals had HTN. The mean age of the study participants was 57.4 ± 10.5 years with a male-to-female ratio of 1:1. The total prevalence rate of HU among individuals with HTN was 22.5% (N = 345). Gender-wise analysis indicated that 51.5% (177) of the males and 48.5% (168) of the females had HU. Among the patients with HTN and HU, 75% were overweight with a body mass index (BMI) of ≥25 kg/m². The region-wise prevalence rate HU are North—17.4% (60), South—18% (62), Central—12.2% (42), East—29.6% (102), and West—22.9% (79).

Conclusion: India’s overall HU prevalence rate (22.5%) was comparable to that in other Asian countries (10–30%). However, the prevalence of HU among HTN patients varies between different regions of India (12.2–29.6%). Results from the participating centers located in an urban setting indicated that the eastern region had the highest HU prevalence (29.6%) and the Central region had the lowest HU prevalence rate (12.2%). The varying prevalence rate can be attributed to the diversity in geographical factors, genetic background or (family history of HU), sociocultural habits, and metabolic perturbations. Understanding this prevalence rate diversity can help strengthen the HU prevention measures to improve quality of life.


INTRODUCTION

Hyperuricemia (HU) has long been recognized to be associated with the risk of developing hypertension (HTN). The prevalence of HU has steadily increased globally during the past 4 decades.1,2 The prevalence of HU has been increasing, especially in Asian countries, including Taiwan (10–52%), India (~25.8%), Japan (20–26%), and China (6–25%) compared to the Western countries, including United States of America (21–22%), Brazil (13%), and Italy (9–12%).1–4 The overall prevalence rate of HU in the Indian population with HTN is 25–28%.5 The major treatments include diet and lifestyle changes and xanthine oxidoreductase inhibitors. Other treatments include pharmacological interventions using angiotensin II/renin inhibitors, atorvastatin, fenofibrate, losartan, metformin, sodium/glucose cotransporter 2 inhibitors, and sevelamer.6 Few studies2,6,7 have documented a higher prevalence of HU (24–37.33%) in patients with HTN as compared to healthy normotensive individuals (6–14%). Losartan, used to treat HTN has also shown effectiveness in the reduction of serum uric acid (SUA) levels in both animal and human studies.1,2,8 HU plays an important part in the development of HTN, often cooccurring and leading to increased health risks.8–10 HTN and HU are independent risk factors for cardiovascular diseases and their co-occurrence increases the risk exponentially. HU can increase the risk of developing HTN by almost 35%. The elevation of SUA is evident throughout all regions of the world. However, considerable regional variation exists in all countries, which can be attributed to anthropometric factors, environmental and genetic factors and geographical and socioeconomic factors.11 In India, a significant variation in the HU prevalence rate is expected across different regions owing to its socioeconomic, geographical, and cultural diversity.

A screening process for HU among the population with HTN is not currently being implemented. HU screening in patients with HTN conducted via SUA estimation can help alleviate further development of urate deposition and prevent further disease-related morbidity and mortality. However, there is a lack of epidemiological data on the prevalence of HU in subjects with type 2 diabetes.12

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Prevalence of Hyperuricemia in Indian Population with Hypertension

In a multicentric observational study involving urban health centers in India, 1,528 individuals had HTN. The mean age of the study participants was 57.4 ± 10.5 years with a male-to-female ratio of 1:1. The total prevalence rate of HU among individuals with HTN is 22.5% (N = 345) with 51.5% (177) of males and 48.5% (168) of females. The centers included, and the distribution of individuals is presented in Table 1.

The region-wise prevalence rates (Fig. 2) of HU are North—17.4% (60); South—18% (62); Central—12.2% (42); East—29.6% (102), and West—22.9% (79). The Eastern region had a higher HU prevalence (29.6%) and the Central region had a lower HU prevalence rate (12.2%).

Over 80% of the individuals suffering from HU were at least 50 years old and above, with a male-to-female ratio of 1:1. The demographic distribution is provided in Figure 3. Around >70% of the study population was 50 years old and above. Almost 90% of the study population was literate. Three-fourths of the study population had a body mass index (BMI) ≥25.

Various studies have reported HU as an independent risk factor for T2DM and HTN. The co-occurrence of HTN and HU is commonly observed, increasing the risk of cardiovascular diseases. Elevated SUA levels in India, 1,528 individuals had HTN. The mean age of the study participants was 57.4 ± 10.5 years with a male-to-female ratio of 1:1. The total prevalence rate of HU among individuals with HTN is 22.5% (N = 345) with 51.5% (177) of males and 48.5% (168) of females. The centers included, and the distribution of individuals is presented in Table 1.

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Prevalence of Hyperuricemia in Indian Population with Hypertension

Hence, screening of SUA levels at regular periods may serve as a suitable, rapid, reliable, affordable, and less invasive procedure to prevent the onset or progression of HTN. Compared to the previous large-scale retrospective studies field conducted in a population-based in India, our study’s prevalence of HU was lower. This could be caused by geographical location, genetic variation, population characteristics (high-risk), therapeutic regimen, and socioeconomic factors. We found a region-wise difference in the prevalence rate of HU (12.2–29.6%) in patients with HTN. Studies have reported HU prevalence of 46.5 and 33% in South India and Northeast India, respectively. This can be attributed to the difference in lifestyle, diet, geographical, and climate features of the specific region. Such differences in the prevalence of HU across various regions should be taken into

Table 1: Distribution of patients in region-wise participating centres

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Name of the doctor</th>
<th>Region</th>
<th>Number of individuals with HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dr Anuradha Kapoor</td>
<td>West</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Dr Kiran Shah</td>
<td>West</td>
<td>145</td>
</tr>
<tr>
<td>3</td>
<td>Dr Aashna Patil</td>
<td>West</td>
<td>295</td>
</tr>
<tr>
<td>4</td>
<td>Dr Bijay Patni</td>
<td>East</td>
<td>155</td>
</tr>
<tr>
<td>5</td>
<td>Dr Saumya Sengupta</td>
<td>East</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>Dr N K Singh</td>
<td>East</td>
<td>173</td>
</tr>
<tr>
<td>7</td>
<td>Dr J. Aravinda</td>
<td>South</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>Dr Mohsin Aslam</td>
<td>South</td>
<td>233</td>
</tr>
<tr>
<td>9</td>
<td>Dr Raka Sheohare</td>
<td>Central</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>Dr Ashish Saxena</td>
<td>North</td>
<td>101</td>
</tr>
<tr>
<td>11</td>
<td>Dr Basab Ghosh</td>
<td>North</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>Dr Dinesh Agarwal</td>
<td>North</td>
<td>100</td>
</tr>
</tbody>
</table>

induce endothelial dysfunction, which reduces insulin-stimulated nitric oxide-induced vasodilatation in skeletal muscles. A 2011 study reported that for every 1mg/dL increase in SUA levels, the relative risk for developing HTN was 1.13. The risk was more pronounced among the younger population and females. Hence, screening of SUA levels at regular periods may serve as a suitable, rapid, reliable, affordable, and less invasive procedure to prevent the onset or progression of HTN.

Figs 3A to E: Demographics of individuals with HU. (A) Age; (B) Gender; (C) Literacy rate; (D) Socioeconomic status; (E) BMI
account, and a large-scale screening must be considered across the country.

The HU and HTN have common risk factors, such as age, gender, obesity, lipid profile, comorbidities, and hypertriglyceridemia. In a cross-sectional study conducted in India, the prevalence rate of HU in normotensive individuals was 12.1% which was significantly lower than the prevalence rate (22.6%) we observed in our study. Therefore, it can be speculated that the prevalence of HU was higher in patients with HTN than in the general population, as HU is considered a positive risk factor for the development of HTN.

In accordance with previous studies, age was confirmed as an independent risk factor for HU. In our study, >80% of the individuals suffering from HU were 50 years or above. The increased incidence of HU in the elderly can be attributed to their increased significant with age in women, but it was not observed in men.

The current study is mainly concentrated on HU prevalence in urban areas. However, a previous study conducted in India reported that the ratio of individuals with HU in urban and rural areas was 1.1:129, indicating that the prevalence of HU is higher in urban areas. This can be because of the different lifestyles and diets among urban and rural regions.

**Conclusion**

The prevalence of HU in HTN patients varies between different regions of India (12.2–29.6%). The varying prevalence rate can be attributed to the diversity in geographical factors, genetic background or (family history of HU), sociocultural habits, and metabolic perturbations. However, the HU prevalence rate is comparable to that in Asian countries (10–30%). Therefore, understanding the diversity in the prevalence rate can help to strengthen the HU prevention measures to improve the quality of life.

**Limitations of the Study**

This study is an observational study with no control group. Uniform testing of patients from a single lab was not done. Number of patients enrolled in different centers was not uniform.

**References**

Assessment of Biomedical Waste Generation in Dialysis Units: A Prospective Observational Study—Is it Time for “Green Dialysis”? 

Manisha Sahay1*, Rakesh K Sahay2, B Seshadri3, Kiranmai Ismal4, Anuradha Kavadi5, Rama Enganti6

Received: 16 May 2023; Accepted: 09 June 2023

ABSTRACT

Introduction: Chronic kidney disease and as a consequence end-stage kidney disease (ESKD) is increasing globally. More and more people across the world are requiring hemodialysis (HD). The HD procedure produces a large quantity of biomedical waste. In addition, HD consumes a large amount of water. In this study, we estimated the waste generated from our government-funded HD unit.

Materials and methods: It is a prospective study that was carried out in the dialysis unit in the nephrology department over a period of 1 year. The daily dialysis waste generated by the unit was measured using a spring balance. The proportion of plastic and nonplastic waste was determined. The quantity of biomedical waste generated per person in 1 year was calculated. The measurement accuracy of the scale used for the dialysis unit was noted. Water consumption per dialysis was calculated. Liquid chemical waste consumed was determined. Electricity consumed by the unit was measured by the electricity meter. The cost of waste disposal was calculated. The cost of electricity consumption and water consumption was also calculated.

Results: The approximate weight of waste disposables generated in one dialysis was 0.75 kg. Approximately each person generates 1.29 kg of waste per dialysis. Each dialysis required 125 L of reverse osmosis (RO) water and to generate 125 L of RO water 250 L of raw water was used. This happens as 125 L of water are rejected during the generation of 125 L of RO water. Thus, the net water consumption for each dialysis was 250 L. Chemical waste generated per dialysis includes 90 mL citric acid per dialysis and 130 mL bleach. Each dialysis consumes 3 kWh (three units) of electricity. The cost of electricity for each dialysis was 25.5 INR and the cost of water was 25 INR per dialysis. The cost of waste disposal for each dialysis bed was 6 INR.

Discussion: Each dialysis patient produced 1.29 kg of waste per dialysis which was like other studies. Unlike other studies, the waste was not being reprocessed or recycled.

Conclusion: Hemodialysis produces substantial biomedical waste. Proper waste disposal techniques and policies to promote reduction, reuse, and recycling will go a long way toward promoting green dialysis and reducing environmental as well as economic burdens.

ORIGINAL ARTICLE

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Conclusion: Hemodialysis produces substantial biomedical waste. Proper waste disposal techniques and policies to promote reduction, reuse, and recycling will go a long way toward promoting green dialysis and reducing environmental as well as economic burdens.

INTRODUCTION

About 2.61 million patients in the world underwent dialysis in the year 2010. It is estimated that in the year 2025, about 4 million patients will be treated with dialysis worldwide.1 Most end-stage kidney disease (ESKD) patients are treated with hemodialysis (HD), peritoneal dialysis is employed less often.2,3 Hemodialysis numbers in India are believed to be 175,000 (0.175 million) annually.4 It is likely that the number of dialysis will increase due to the dialysis initiative by the government of India.

Public-funded dialysis was initiated for the first time in the country in 2009 in the erstwhile Andhra Pradesh. Currently, the Telangana government has developed the hub-and-spoke model of dialysis. There are three major hub centers in Hyderabad and each of these centers caters to 20–30 spoke centers which are located in the districts under them. These units are providing dialysis at the doorstep for most of the patients.5

There is an enormous generation of biomedical waste from hospitals. Hemodialysis is a major contributor toward biomedical waste. Improper waste disposal damages the natural fauna and flora and is a harbinger of many infectious diseases. The disposal of biomedical waste is very expensive. There are very few studies on the magnitude of biomedical waste generation from dialysis units in India and this prompted us to take up the study.

MATERIALS AND METHODS

This was a prospective study that was performed in the nephrology dialysis unit over a 1 year period from April 2022 to March 2023. The measurement accuracy of the scale used for the measurement of dialysis disposables was 0.1 gm. The daily dialysis waste generated by the unit was measured using a spring balance. The proportion of plastic and nonplastic waste was determined. The quantity of biomedical waste generated per person in 1 year was calculated. Water input to the dialysis unit was noted. Water consumption per dialysis was calculated. Liquid chemical waste consumed was determined. Electricity consumed by the unit was measured by the electricity meter. The cost of waste disposal was calculated. The cost of electricity consumption and water consumption was also calculated.

Variables are expressed as mean ± standard deviation or percentages or frequencies. Student’s t-test or analysis of variance was used to analyze continuous variables. Normality was tested using Kolmogorov–Smirnov test. Nonparametric variables were compared using Mann–Whitney U or Kruskal–Wallis tests were used as appropriate to compare nonparametric variables while categorical variables were tested using Pearson’s χ2 test or Fisher’s exact test. A p-value of <0.05 was considered to be statistically significant. Epi Info™ version 7.1 was used for statistical analysis (Division of Health Informatics and Surveillance, Center for Disease Control, Atlanta, United States of America). The Institutional Ethics Committee provided the approval for the study.

RESULTS

The approximate weight of waste disposables generated in one dialysis is

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Assessment of Biomedical Waste Generation in Dialysis Units

Table 1: Waste estimated from one dialysis

<table>
<thead>
<tr>
<th>Material</th>
<th>Weight</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialyzer</td>
<td>Polycarbonate</td>
<td>Plastic</td>
</tr>
<tr>
<td>Blood tubings</td>
<td>PVC</td>
<td>Plastic</td>
</tr>
<tr>
<td>Packing of dialyzer+ blood tubings +</td>
<td>PVC</td>
<td>Plastic</td>
</tr>
<tr>
<td>syringes and fistula needle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistula needles (×2)</td>
<td>Silicon + metal</td>
<td>Silicon + metal</td>
</tr>
<tr>
<td>Saline bottles empty × 4</td>
<td>PP</td>
<td>Plastic</td>
</tr>
<tr>
<td>Gauze</td>
<td>Cotton</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.7 kg (wet)</td>
<td>0.5 kg dry</td>
</tr>
</tbody>
</table>

Table 2: Measured waste generated per month in the dialysis unit

<table>
<thead>
<tr>
<th>Total waste per month (kg)</th>
<th>Dialysis number/month</th>
<th>Kg/patient per dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>April</td>
<td>2340</td>
<td>1,800</td>
</tr>
<tr>
<td>May</td>
<td>2088</td>
<td>1,740</td>
</tr>
<tr>
<td>June</td>
<td>2222.84</td>
<td>1,822</td>
</tr>
<tr>
<td>July</td>
<td>2238.2</td>
<td>1,805</td>
</tr>
<tr>
<td>August</td>
<td>2441.8</td>
<td>1,864</td>
</tr>
<tr>
<td>September</td>
<td>2156.28</td>
<td>1,812</td>
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<td>October</td>
<td>2239.8</td>
<td>1,821</td>
</tr>
<tr>
<td>November</td>
<td>2287.5</td>
<td>1,830</td>
</tr>
<tr>
<td>December</td>
<td>2188.8</td>
<td>1,824</td>
</tr>
<tr>
<td>January</td>
<td>2337.4</td>
<td>1,798</td>
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<tr>
<td>February</td>
<td>2246.8</td>
<td>1,812</td>
</tr>
<tr>
<td>March</td>
<td>2416.76</td>
<td>1,804</td>
</tr>
</tbody>
</table>

Shown in Table 1. The waste generated per month and yearly from the dialysis unit is given in Table 2. Each person generates approximately 1.2 kg of waste per dialysis. Each dialysis required 120 L of reverse osmosis (RO) water and to generate 120 L of RO water 250 L of raw water was used. This happens as 125 L of water is rejected during the generation of 125 L of RO water. Thus, the net water consumption for each dialysis was 250 L. Chemical waste generated per dialysis includes 90 mL citric acid per dialysis and 130 mL bleach.

Each dialysis consumes 3 KV of electricity. The cost of electricity for each dialysis was 8.5 INR per unit, that is, 25.5 INR per dialysis and the cost of water was 100 INR/KL, that is, 25 INR for each dialysis. The cost of waste disposal for each dialysis bed was 6 INR.

**DISCUSSION**

Hemodialysis produces significant biomedical waste. Liyanage et al. showed that about 2.7 million patients receive dialysis in the world with each person receiving 156 HD per year. In 420 million HD sessions >420 million kg of medical waste is generated in 1 year. There are 1.75 lakh patients on HD in India. The data on waste generation from dialysis units is sparse. Hence this study was conducted to determine the biomedical waste produced from a publicly funded dialysis unit. The average number of dialysis done in our center per month was around 2,000.

**Solid Waste**

In our study, we found that the weight of disposables used in dialysis was 0.85 kg. Each person generated 1.239 kg of biomedical waste per dialysis in our study. If we take 144 sessions of dialysis each year for each person (assuming three dialysis per week) then each dialysis patient will generate 178.4 kg waste per year. In another study by Abhilash and Yadla Manjusha, the approximate waste generated per person per year was 1.08 kg/dialysis.

The percentage of plastic waste was 70% in our study. In the study by Piccoli et al., each dialysis session produced plastic waste produced per dialysis session ranging from 1.5 to 8 kg waste of plastic. Only 25% of plastic waste is recyclable. Polyvinyl chloride (PVC) and polypropylene (PP) are recyclable. However PVC and PP are often mixed with plastic tags, inks, and glues which interfere with recycling. Another issue is that though PVC is recyclable, PVC incineration is environmentally sensitive. Furthermore, Hoenich et al. demonstrated that blood tubing sets contain plasticizers such as di(2-ethylhexyl) phthalate (DEHP), which pose health risks to patients. The use of different types of plastic in the same device should be avoided as this may help in recycling. In addition to plastic, each dialysis session produces other recyclable waste like paper and cardboard and this accounts for 223–736 gm per dialysis session in a study by Piccoli et al.

The most important hazardous waste in dialysis includes dialyzers, bloodlines, and needles. Infectious waste amounted to 1 kg per dialysis in our study. In the study by Piccoli et al., potentially hazardous wastes varied from 1.1 to 8 kg, which varies with the type of dialysis machine and dialyzers, differentiation, and emptying policies. Żebrowski et al. in their study classified the dialyzers depending on the surface—(1) 1.4 m², (2) 1.5–1.6 m², (3) 1.7–1.8 m², and (4) 2.0–2.2 m². The lightest dialyzers in each group were FX class dialyzers while the polyflux were the heaviest. The weight difference between the lightest and heaviest dialyzers was 95 gm. PP was the lightest housing material, whereas the housing of the heavy dialyzers was polycarbonate.

The density of polycarbonate is approximately 20% greater than the density of PP. In our study, the dialyzers used were of a single variety, that is, Elisio. These are made of polymers not containing bisphenol A or DEHP.

In our study, Elisio dialyzers were used with a fill volume of 80 mL. The filling volume was lowest in FX dialyzers whereas it was highest in Elisio dialyzers. The difference was 20 mL. Thus, choosing the lightest dialyzer with minimum fill volume can reduce dialysis waste. In a year, Żebrowski et al. estimated that a lighter dialysis set can decrease biomedical waste generation by 17 million kg. In our study dialyzers were completely emptied manually before discard. Fresenius 6008 machine allows for an emptying process at the end of dialysis unlike Fresenius 4008 and 5008 machines and reduces waste by 150 gm. However our machines did not have this facility. Hence, we practiced manual emptying of the dialyzer before discard.

About 1 minute time is required at the end of the dialysis session for differentiation between hazardous and nonhazardous waste and for separation of plastic and paper from among the nonhazardous waste in our study which is comparable to other studies. Segregation at source helps in reducing, reusing, and recycling.
In the developed world SteriMed, Sterishred, Meteka, and Celitron are systems that steam sterilize and then plastic waste is shredded into fine, confetti-like products. Plastics can be classified into VII grades. These include—(1) polyethylene terephthalate, (2) high-density polyethylene, (3) PVC, (4) low-density polyethylene, (5) PP, (6) polystyrene, and (7) other plastics, such as acrylic, nylon, polycarbonate, and polylactic acid. The numbers indicate ease of recycling, with one being the easiest. In dialysis units, PVC, PP, and polycarbonate are used. Also, some dialysis materials may have mixed plastics. Mixed plastics cannot be recycled easily. However, they can be incorporated into building materials—concrete bricks or can be added to molten bitumen (asphalt) which is then used for making the road surfacing. Studies in India and the Netherlands have shown that the ideal ratio is one part shredded plastic added to 10 parts bitumen. Plasticization of road surfaces has several benefits—(1) it increases the flexibility and durability of the surface, (2) it makes the road resistant to both extremes of heat and cold, (3) pothole formation is prevented, and (4) cracking of roads is reduced. Thus, even mixed nonrecyclable plastic can be utilized in laying roads. This is presently not being practiced in our unit.

**Water Waste**

The RO water used during each dialysis was 125 L which contributes to dialysis effluent waste. To generate this RO water around 250 L of raw water was used in our study (50% of rejected water is produced during RO water generation). However, another study by Agar et al. demonstrated that 500 mL of water was used for each session. Here, they had included water for priming, washing etc. Thus, dialysis contributes to a huge waste of water resources. This reject water generated by most RO systems though unfit for dialysis, meets the potable water criteria as it is already cleaned by the sand filter, carbon filter, and softener. However, in most places, it is “unacceptable” to drink. Agar et al. have used rejected water for steam sterilization, toilets, car washes, and gardening. Dialysis effluent can be used for toilet flushing. It is interesting to note that each toilet flush utilizes 5 L of water. Presently this RO reject water or effluent is not being utilized in our unit.

Chemical waste generated per dialysis includes 90 mL citric acid per dialysis and 130 mL bleach which is produced during machine sterilization. Ours is a single-use dialysis setup hence chemicals are not required for dialyzers and tubing reuse. In hospitals where reuse is practiced, chemicals needed for reuse, that is, renalin (peracetic acid) will also add to the liquid chemical waste.

Electricity used for each dialysis in our unit was 3 kWh which was comparable to a study by Nickel et al. in which per treatment electricity used was 3.5 kWh. This includes a pretreatment period of 60 minutes during which the hemodialysis machines undergo automatic system checks and there is also a 45-minute heat disinfection cycle after dialysis. Instead, cold disinfection and organic acids may be used to disinfect the dialyzers and machines to reduce electricity.

Carbon footprint is defined as carbon dioxide emissions associated with all the activities of a dialysis patient. It consists of direct emissions from fossil-fuel combustion in heating and transportation, emissions required to generate electricity, and emissions of other greenhouse gases, such as chlorofluorocarbons, nitrous oxide, and methane. The annual per-patient carbon footprint of satellite conventional HD is 10.2 tonnes of carbon dioxide equivalents in Australia while NHS estimates it to be about 7 tonnes per patient annually. The average carbon footprint of a person not on dialysis is 4 tonnes. In our study, we did not calculate the carbon footprint.

**Conclusion**

A huge quantity of waste is generated during each dialysis. Proper segregation of waste at source, separation of biohazardous waste and recyclable waste helps in reducing the quantity of biomedical waste and thus protects the environment and reduces costs. Similarly repurposing dialysis reject water and effluent water in toilets and reusing the dialyzer waste as concrete may further decrease waste generation. Installation of solar panels may reduce electricity consumption and reduce carbon footprint. Formulation of state and national policy on green dialysis may be an important step forward.

**Limitation**

It was a single-center study. The carbon footprint of the unit was not calculated.

**Acknowledgment**

We wish to thank the Telangana Council of Science and Technology (TCOST) for funding the study.

**References**

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Prof. Dr. Mangesh Tiwaskar
Editor-in-Chief, JAPI
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 2000 mg 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 diarrhoea 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, diarrhoea, 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 WBC B12 absorption, very rarely acute lactic acidosis, hemolytic anaemia, reduction of thyrotopin level in patients with hypothyroidism, hypoglycaemia in the context of diarrhoea, encephalopathy, photosensitivity, hepatobiliary disorders.

Warnings and Precautions:

For Glimepiride: Patient should be advised to report promptly excessive 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 is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly. 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 precoma). Severe renal failure (GFR < 30 ml/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

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Clinical Spectrum of Patients Admitted with Hymenoptera (Bees and Wasps) Stings in a Medical College Hospital of Himachal Pradesh, India

Muhammad Sadil KP1, Sujeet Raina2*, Rashmi Kaul3, Vivek Sood4

Received: 22 April 2023; Accepted: 16 May 2023

ABSTRACT

Objective: Hymenoptera (bees and wasps) stings are a common health hazard in the tropics, particularly in rural areas. The study was planned to describe the clinical spectrum of patients with Hymenoptera (bees and wasps) stings admitted to a medical college hospital in Himachal Pradesh, India.

Materials and methods: This was a hospital-based open cohort prospective study conducted on patients admitted with a history of Hymenoptera (bees and wasps) stings. The study period was 1 year, and patients were recruited using a nonprobability sampling method. Demography, clinical and laboratory data, complications, and outcomes were recorded and analyzed. Systemic allergic reactions were classified according to the British Society for Allergy and Clinical Immunology (BSACI) guidelines.

Results: A total of 44 patients (25 males and 19 females) were included in the study. All the patients reported in the warmer months from April to November were stung between 6 am and 8 pm and reported within three from the time of the incident. The most common local symptoms of pain and pruritus were reported by 100 and 31.8% of patients, respectively. Features of systemic envenomation reported were dizziness, nausea, vomiting, decreased urine output, hematuria and cola-colored urine, pain abdomen, cough, and wheezing. On examination, local redness and swelling were observed at 100 and 72.7%, respectively. The size of swellings was <10 cm in all of the patients. As per BSACI guidelines, the severity of systemic allergic reactions was mild, moderate, and severe in 70.4, 13.6, and 15.9%, respectively. Transaminases were observed in 40.9% of patients. Acute kidney injury (AKI) developed in 22.7% of patients. The mortality was 4.5% in this study.

Conclusion: This is one of the largest studies on Hymenoptera envenomation in India and contributes to our understanding of the subject.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0347

INTRODUCTION

The human-animal interface is responsible for significant morbidity and mortality among humankind. The interaction has intensified due to natural or human-influenced changes in population, ecology, and behavior. Hymenoptera (bees and wasps) stings are a common health hazard in the tropics. Hymenoptera is an order of class Insecta and includes stinging insects like bees, hornets, wasps and yellow jackets. They are ubiquitous.¹ A checklist of Hymenoptera fauna of the state of Himachal Pradesh, India, has revealed the presence of the medically important Apidae family (social honeybees, solitary bees, and bumblebees) and Vespidae family (hornets, wasps, and yellow jackets). Hymenoptera toxins are complex mixtures of amines, kinins, enzymes, and peptides. The amines are histamine, dopamine, norepinephrine, serotonin, and kinins, which account for the painful, erythematous swelling and itching at the site of the sting. The enzymes are phospholipase A (PLA), phospholipase B (PLB) and hyaluronidase. PLA 2 (PLA2) is a predominant component of bee venoms, and PLA 1 (PLA1) is highly abundant in wasps. These enzymes are the allergens causing immunoglobulin E-mediated anaphylaxis. The peptides in wasp venom are mastoparans, neurotoxin apamin, antigen 5, antiinflammatory compound ado lapin, and mast cell degranulating peptide. Melittin is the dominant peptide in bee venoms.²,³ The venoms of hymenopterans are biochemically and immunologically species-specific, with little cross-sensitization between the venoms of honeybees and wasps.⁴ Hymenoptera envenomation is a medical emergency. The toxidrome includes local reactions and serious complications like anaphylaxis and multiple organ dysfunction syndromes. Treatment is mainly supportive and there is no antivenom. Bee and wasp stings have been greatly underestimated and have not been systematically studied. The limited data on epidemiology, clinical features, morbidity, and mortality is available through hospital-based retrospective studies and case reports. Himachal Pradesh is a Northern Indian hill state situated in the Western Himalayas. The state has extensive geographical biodiversity, which offers eco-rich vegetation and abundance of flora and fauna. The state has a predominantly rural population scattered around rural and forest lands, and this makes people in these areas vulnerable to insect stings. This study was carried out to describe the clinical profile of patients with Hymenoptera (bees and wasps) stings from a tertiary care hospital in Himachal Pradesh, India.

MATERIALS AND METHODS

This was a hospital-based open cohort prospective study. The recruitment period was one year between December 2021 and November 2022 using a nonprobability sampling method. The inclusion criteria were patients above the age of 18 years presenting with envenomation features following the history of Hymenoptera (bees and wasps) stings. Patients recruited to the study had demographic details, circumstances of suffering from the sting, time of the sting, site of the sting, any preadmission treatment (alternative or allopathic), time from the sting to hospital admission, clinical findings, investigation results and treatment prescribed recorded as per proforma. Species identification into bees and wasps was attempted by the information provided by the patient or attendants and the presence/absence of a stinger. For corroboration, the patient or attendant was shown different species of bees and wasps prevalent in the state of Himachal Pradesh and available in the public domain by the authors MS and SR.

1Postgraduate student; 2Associate Professor; 3Professor; 4Associate Professor, Dr Rajendra Prasad Govt Medical College, Kangra, Himachal Pradesh, India; *Corresponding Author

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in identifying the species was recorded as unidentified. Stingers present on the skin were immediately removed (Fig. 1). Information was obtained if any stinger was removed before arrival at the hospital. All the recruited patients underwent complete hemogram, peripheral smear, reticulocyte count, liver function tests, renal function tests, urine examination, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio, serum lactate dehydrogenase (LDH), and creatine kinase (CK). The peak value at the time of clinical manifestation was taken for the diagnosis. Electrocardiogram (ECG) was done for all the patients. The urine specimen was analyzed by dipstick. If the dipstick test was positive for hematuria, it was followed by microscopic examination for red blood cells. A salt precipitation test was used on freshly voided urine to differentiate hemoglobin from myoglobin in the urine. All the patients were followed up during the hospital stay to look for development of new complications and to document the outcome at the time of discharge.

Definitions

**Anaphylaxis**

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) and at least one of the following—(1) respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, and hypoxemia) and (2) reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, and incontinence). Systemic allergic reactions to bee or wasp stings were classified according to the British Society for Allergy and Clinical Immunology (BSACI) guidelines.

**Acute kidney injury (AKI)**

Acute kidney injury (AKI) will be defined according to the Kidney Disease Improving Global Outcome 2012 guidelines. Complete recovery of kidney function was defined as a decrease in the serum creatinine level to within a normal range.

**Rhabdomyolysis**

Mild rhabdomyolysis—clinical syndrome of acute muscle weakness, myalgia, and swelling combined with a CK cut-off value of >1000 IU/L or CK > 5 x upper limit of normal. Severe rhabdomyolysis—features of mild rhabdomyolysis plus myoglobinuria and AKI.

Data was entered in the Microsoft Office Excel sheet and analyzed using Statistical Package for the Social Sciences version 21 (IBM corporation, Armonk, New York, United States of America). Quantitative variables were expressed as mean with standard deviation and categorical variables as frequencies and percentages. Median ± interquartile range (IQR) was calculated for data with uneven and wide distribution and extreme values. For analysis of continuous variables, the student’s t-test was applied, and the Chi-squared test for proportions. A value of $p < 0.05$ was considered significant. The study was approved by the Institutional Ethics Committee vide no HFW-H DRPGMC/Ethics/2021/99.

**Results**

In this observational study, a total of 44 patients were recruited. The baseline characteristics, duration of admission and outcome are shown in (Table 1). All the patients belonged to rural areas. Most of the patients were farmers (79.5%) and none of the patients were beekeepers. All the patients reported in the eight months from April to November. All the patients reported between 6 am and 8 pm. None of the patients had a prior history of Hymenoptera sting. Out of 44 patients, 21 (47.72%) stings were provoked and 23 (52.27%) were unprovoked. All the patients had reported to a health care center within 3 hours of the sting. The patients or their attendants were able to identify the stinging insects as a wasp (Vespa sp.) in 43.1% (19/44), Rangad (local name for Vespa velutina) in 45.4% (20/44), and as honeybee (Apis sp.) in 11.3% (5/44). The clinical features of the patients are shown in (Fig. 2). Out of 44 patients, three (6.8%) patients were detected to have hypertension, four (9.0%) patients had hypotension, seven (15.9%) patients had tachycardia, and three (6.8%) patients presented with tachypnoea. One of the patients presented with paroxysmal supraventricular tachycardia (Fig. 3A). The frequency distribution of the laboratory profile of the study subjects is shown in (Table 2). The evidence of microangiopathy in the form of the presence of schistocytes on peripheral smear was observed in four (9.7%) patients (Fig. 3B).
unconjugated hyperbilirubinemia had the presence of schistocytes. PT and aPTT remained normal in all the patients. Alkaline phosphatase was raised in patients and was not proportionate to the rise in transaminases. In the present study, three patients had markedly elevated peak levels of aspartate transaminase (AST) and alanine transaminase (ALT) (5410 U/L and 444 U/L, 2025 U/L and 2023 U/L, and 1254 U/L and 1182 U/L, respectively). The majority (39/44 88.6%) of the patients have managed in a nonintensive care unit (ICU) setup, and five (11.3%) patients required ICU management. Two patients died during the hospital course.

**Discussion**

Limited clinical-epidemiological data on Hymenoptera envenomation is available from the geographic regions of China, India, Sri Lanka, Vietnam, Thailand, Malaysia, Nepal, and the United States.10–17 Hornet, wasp, and bee stings were responsible for 1,109 deaths in the United States from 2000 to 2017.18 Hymenoptera (bees and wasps) stings are a common health hazard in the state of Himachal Pradesh.15,19,20 On 28th March 2022, the disaster management cell of the state revenue department of the government of Himachal Pradesh has included deaths caused due to honeybee, hornet and wasp sting in the Himachal Pradesh Disaster and Relief Norms, 2012.

In the present study, the victims were in the physically active age-group, and all belonged to rural areas. The location of exposure was while working in the fields and without either provocation or minimal provocation in most of the subjects. None of the patients was involved in beekeeping or honey hunting. Females were almost equally involved as they were involved in agriculture activities, grass cutting, and fodder collection along with males in this region. All the victims suffered stings during the time from 6 am to 8 pm. The daytime activity, social behavior, feeding habits, and environmental conditions are responsible for the diurnal variation in the timing of inflicting stings. All the cases were reported in the warmer months of April to November. Bees and wasps are summertime pests. Most of the wasps and hornets hibernate during the winter months, although honeybees don’t hibernate.14 An attempt was made to identify the stinging insect in this study although exact species identification may not have been possible. All the patients were able to name the stinging insect, both in Hindi and in the vernacular language. Wasps were responsible for most of the stings in the present study. Wasps have been documented to be the dominant species.
responsible for Hymenoptera envenomation in various other studies. In this study, 79.5% of patients sought first aid within 1 hour of being stung either in a primary healthcare center or directly in the tertiary care health center. All the patients received first aid within 3 hours of suffering stings. None of the patients had visited alternate system practitioners. The possible reason is that no alternate faith or treatment has been exercised for Hymenoptera envenomation. The majority had mild symptoms. Symptoms due to local inflammatory reactions in the form of pain and pruritis were reported by the patients. Symptoms in the form of systemic envenomation reported were dizziness, nausea, vomiting, decreased urine output, cola-colored urine, pain abdomen, cough, and wheezing. Systemic allergic reactions in the form of wheezing and coughing were also observed. According to the BSACI guidelines, 70.4, 13.6, and 15.9% of patients had mild, moderate, and severe systemic allergic reactions, respectively. Mild signs due to local inflammatory reactions in the form of redness and swelling were frequently reported by the patients. The size of swellings was less than 10 cm in 72.7% of patients. The median duration of admission of patients was 22–23 days (IQR). Leucocytosis, the common hematological abnormality observed in this study, is a manifestation of the acute phase of systemic inflammatory response. The chemotactic peptides of the Hymenoptera venom recruit polymorph nuclear leucocytosis. A study from Colombia reported leucocytosis in 89% of cases with Africanized bee stings. The presence of schistocytes indicates vascular damage manifesting as microangiopathic hemolysis. Though wasp venom has an anticoagulant effect none of the patients had prolonged aPTT or PT. Thrombocytopenia was observed in 18.1% of patients. Wasp venom inhibits platelet aggregation.

AKI was observed in 22.7% of patients in this study. Hymenoptera-envenomation induced AKI has been reported in 15.2–48.2% of cases. Elevated CK was observed in 38.6% of patients, including six patients with rhabdomyolysis.

In this study, rhabdomyolysis was defined as per the recommendation of Stahl et al.
Clinical Spectrum of Patients Admitted with Hymenoptera (Bees and Wasps) Stings

Table 2: Showing distribution of laboratory and hematology parameters among study subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 44)</th>
<th>Males (n = 25)</th>
<th>Females (n = 19)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2 (4.5%)</td>
<td>1 (4%)</td>
<td>1 (5.2%)</td>
<td>0.606</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (18.1%)</td>
<td>6 (24%)</td>
<td>2 (10.5%)</td>
<td>0.496</td>
</tr>
<tr>
<td>Leucocytosis</td>
<td>27 (61.3%)</td>
<td>11 (44%)</td>
<td>16 (84%)</td>
<td>0.065</td>
</tr>
<tr>
<td>Schistocytes</td>
<td>4 (9%)</td>
<td>3 (12%)</td>
<td>1 (5.2%)</td>
<td>0.824</td>
</tr>
<tr>
<td>AKI</td>
<td>10 (22.7%)</td>
<td>5 (20%)</td>
<td>5 (26.3%)</td>
<td>0.643</td>
</tr>
<tr>
<td>Transaminemia (AST&gt;ALT)</td>
<td>18 (40.9%)</td>
<td>13 (52%)</td>
<td>5 (26.3%)</td>
<td>0.174</td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>7 (15.9%)</td>
<td>4 (16%)</td>
<td>3 (15.7%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Hemoglobinuria</td>
<td>2 (4.5%)</td>
<td>1 (4%)</td>
<td>1 (5.2%)</td>
<td>0.606</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>6 (13.6%)</td>
<td>4 (16%)</td>
<td>2 (10.5%)</td>
<td>0.949</td>
</tr>
<tr>
<td>Raised CK</td>
<td>17 (38.6%)</td>
<td>11 (44%)</td>
<td>6 (31.5%)</td>
<td>0.506</td>
</tr>
<tr>
<td>Raised LDH</td>
<td>13 (29.5%)</td>
<td>8 (32%)</td>
<td>5 (26.3%)</td>
<td>0.962</td>
</tr>
<tr>
<td>Raised CRP</td>
<td>6 (13.6%)</td>
<td>2 (8%)</td>
<td>4 (21%)</td>
<td>0.439</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>7 (15.9%)</td>
<td>5 (20%)</td>
<td>2 (10.5%)</td>
<td>0.434</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>7 (15.9%)</td>
<td>3 (12%)</td>
<td>4 (21%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Thrombocytopenia and AKI</td>
<td>6 (13.6%)</td>
<td>4 (16%)</td>
<td>2 (10.5%)</td>
<td>0.949</td>
</tr>
<tr>
<td>Thrombocytopenia and schistocytes</td>
<td>1 (2.2%)</td>
<td>1 (4%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AKI and Transaminemia</td>
<td>6 (13.6%)</td>
<td>4 (16%)</td>
<td>2 (10.5%)</td>
<td>0.949</td>
</tr>
<tr>
<td>AKI and raised CK</td>
<td>3 (6.8%)</td>
<td>2 (8%)</td>
<td>1 (5.2%)</td>
<td>0.803</td>
</tr>
<tr>
<td>AKI and schistocytes</td>
<td>2 (4.5%)</td>
<td>1 (4%)</td>
<td>1 (5.2%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Transaminemia and schistocytes</td>
<td>4 (9%)</td>
<td>2 (8%)</td>
<td>2 (10.5%)</td>
<td>0.824</td>
</tr>
<tr>
<td>Rhabdomyolysis and schistocytes</td>
<td>1 (2.2%)</td>
<td>–</td>
<td>1 (5.2%)</td>
<td>–</td>
</tr>
<tr>
<td>Rhabdomyolysis and transaminemia</td>
<td>4 (9%)</td>
<td>2 (8%)</td>
<td>2 (10.5%)</td>
<td>0.824</td>
</tr>
<tr>
<td>AKI and microscropic hematuria</td>
<td>6 (13.6%)</td>
<td>3 (12%)</td>
<td>3 (15.7%)</td>
<td>0.949</td>
</tr>
<tr>
<td>Rhabdomyolysis, AKI, and transaminemia</td>
<td>2 (4.5%)</td>
<td>1 (4%)</td>
<td>1 (5.2%)</td>
<td>0.803</td>
</tr>
<tr>
<td>Rhabdomyolysis, AKI, and unconjugated hyperbilirubinemia</td>
<td>2 (4.5%)</td>
<td>–</td>
<td>1 (4%)</td>
<td>1(4%)</td>
</tr>
<tr>
<td>RBC morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocytic normochromic</td>
<td>37 (84.1%)</td>
<td>21 (84%)</td>
<td>16 (84%)</td>
<td>0.965</td>
</tr>
<tr>
<td>Microcytic hypochromic</td>
<td>7 (15.9%)</td>
<td>4 (16%)</td>
<td>3 (15.7%)</td>
<td>0.803</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; ALT, alanine transaminases; AST, aspartate transaminases; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase; n, number; RBC, red blood cell

Applying the criteria, all the patients had mild type rhabdomyolysis. None of the patients had myoglobinuria and thus did not fulfill the diagnostic criteria of a severe type of rhabdomyolysis. The rise in CK and rhabdomyolysis is due to toxin-induced muscle cell membrane disruption and acute muscle cell injury. Elevated CK was found in 53.7% of patients, whereas 24.1% were diagnosed with rhabdomyolysis in a multicenter retrospective study from China.16

Transaminases were raised more frequently in patients in this study in comparison to deranged renal functions. The pattern of elevated transaminases was that AST was disproportionately raised in comparison to ALT. The concomitant rise of alkaline phosphatase was not proportionate to the rise in transaminases. The concomitant rise in unconjugated hyperbilirubinemia pointed towards associated hemolysis. Drawing a line diagram to assess the comparative pattern between AST, ALT, and CK, it is observed that there are parallel peaks between transaminases only and are independent of CK peaks (Fig. 4). Analysis of the pattern of deranged liver function tests makes identification of hepatic injury complicated. The presence of rhabdomyolysis and hemolysis interferes with the analysis of deranged liver function tests. Features of acute liver failure were not present in any patient in this study. Hepatotoxicity following wasp and bee stings have been reported in 30–50% of patients.1,13,16,25 Acute toxic hepatitis has been described due to centrilobular necrosis, portal triaditis, and periportal cholangitis on histopathology.1

Among the cardiovascular effects observed in this study were hypotension, hypotension, and paroxysmal supraventricular tachycardia (in one patient). ECG was performed in all the patients, and ST/T Segment changes were not observed among any of the patients. Similarly, ECG was found to be normal in 89.5% in a study from Mysore, India.26 Cardiovascular effects reported in various studies include shock, myocardial injury due to myocardial infarction, hypersensitivity myocarditis, stress cardiomyopathy, rhythm disturbances like atrial fibrillation, atrial flutter, and ventricular tachycardia (VT) following wasp stings.7,28

The triad of rhabdomyolysis, AKI, and transaminases was observed in two patients. This triad of complications has been reported in the literature with wasp envenomation.29 We investigated patients in this study for TMA. None of the patients fulfilled the criteria for the diagnosis of TMA. Hymenoptera envenomation-related TMA has been reported from India to Sri Lanka.30,31

The mortality was 4.5% in this study. The in-hospital mortality following wasp envenomation ranges from 4 to 12%.16,20,22,32 AKI was found to be a predictor of mortality in the present study. Deaths immediately after stings are mostly because of severe anaphylaxis and cardiac events.16 In comparison to anaphylactic shock, predominantly nonanaphylaxis organ dysfunction like AKI has been reported as a predictor of in-hospital mortality in other studies.16,19,23
Most of the patients were treated with intravenous fluids, antihistamines, and steroids. The mild envenomation features were either self-resolving within a few hours or the recovery was hastened by the symptomatic treatment. The specific role of antihistamines and steroids cannot be extrapolated/deciphered in the absence of a randomized control trial. Most of the patients received antibiotics empirically in the absence of an evident infection. The presence of leucocytosis could be the reason for initiating antibiotics, thus reflecting the treating clinician’s uncertainty of a coexisting infection. Possibly the time has arrived to develop national protocols and guidelines for the management of Hymenoptera stings.

Limitations

Firstly, the subject population is small as the study period was for 1 year. Secondly, the outcome of all the patients with AKI couldn’t be determined in this study. Two patients with AKI were lost in follow-up as they took referrals for getting nephrology services outside the hospital.

Future

Hospital-based data on Hymenoptera envenomation is an underestimate as most victims in rural India do not get represented in National registries. Multicentric studies should be designed in India to determine the epidemiology, clinical spectrum, and economic burden of Hymenoptera envenomation covering different geographical zones of the country. Community-level surveillance and monitoring are desired in identifying and reporting all the events related to the human Hymenoptera interface.

Acknowledgments

Mr Sushant Sharma, lecturer of statistics, Dr Rajendra Prasad Govt Medical College, Kangra (Himachal Pradesh) for helping in statistical analysis. Mr Rakeshwar Kapoor, Research scholar, Department of Zoology and Environmental Sciences, Punjab University, Patiala, Punjab, India for identifying the Hymenoptera species.

References

11. Wiwanitkit V. Renal failure from wasp stings: an appraisal on the previous reported Thai cases. Nephrológ (Carleton) 2002(10):537.
Clinical Spectrum of Patients Admitted with Hymenoptera (Bees and Wasps) Stings


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**BOOK REVIEW**

**IAN Textbook of Neurology**

Editors : Satish V Khadilkar, Gagandeep Singh
Edition : 2nd edition
Volume : 1 and 2
Publisher : Jaypee Brothers Medical Publishers
Year : 2024
Number of Pages : 1630
ISBN : 9789354656828

Most of the neurological disorders have distinct symptomatology and it needs a proper approach including meticulous history taking, detailed clinical examination, analysis of symptoms, appropriate imaging and other investigations to arrive at a diagnosis and for proper treatment strategy.

The methodical approach is slowly on the decline now, as more emphasis is placed upon investigations, mainly imaging. Even in the modern era of advanced imaging technology, clinical neurology has lots of relevance.

The IAN Textbook of Neurology edited by Dr. Satish V Khadilkar and Dr. Gagandeep Singh has to be commended for the dedication and effort of the editors.

The book in focus is an effort at symptom based approach to clinical diagnosis of neurological problems, relevant investigations and treatment.

Each chapter has been authored by senior neurologists in the country with expertise in the concerned fields and exhibits the quality of content. Use of appropriate diagrams, photographs, flow charts and tables has added value to this publication.

Inclusion of topics such as Neuro infections, Neuro rehabilitation, Art of history taking, Cognitive Testing etc., is a much-needed enhancement to the book.

Each chapter deals with a stepwise approach to arrive at a clinical diagnosis and recommends relevant investigations to establish the diagnosis and also proper treatment.

I strongly recommend this book not only to physicians but also to the neurologists as a ready reckoner in day-to-day clinical practice.

K. Mugundhan
Department of Neurology
Govt. Stanley Medical college
Chennai – 600 001, Tamil Nadu, India
Secondary Spontaneous Pneumothorax in Patients with Silicosis

Momkesh Bairwa1, Ambika Sharma2*, Meengandha Luniwal3
Received: 10 February 2023; Revised: 24 April 2023; Accepted: 12 May 2023

ABSTRACT

Background and aims: Patients with silicosis are at increased risk of pneumothorax. However, the true incidence of pneumothorax in these patients is yet unknown. Our objective was to study the proportion of secondary spontaneous pneumothorax (SSP) in patients with silicosis who present with acute respiratory deterioration. We also analyzed the risk factors, clinical course, actual management, and treatment outcomes of pneumothorax in patients with silicosis.

Materials and methods: It was a hospital-based descriptive cross-sectional study. A total of 100 silicosis patients presenting with any acute worsening respiratory symptoms (dyspnea, cough, and chest pain) warranting admission were enrolled. A detailed history, clinical examination, and radiological investigations were done in all cases.

Results: A total of 100 patients were included in this study. The mean age of subjects was 51.6 years. Breathlessness was the most common presenting symptom followed by chest pain. A total of 43 (43%) patients had pneumothorax at presentation. Right-sided pneumothorax was seen in 26 (26%) cases, left-sided in 11 (11%) cases, and six patients (6%) had bilateral pneumothorax. No significant correlation of smoking with pneumothorax was observed in the present study. Around 42% of patients had pulmonary tuberculosis which was microbiologically confirmed.

Conclusion: The present study emphasizes that all patients of silicosis who present with acute worsening shortness of breath and or chest pain need to be evaluated for pneumothorax.

INTRODUCTION

Pulmonary complications of inhalation of toxic substances at workplaces are well described in the literature. Silicosis results due to inhalation of silica dust. The crystalline form of silicon dioxide is responsible for pulmonary disease. Generation of respirable crystalline silica occurs due to cutting, grinding, blasting, and crushing of silica-containing materials.1 There are several populations in India at excessive risk of developing silicosis. The employees in gold, mica, and coal mines, and those employed in the ceramic and pottery industry, agate and slate pencil industry, brick employees, and stone cutters are particularly at risk. In India, silicosis is prevalent in Gujarat, Rajasthan, Pondicherry, Haryana, Uttar Pradesh, Bihar, Chhattisgarh, Jharkhand, Orissa, and West Bengal. The prevalence of silicosis in India ranges widely from 3.5% in ordnance factories to 54.6% in the slate–pencil industry. In the presence of worsening respiratory symptoms complications associated with the disease should be kept in mind such as tuberculosis, pneumothorax, lung cancer, respiratory failure, respiratory infection, cor pulmonale, etc. Although involvement of pleura is uncommon in silicosis, secondary spontaneous pneumothorax (SSP) is reported in the literature. SSP can be unilateral or bilateral in these patients.2 The exact incidence and prevalence of SSP in silicosis is yet unknown. This study aimed to find the proportion of SSP in patients with silicosis admitted with acute respiratory deterioration.

MATERIALS AND METHODS

It was a hospital-based descriptive cross-sectional study. A total of 100 silicosis patients presenting with any acute worsening respiratory symptoms (dyspnea, cough, and chest pain) warranting admission were prospectively studied. A detailed history (including occupational history), clinical examination, radiological, blood, and sputum investigations were done in all cases. Pneumothorax was confirmed on a chest X-ray. Diagnosis of silicosis was based on a combination of the history of occupational exposure to silica dust and typical radiological features in chest radiographs and or computed tomography of the chest.

RESULTS

A total of 100 patients were included in the study and the mean age of the study group was 51.6 years. The majority of (51%) patients were in the age-group 41–60 years followed by 25% of patients in the 20–40 years age-group (Table 1). Around 92% study population was male and 8% were female. Around 66% of the study cohort were smokers. The mean duration of exposure to silica particles was 14 years and 11 months. Breathlessness was the most common presenting symptom and was found in all patients followed by chest pain (Table 2). Respiratory failure at admission was seen in all patients on admission which was measured by peripheral oxygen saturation by pulse oximetry and later confirmed on arterial blood gas analysis. Most of the silicosis patients were from the mining and stone-cutting industry (Table 3).

Among admitted patients with silicosis, 43% of patients had pneumothorax at presentation (Table 4). Right-sided pneumothorax was seen in 26 cases (26%) (Fig. 1), left-sided in 11 cases (11%) (Fig. 2), and six patients (6%) had a bilateral pneumothorax (Fig. 3).

Around 42% of patients had pulmonary tuberculosis which was microbiologically confirmed by the sputum acid-fast bacilli (AFB) test and or cartridge-based nucleic acid amplification test (CBNAAT). Around 39% of patients were rifampicin sensitive tuberculosis and the remaining three (3%) were resistant (Table 5).

DISCUSSION

A wide range of pulmonary diseases is associated with secondary spontaneous pneumothorax. There are few studies in which unilateral or bilateral pneumothorax has been reported in patients with silicosis.2,6,7 Only scanty literature is available which has studied the incidence of pneumothorax and associated risk factors for the same in silicosis patients.2,6,7 Present study demonstrates that SSP is a common complication in patients with silicosis and was seen in nearly

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Secondary Spontaneous Pneumothorax in Patients with Silicosis

Table 1: Distribution of cases according to age

<table>
<thead>
<tr>
<th>Age distribution (in years)</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–40</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>41–60</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>61–80</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Mean ± SD = 51.6±13.7

Table 2: Presenting complaints of patients

<table>
<thead>
<tr>
<th>Presenting complaints</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Chest pain</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Cough with expectoration</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Facial puffiness</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cough (dry)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 3: Distribution of cases according to occupation

<table>
<thead>
<tr>
<th>Occupation distribution</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mines</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Stone cutting</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Sculpture</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Construction</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Brickyard</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4: Distribution of cases according to pneumothorax

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Bilateral pneumothorax</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Left pneumothorax</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Right pneumothorax</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 5: Distribution of cases according to sputum CBNAAT-MTB

<table>
<thead>
<tr>
<th>Sputum CBNAAT*</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Positive rifampicin sensitive</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Positive rifampicin resistant</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*CBNAAT-MTB, cartridge-based nucleic acid amplification test-mycobacterium tuberculosis

Table 6: Association of pneumothorax with smoking in patients with silicosis

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Pneumothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>19 (55.88%)</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (57.58%)</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
</tr>
</tbody>
</table>

(p-value is 0.43 which is nonsignificant)

Table 7: Modalities of treatment in patients with pneumothorax (n = 43)

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Modality of treatment</th>
<th>No. (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Supplemental oxygen</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>2</td>
<td>Chest tube drainage</td>
<td>40 (93%)</td>
</tr>
<tr>
<td>3</td>
<td>Needle aspiration</td>
<td>2 (4.6%)</td>
</tr>
<tr>
<td>4</td>
<td>Observation with high-flow supplemental oxygen</td>
<td>1 (2.3%)</td>
</tr>
</tbody>
</table>

Fig. 1: Chest radiograph showing right-sided pneumothorax with bilateral upper and mid-zone progressive massive fibrosis and egg-shell calcification of mediastinal lymph nodes

Fig. 2: Chest radiograph showing left-sided pneumothorax with bilateral upper and mid-zone nodularity with progressive massive fibrosis half (43%) of the study population. This is similar to a study done by Meena et al. in Western Rajasthan, India. In another study by Mohebbi et al., the incidence of SSP was found to be 34% which was lower than the present study. Most of the patients in our study had unilateral pneumothorax as seen in other studies.

In our study, 66% were smokers. As per the literature, smoking is a known risk factor for pneumothorax. No significant correlation between smoking with pneumothorax was observed in the present study (Table 6).

Patients with silicosis are at higher risk of pulmonary tuberculosis. We found that it was another common cause of respiratory worsening in silicosis patients and was seen in one-fourth of total admitted cases. CBNAAT for mycobacterium tuberculosis was superior to AFB stain in the diagnosis of tuberculosis in our study. There were 26 cases of smear-negative tuberculosis which showed positive CBNAAT. As per a study by Prakash et al. in smear-negative individuals, the sensitivity of CBNAAT is 80.9%.

Three of all pulmonary tuberculosis patients were drug-resistant cases.

Management of SSP requires primarily intercostal chest tube drainage (ICD) and other treatment modalities as mentioned in (Table 7). In our study, all cases required ICD insertion except in three patients where pneumothorax was managed conservatively. The median duration for ICD in situ was 10 days. All patients required oxygen supplementation with no need for mechanical ventilation. None of the patients had tension pneumothorax. There was no mortality during hospitalization. Antituberculosis treatment was started in patients with confirmed tuberculosis as per the National Tuberculosis Elimination Program guideline.
CONCLUSION
The present study emphasizes evaluating all known silicosis patients for spontaneous pneumothorax if they present with worsening shortness of breath and or chest pain. The study found a high incidence of secondary spontaneous pneumothorax in such patients. A pneumothorax can be life-threatening in patients with silicosis as they already have poor pulmonary reserve and require immediate medical intervention.

ACKNOWLEDGMENT
Special thanks to the Late Dr R K Jenaw, Senior Professor, Institute of Respiratory Diseases, SMS Medical College, Jaipur, Rajasthan, India, for his persistent supervision, guidance, and valuable input for this research.

REFERENCES
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Consensus on Current Landscape and Treatment Trends of Obesity in India for Primary Care Physicians

Neeta Rohit Deshpande1*, Nitin Kapoor2, Jamshed J Dalal3, Nandita Palshetkar4, Shashank Shah5, Brij Mohan Makkar6, Jasjeet Wasir7, Chitra Selvan8

Received: 21 April 2023; Accepted: 25 May 2023

ABSTRACT

Objectives: The objective of this consensus article was to form a list of expert recommendations and an easily adaptable algorithm for obesity management in India by primary care physicians (PCPs).

Methods: A Delphi-based model was followed to form a list of the consensus recommendations. Consensus statements were created from the results of a literature review that were graded as per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria. After being evaluated by an expert panel comprising diabetologists, endocrinologists, cardiologists, bariatric surgeons, and gynecologists, the statements were revised and reevaluated by a larger group of practitioners, including PCPs and diabetologists, to arrive at a consensus.

Results: The panel opined that obesity is increasing in prevalence in India and is projected to rise in the coming years. Body mass index and waist circumference were both recommended for better identification of people at risk of obesity-related comorbidities than either of them alone. The Edmonton Obesity Staging System (EOSS) was suggested as being most suitable for the assessment (staging) of obesity. A multidisciplinary team was considered invaluable for assessing and managing patients with obesity. The use of once-a-week semaglutide (2.4 mg) via the subcutaneous route was suggested as the first-choice anti-obesity treatment when pharmacotherapy is deemed necessary. An algorithm considering all these aspects was proposed.

Conclusion: Obesity needs to be recognized as a significant contributor to other comorbidities. The diagnosis and management of obesity should be comprehensive and consider patient psychology, the presence or absence of comorbidities, available pharmacologic agents, and long-term outcomes. The proposed algorithm could help clinicians in this aspect and improve the overall outcomes.

INTRODUCTION

Globally, obesity is a major health issue associated with diseases like type 2 diabetes mellitus (T2DM), fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnea, and several cancers.1,2 The stigma and bias associated with obesity may also cause significant economic burdens due to unemployment, social disadvantages, and reduced socioeconomic productivity.1 Notably, >650 million people live with obesity across the world.3 It is predicted that by 2030, 20% of women and 14% of men will have obesity (body mass index (BMI) ≥30 kg/m²); this means that globally, over 1 billion people will have obesity.5

According to a systematic review, >135 million people live with obesity in India.5 About 38.4% of men and 36.2% of women are living with obesity in India.3 The economic impact of obesity in India (as per 2019 data) is estimated to be $23 billion [0.8% of gross domestic product (GDP)].4 Notably, the Asian-Indian phenotype includes a greater fat mass (%), both total and abdominal (including visceral), with less lean mass (skeletal muscle and bone mineral) compared to other ethnic groups—commonly referred to as “thin-fat” Indians.6,7 This ethnic predilection is one of the important reasons why noncommunicable diseases occur almost 10 years earlier in Asian Indians than in their Western counterparts.

Considering the overall burden of obesity and the recommendation from the World Health Organization, recognizing and managing obesity in India requires the active participation of primary care physicians (PCPs). It is imperative that PCPs are sensitized about the need for recognizing obesity, as a chronic disease, as most patients visit PCPs for evaluation. India has been ranked 99th in global preparedness for addressing obesity and related issues.4 We currently have two consensus statements for obesity in India—one from Misra et al. and the other from the Endocrine Society of India (ESI) (obesity guidelines in 2022).8,9 The 2022 Research Society for the Study of Diabetes in India (RSSDI) clinical guidelines also include a separate section on obesity and T2DM, given the established relationship between the two.11 Considering the presence of the thin-fat Indian phenotype, customized guidance on when and how to initiate different treatment modalities of obesity care is currently lacking. A simple treatment algorithm that can be easily adapted by PCPs is much needed in the current obesity treatment landscape of India.

METHODOLOGY

A Delphi-based model was followed to form a consensus with the following objectives: to evaluate the current burden and assessment process/modalities of obesity in India and identify the treatment gaps; to assess the emerging treatment options for obesity and their applicability in the Indian scenario; to agree upon effective treatment approaches and develop a feasible treatment algorithm for the management of obesity; and suggest a referral (to specialized obesity centers) for PCPs in India. A detailed literature review of related articles available on PubMed was conducted to evaluate the available data. Grading of the evidence was as per the...
Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria (see Appendix I for GRADE criteria). A. An expert panel meeting involving diabetologists, endocrinologists, cardiologists, bariatric surgeons, and gynecologists was then held as the first round of the Delphi consensus to evaluate the statements. Minor modifications were carried out as per the expert evaluation, and the second round of the Delphi consensus meeting, involving a larger group of 20 practitioners, including PCPs and diabetologists, was held to assess the applicability of the statements in the Indian scenario. The consensus statements were finalized based on the agreement during the second meeting.

**Results**

**Obesity Epidemiology and Related Complications**

According to a recent nationwide cross-sectional study that evaluated data from 100,531 adults in a randomized cluster sample across India, obesity prevalence in the country is 40.3%, with a higher incidence among women, urban populations, and individuals aged >40 years. Further, the incidence was highest among South Indians (46.51%) and lowest among East Indians (32.96%).

Based on the evaluation of the outcomes noted in the National Family Health Survey (NFHS) 3 and 4, it has been estimated that from 2010 to 2040, the obesity prevalence will triple, whereas the number of overweight people in India between the ages of 20 and 69 years would more than double. Notably, physical inactivity and aging are significantly associated with obesity in India. According to the findings reported in the NFHS-5, the percentage of adults with an increased waist-to-hip ratio (WHR) also increased with age in both women (from 46 to 65%) and men (from 28 to 60%) aged 15–19 and 40–49 years.

The concept of the thin–fat Indian phenotype is well accepted. Notably, the percentage of body fat and abdominal adiposity among Asian Indians is higher at lower BMIs or similar BMIs when compared with Caucasians. According to the Indian Council of Medical Research–India Diabetes (ICMR–INDIAB) phase I study, in India, both abdominal obesity [when waist circumference (WC) is ≥90 cm in men and ≥80 cm in women] and generalized obesity (BMI ≥25 kg/m²) are highly prevalent. The prevalence rate of abdominal obesity was 16.9–36.3%, and that of generalized obesity was 11.8–31.3%. The prevalence of normal weight obesity (excess body fat among individuals with normal BMI) in the Indian population has been estimated to be about 32% [95% confidence interval (CI): 29.1–34.5].

Furthermore, as compared to Caucasians, Asian Indians have a higher risk of developing resistance to insulin and cardiovascular problems at lower BMI levels. Higher BMI levels are associated with higher risks of developing asthma, chronic obstructive pulmonary disease, circulatory system diseases, digestive system diseases, multiple sclerosis, musculoskeletal system diseases, T2DM, and malignancies in the digestive system, uterus, kidney, and bladder.

**Consensus Statements**

- The prevalence of obesity is increasing in India and is projected to rise in the coming years (grade of recommendation: A; level of evidence: 1a).
- Abdominal obesity is very prevalent in Asian Indians and is an important causative reason for the rapid increase in noncommunicable diseases and their outcomes (grade of recommendation: B; level of evidence: 2a).
- Obesity leads to cardiometabolic, mechanical, psychological, and behavioral complications, which need to be identified and managed for a better prognosis (grade of recommendation: A; level of evidence: 1a).
- The presence or absence of the following complications should be assessed during obesity evaluation (grade of recommendation: A; level of evidence: 1a):
  - Metabolic conditions [prediabetes, metabolic syndrome, T2DM, hypertension, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH)]
  - Cardiovascular disease risk
  - Gynecologic complications [polycystic ovary syndrome (PCOS), infertility]
  - Osteoarthritis
  - Stress incontinence
  - Gastroesophageal reflux disease (GERD)
  - Obstructive sleep apnea
  - Disability/immobility
  - Psychological disorder or stigmatization
  - Cancer

**Clinical Assessment and Diagnosis of Obesity**

One of the critical aspects in diagnosing and managing obesity is addressing the weight bias among practicing clinicians and support staff. Studies have reported that weight bias among medical doctors is as pervasive as in the general population. PCPs, cardiologists, endocrinologists, nurses, and dieticians often feel that individuals with obesity are themselves to be blamed for noncompliance with treatment, lack of willpower, or laziness. Such bias can negatively impact obesity management. Hence, it is important to set up a clinical unit that is accommodating and trained to manage patients with obesity without any bias.

Body mass index (BMI) assessment is one of the most common measures of obesity. However, BMI does not exactly measure/ correlate with the total content of body fat; this is because the total content of body fat in two individuals having the same BMI could differ by a factor of two. Assessments of the usefulness of BMI in detecting body adiposity indicate that although BMI cutoff values have high specificity, they lack sensitivity in identifying adiposity (percentage body fat). Also, BMI evaluation is insufficient for identifying individuals with excess body fat percentage in 50% of the cases.

Importantly, BMI assessment alone does not adequately predict associated comorbidities or disease risk, and changes in BMI do not adequately indicate improvements in overall wellness.

According to the consensus guidelines by Misra et al., BMI and WC must be given equal weightage when stratifying population-based clinical, metabolic, and cardiovascular risks. Further, the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) guidelines mention that population and ethnicity-specific threshold values should be considered while making these assessments.

The consensus statement by Misra et al. has proposed the cutoff values for categorizing people based on BMI and WC as mentioned in Table 1.

**Table 1: Proposed cutoffs for categorizing people as per BMI and WC values**

<table>
<thead>
<tr>
<th>Category</th>
<th>Indian guideline (BMI cutoff)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18–22.9 kg/m²</td>
</tr>
<tr>
<td>Overweight</td>
<td>23–24.9 kg/m²</td>
</tr>
<tr>
<td>Obesity</td>
<td>&gt;25 kg/m²</td>
</tr>
<tr>
<td>WC-based</td>
<td></td>
</tr>
<tr>
<td>Need lifestyle measures</td>
<td>Men: &gt;78–90 cm; women: &gt;72–80 cm</td>
</tr>
<tr>
<td>Need medical attention</td>
<td>Men: &gt;90 cm; women: &gt;80 cm</td>
</tr>
</tbody>
</table>

BMI, body mass index; WC, waist circumference
in those without T2DM, and these measures can be useful for identifying those at risk of developing T2DM. It was found that WC and WHR were the most reliable factors for predicting metabolic disorders and hypertension, whereas NC values of ≥37 cm in men and ≥34 cm in women were useful predictors of metabolic syndrome. A value of 7.3 in the METS-VF score was sensitive and specific enough to identify those with higher visceral adipose tissue levels. However, these parameters need to be explored further, and these measures are also considered time-consuming; hence, they may not be practical in busy clinical settings. Nevertheless, as the METS-VF test is easily available, reliable, and inexpensive, it may be widely used in lower and middle-income countries in the future.

An approach centered on the management of complications will enable the use of aggressive, targeted, and individualized approaches in patients with complications related to obesity who are more likely to benefit from treatment. This will optimize resource utilization, cost-effectiveness, outcomes for patients, and interventional benefit/risk ratios.

Consensus Statements

• The BMI-centric approach to the diagnosis and management of obesity has limitations (grade of recommendation: B; level of evidence: 2a).
• The combined use of BMI and WC is recommended for better identification of people at risk of obesity-related comorbidities than either of them alone (grade of recommendation: B; level of evidence: 2a).
• Ethnic-based cutoff points for BMI and WC should be used for optimally defining obesity (grade of recommendation: B; level of evidence: 2a).
• Complication-centric obesity management can help individualize management, optimize patient outcomes, and improve the benefit/risk ratio and cost-effectiveness of interventions (grade of recommendation: B; level of evidence: 2a).

Complication-centric Staging

Traditionally, the obesity grade was defined by WC and BMI values. Recent evidence suggests that BMI and/or WC are suboptimal in defining the true health impact of obesity in an individual and that metabolic, functional, and mental comorbidities (staging) when applied to the BMI/WC, can help to define the overall health impact of obesity in a better way.

The Edmonton Obesity Staging System (EOSS) is frequently used to optimally categorize an individual’s associated health risk of obesity and is also very helpful in defining treatment aggression. The EOSS acknowledges all three (metabolic, functional, and mental) aspects of obesity, thereby helping in creating a well-rounded diagnostic and management system for obesity. The EOSS provides options for recording and tracking the progress of risk factors and their severity. This also simplifies the adoption of adequate, timely, and correct therapy changes over time for achieving the desired health outcomes. This system, together with current anthropometric classification systems, forms a simple tool for making decisions in regular clinical practice.

A similar staging framework has also been introduced by the AACE/ACE. This was based on the belief that obesity is caused by multifaceted interactions between biological, environmental, and behavioral factors. However, the staging system suggested by the AACE/ACE is an elaborate staging mechanism, and Indian PCPs may not have adequate time to evaluate all the aspects of their patients’ data required by this system. The EOSS is an easier option that uses BMI as a base to identify individuals with obesity and then classify them on the basis of absence/presence of comorbidities. Notably, the BMI values need to be individualized for the Indian population (thin-fat phenotype) as described in the consensus statement by Misra et al.

Consensus Statements

• The EOSS is most suitable for the assessment (staging) of obesity and is very helpful in treatment planning in primary care settings (grade of recommendation: B; level of evidence: 2a).

Multidisciplinary Approach and Setting Realistic Goals in Obesity Management

A multidisciplinary team involving different specialties is vital for ensuring that diagnosing and managing obesity and its associated complications are based on reliable evidence. This team should be customized as per the availability of specialists and the hospital setting (urban or rural). Underlying comorbidities and medication history must be evaluated and noted to record their influence on obesity and should be appropriately managed first. This should be followed by further evaluation of other risk factors and obesity therapy planning.

The involvement of a multidisciplinary team is a must to ensure holistic support to patients in terms of nutrition, fitness, pharmacotherapy, psychological, and surgical aspects. Additionally, each specialty can ensure the implementation of an evidence-based treatment plan to help patients with obesity achieve desired treatment goals via personalized and effective approaches. Shared decision-making, which involves initial assessment by an appropriate team followed by periodic assessment by the multidisciplinary team, along with appropriate customization and modifications in the treatment approach, is essential for optimal and sustained outcomes.

Setting realistic goals is the key to successful obesity management. Very importantly, it improves patient adherence to

![Fig. 1: Edmonton Obesity Staging System (EOSS)](image-url)
the planned treatment approach. In general, the treatment goals should be realistic and sustainable. The aspects that drive weight gain (such as stress, depression, lack of time, and underlying comorbidities) should always be assessed and addressed appropriately. The treatment success should be evaluated in terms of improvement in all parameters, including metabolic, mental, and functional health.26

Realistic goals for metabolic, functional, and mental parameters should follow the Specific–Measurable–Achievable–Rewarding–Timely (SMART) principles. Self-monitoring with a lifestyle (nutrition, fitness, and behavior) journal helps initiate and sustain achieved goals.26 Successful weight loss achieved has a linear relationship with health outcomes (metabolic, functional, and mental). Greater weight loss is associated with better outcomes; for example, a weight loss of >15% has the potential to remit T2DM, heart failure with preserved ejection fraction (HFpEF), and possibly impact mortality. Notably, a 2–5% loss in weight led to significant reductions in systolic blood pressure (BP) and serum levels of glucose, glycated hemoglobin (HbA1c), and triglycerides.27 Furthermore, 5–10% weight loss in individuals with obesity/who are overweight with associated comorbidities can significantly reduce the development of T2DM and improve health outcomes in individuals with dyslipidemia, hyperglycemia, osteoarthritis, stress incontinence, GERD, hypertension, and PCOS.28 According to the Look AHEAD study (N = 5,145), weight loss in 1 year was highly significantly (p < 0.0001) related to lower serum glucose levels, BP, serum triglyceride levels, and serum high-density lipoprotein cholesterol levels.27

Consensus Statements
A multidisciplinary team should be involved in the assessment and management of patients with obesity (grade of recommendation: B; level of evidence: 2b).

The following members should be a part of the multidisciplinary team for addressing comorbidities in patients with obesity (grade of recommendation: B; level of evidence: 2b):

- Core team: Physician, dietician, physiotherapist, psychologist, bariatric surgeon, endocrinologist, and gynecologist.
- Others (on call as per comorbidity): Cardiologist, chest physician, orthopedist, gastroenterologist, and psychiatrist.

In individuals with obesity/who are overweight, weight loss is important to prevent or improve control of obesity-related comorbidities (grade of recommendation: A; level of evidence: 1a).

Setting realistic goals is important for the simpler and more effective management of obesity and related complications (grade of recommendation: B; level of evidence: 2b).

The weight loss target should be individualized based on the type of comorbidity (grade of recommendation: B; level of evidence: 2a).

Lifestyle Interventions
The diagnosis of obesity, abdominal obesity, and metabolic syndrome in Asian Indians requires that dietary intake should be planned as follows:6

- Carbohydrate intake must be 50–60% of the total energy per day, with a preference for complex carbohydrates and low glycemic index foods.
- Fiber intake must be 25–40 g per day.
- Saturated fats must be <10% of the total energy per day.
- The ratio of essential fatty acids per day must be 1–2% of total energy and must include linolenic acid (LA), 5–8%, and alpha-linolenic acid (ALA), at an optimal ratio of LA/ALA, 5:10%; the cis-monounsaturated fatty acids must make up 10–15%; and trans fatty acids <1% of the total energy.
- Protein consumption must be 10–15% of the total energy per day.
- Salt intake must be 5 gm per day.
- Sugar intake must be <10% of the total energy per day.

Medical nutrition therapy (MNT) is a widely discussed option in the West. It mainly involves nutritional assessment, counseling, advice, and follow-up by a qualified or trained PCP. However, some challenges hinder the initiation of MNT in the Indian population. Some of the key challenges include the nonavailability of insurance coverage, lack of awareness among physicians, inability to individualize MNT, and lack of nutritionists trained in MNT. The MNT is often preferred/opted for by individuals with a busy lifestyle (who find it difficult to plan their regular diet) and those who can afford it.10 A detailed approach for individualizing MNT among South Asians has been published in the Consensus on Medical Nutrition Therapy for Diabesity by Kapoor et al.29

Lifestyle intervention that mainly involves dietary modifications remains important for the successful management of obesity in India. Exercise is vital, along with dietary modifications, to achieve the weight loss targets and control metabolic comorbidities. The intensity and type of activity are to be individualized based on the comorbidities and physical activity levels of patients.

Unlike other care programs, promoting both diet and physical activity lowered T2DM incidence (risk ratio: 0.59), body weight (net change: 2.2% [CI, 2.9–1.4%]), and fasting blood glucose levels (net change: 2.2 mg/dL) and other cardiometabolic risks.30 A study that analyzed 32 randomized controlled trials (RCTs) demonstrated that an average exercise session of 45 minutes per day and mean exercise frequency of 3.25 days/week significantly decreased HbA1c levels (p < 0.0001), fasting blood glucose levels (p < 0.03), BMI (p < 0.04), and WC (p < 0.007) in the exercise group when compared with the group that did not exercise.31

Weekly targets for exercise can be set to 75–150 minutes of vigorous exercise or 150–300 minutes of moderate exercise.10,32 Resistance training is useful as it preserves lean body mass during weight loss regimes and not only helps with fat loss but also improves metabolic and physical function.33 Combining resistance training with aerobic exercise and restricting calories significantly reduced regional adiposity and body weight in individuals with obesity and overweight, as per a large meta-analysis of 114 trials by Lopez et al which included 4184 participants (p < 0.001).34

Consensus Statements
• The dietary targets set in the consensus statement by Misra et al.5 can be followed for obesity management in India (grade of recommendation: B; level of evidence: 2a).
• Physical activity reduces the risk of developing obesity-associated comorbidities and should hence be advocated along with dietary modifications (grade of recommendation: A; level of evidence: 1a).
• Physical activity target for moderate-to-vigorous exercise should be as follows (grade of recommendation: D; level of evidence: 5):
  - About 150–300 minutes of moderate physical activity per week.
  - About 75–150 minutes of vigorous physical activity per week.
• Resistance training is an important aspect of lifestyle interventions for weight management in Asian Indians (grade of recommendation: B; level of evidence: 2a).

Pharmacotherapy
A detailed assessment of the steps taken by patients or PCPs to address obesity is essential before initiating pharmacotherapy for obesity. It must be ensured that patients put in adequate efforts in terms of lifestyle...
measures and physical activity. Additionally, the effects of medications being taken by patients with comorbidities need to be assessed. Medications such as antidiabetics, antihypertensives, antipsychotics, antihistamines, and antidepressants are known to cause weight gain. Weight neutrality or the weight loss potential of a drug should be considered when choosing any pharmacotherapy for a patient with obesity. For example, glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as liraglutide, semaglutide or dulaglutide, and sodium–glucose cotransporter-2 inhibitors (SGLT2Is), such as dapagliflozin, canagliflozin, or empagliflozin, among patients with T2DM, help in maintaining glycemic control while also promoting a safe and effective loss of weight along with pleiotropic benefits, including end-organ protection.

Among other patients who have been advised only lifestyle interventions (nutrition, fitness, and behavior therapy), there may be a saturation point or set point where further weight loss will not happen. Individuals thereon may start gaining weight again despite these measures, as neurohormonal mechanisms, including reduced resting metabolic rate or increased appetite, are triggered, driving a significant weight gain. Hence, continued management of obesity is important for sustained weight loss, retention of the weight loss, and long-term health benefits. Long-term strategies (such as pharmacotherapy) can positively impact the counter-regulatory mechanism and hence prevent obesity relapse. Pharmacotherapy is also considered essential for bridging the gaps in managing obesity.

According to the consensus statement by Misra et al., pharmacotherapy is advisable for people with BMI ≥27 kg/m² and no comorbidities or people with BMI ≥25 kg/m² with comorbidities. For initiating pharmacotherapy, WC cutoff values of 80 cm for Asian Indian women and 90 cm for Asian Indian men were unanimously agreed upon. An individualized approach to pharmacotherapy is required; this must include considerations of comorbidities, preferences, insurance coverage, and costs. In addition, combination therapy is less preferable than single weight-loss drugs. Multiple agents may be considered in patients with difficulty in reducing weight. Currently, the approved medications for managing obesity in India include orlistat 120 mg (oral) and semaglutide 2.4 mg (subcutaneous injection). Other medications and their characteristics have been enumerated in Table 2.

**Orlistat**

Orlistat exerts its action by inhibiting lipases. It bonds covalently with an active site serine residue in gastric lipases and pancreatic lipases and irreversibly inactivates them. It also inhibits triglyceride hydrolysis partially and reduces monoaoylglycerolides and free fatty acid absorption. The XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study was one of the largest RCTs that evaluated the efficacy of orlistat in 3,305 individuals with obesity. The use of orlistat led to a 2.4% net weight loss after 4 years. Notably, this lowered the risk of T2DM development in the group taking orlistat than the placebo group (9 vs 6%, respectively). According to a study in India, orlistat was associated with a significant (p < 0.05) weight reduction (4.65 kg) compared to a placebo (2.5 kg; Fig. 2) and reductions in WC, BMI, and cholesterol levels.

![Fig. 2: Weight loss noted with orlistat or placebo](image)

**Table 2: Medications for managing obesity**

<table>
<thead>
<tr>
<th></th>
<th>Orlistat 120 mg</th>
<th>Naltrexone/ bupropion</th>
<th>Phenetermine/topiramate 3.75/23 mg and 15/92 mg</th>
<th>Liraglutide 3.0 mg</th>
<th>Semaglutide 2.4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MoA</strong></td>
<td>Energy wastage</td>
<td>Appetite suppressant</td>
<td>Appetite suppressant</td>
<td>Appetite suppressant</td>
<td>Appetite suppressant Reduced energy intake</td>
</tr>
<tr>
<td><strong>Weight loss (1 year, US label)</strong></td>
<td>3.8% Placebo: 1.27%</td>
<td>5.4/8.1% Placebo: 1.3/4.9%</td>
<td>5.1/10.9% Placebo: 1.6%</td>
<td>Not established</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Effect on cardiovascular morbidity/mortality</strong></td>
<td><strong>Cardiovascular risk factors lowered: BP and serum lipid levels</strong></td>
<td><strong>Not established</strong></td>
<td><strong>Not established</strong></td>
<td><strong>Liraglutide 1.8 mg CVOT LEADER safety data have been added to the label</strong></td>
<td><strong>SUSTAIN 6 and PIONEER 6 safety data have established cardiovascular safety</strong></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Three times daily, oral</td>
<td>Two times daily, oral</td>
<td>Once daily, oral</td>
<td>Once daily, subcutaneous injection</td>
<td>Once weekly, subcutaneous injection</td>
</tr>
<tr>
<td><strong>Most common AEs (&gt;5%)</strong></td>
<td>Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence</td>
<td>Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea</td>
<td>Paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth</td>
<td>Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, and abdominal pain</td>
<td>Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, and abdominal distension</td>
</tr>
<tr>
<td><strong>Approval in India</strong></td>
<td>Approved</td>
<td>Not approved</td>
<td>Not approved</td>
<td>Not approved</td>
<td>Approved (not yet available in the Indian market)</td>
</tr>
</tbody>
</table>

*Data from the phase III CONTRAVE obesity research I and II studies, respectively; †Data are for 3.75/23 mg and 15/92 mg doses of phenetermine/topiramate, respectively; AEs, adverse events; CVOT, cardiovascular outcome trial; MoA, mechanism of action.
The safety assessment of orlistat based on seven multicenter, placebo-controlled, double-blind clinical trials with 1,913 individuals treated with orlistat and 1,466 individuals receiving placebo revealed that 8.8% of patients given orlistat and 5.0% of patients given the placebo discontinued treatment due to adverse events. The most common adverse reactions included oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence.

**Semaglutide**
A long-acting GLP-1 analog, semaglutide is a native GLP-1 mimetic and reduces energy intake, thereby causing loss of weight; it also reduces gastric emptying, increases satiety, reduces hunger, and improves glycemic control. Alongside weight loss and blood glucose effectiveness, GLP1-RAs also protect vital organs (heart, liver, kidney, and brain).

In a double-blind trial involving 1,961 adults with obesity, treatment with once-weekly 2.4 mg semaglutide therapy with changes in their lifestyles led to a reduction of 14.9% of their weight at week 68 along with greater improvements in cardiovascular risk compared to treatment with a placebo. The most common adverse events included diarrhea and nausea.

As per the semaglutide treatment effect in people with obesity (STEP) program, a series of five phase III clinical trials measuring the efficacy of subcutaneously administering 2.4 mg of semaglutide once a week for managing weight in people with obesity and with/without T2DM, semaglutide treatment was associated with substantial weight loss across all trials. The comparative mean loss in weight noted in the STEP 1–5 trials has been enumerated in Figure 3. However, semaglutide use was associated with gastrointestinal adverse events.

Although injectable semaglutide (2.4 mg) is approved for use in India by the Central Drugs Standard Control Organization for obesity management, it is not yet available in the Indian market.

**Consensus Statements**
Pharmacotherapy is a vital cog in obesity care for weight loss, long-term weight maintenance, prevention of weight regain, and protection of end organs (grade of recommendation: A; level of evidence: 1b). Based on the safety, durability, and effectiveness, once-weekly subcutaneous semaglutide 2.4 mg could be the first-choice anti-obesity medication (expert recommendation).

A pharmacotherapeutic approach should be initiated in the following population of Asian Indians (grade of recommendation: D; level of evidence: 5):

- **BMI ≥27 kg/m²** with or without comorbidity.
- **BMI ≥25 kg/m²** with at least one associated comorbid medical condition, such as hypertension, dyslipidemia, T2DM, and obstructive sleep apnea.

**Bariatric surgery**
According to the Obesity and Metabolic Surgery Society of India (OSSI) 2020 guidelines, the following population groups are eligible for bariatric surgery:

- **BMI ≥35 kg/m²**, with/without any comorbidities related to obesity
- **BMI ≥32.5 kg/m²** with >1 comorbidity related to obesity (OSSI 2013 guidelines)
- **BMI ≥30 kg/m²**, with >2 comorbidities related to obesity
- **BMI ≥27.5 kg/m²**, having uncontrolled T2DM despite treatment
- Women with WC of ≥80 cm and men with WC of ≥90 cm having comorbidities related to obesity.

Currently, all bariatric and metabolic surgeries rely on procedures that are restrictive, malabsorptive, or a combination of the two and include one-anastomosis gastric bypass (OAGB), Roux-en-Y gastric bypass, and sleeve gastrectomy (SG). Recently, in India, OAGB surgery is the second most popular procedure after SG due to significantly high weight loss and satisfaction rates, low rates of complications, and a low reversal rate of only 0.2%.

**Newer Approaches**
New medications, such as tirzepatide, which is a dual gastric inhibitory polypeptide and GLP-1RA, and CagriSema, a combination of cagrilintide (amylin analog) with semaglutide (GLP-1RA), are currently under development. Looking at the promising pipeline of anti-obesity medications, we can expect a change in the treatment landscape for obesity.

Patients who are now candidates for bariatric surgery may be managed with newer anti-obesity medications in the future.

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**Fig. 3:** Weight loss across STEP trials with Semaglutide (Trial product estimand)
**Proposed Obesity Management Algorithm**

In India, the following approach has been suggested for diagnosing and managing obesity. A summary of the same has been provided in Figure 4.

**Step 1: Anthropometric evaluation**
- During the initial visit, anthropometric values including height, weight, BMI, WC, hip circumference, WHtR, and WHR are to be measured.

**Step 2: Clinical evaluation (including laboratory tests) for comorbidities and impacts**
- Evaluate complications and consequences (including comorbidities and physiological and psychological impacts).
- Endocrine evaluation tests (if applicable/necessary in the particular case).
- Socioeconomic status.

**Step 3: Risk stratification and management**

As per step 1 findings (anthropometric evaluation):

<table>
<thead>
<tr>
<th>BMI &lt;23 kg/m² AND waist circumference ≤80 cm in women, ≤80 cm in men</th>
<th>BMI ≥23 kg/m² AND/OR waist circumference &gt;80 cm in women, &gt;90 cm in men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent weight gain -&gt; Healthy meal, physical activity, and health education</td>
<td>Perform EOSS staging* considering the step 2 findings (clinical evaluation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>Stage 0</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>No risk factor</td>
<td>Pre-clinical</td>
<td>Comorbidity</td>
<td>End-organ damage</td>
<td>End stage</td>
</tr>
<tr>
<td>Psychological</td>
<td>Absent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
</tr>
<tr>
<td>Functional</td>
<td>Absent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

**Management modality as per staging**

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
</table>

**Lifestyle modifications**
- Calorie restriction, physical activity, and behavioral therapy.
- For stage 1, pharmacotherapy can be considered if BMI ≥27 kg/m² and lifestyle interventions alone are not effective.

**Pharmacotherapy (BMI ≥27 kg/m²)**
- Once weekly injectable semaglutide 2.4 mg**/Tab orlistat 120 mg.
- For stage 2, bariatric surgery may be considered if BMI ≥35 kg/m² on a case-by-case basis if lifestyle interventions and pharmacotherapy are not effective.

**Bariatric surgery if BMI ≥35 kg/m²**

*Refer to figure 1 for more details on EOSS staging; **Semaglutide 2.4 mg has been approved for obesity management, but not yet available in the Indian market.

**Step 4: Follow-up**
- Plan the follow-up dates/periods–2/3/6 months and set targets to be evaluated
- Modify treatment plan (if needed)

BMI: Body mass index; EOSS: Edmonton Obesity Staging System.

*Fig. 4: Proposed diagnosis and management algorithm for obesity*
Step 3: Risk stratification and management
All patients must be first broadly categorized based on step 1 findings (anthropometric evaluation) as “normal weight” OR “overweight/obesity.” The normal-weight patients can be managed with preventive care while the patients who are classified under overweight/obesity (as per Asian BMI and WC cut-offs) need to be further subclassified using the EOSS to evaluate the clinical stage based on the findings in step 2 of the algorithm. The management of the patients can be individualized accordingly. Lifestyle modification will apply to patients in all stages, while pharmacotherapy needs to be initiated in patients categorized as stage 1 and with BMI ≥27 kg/m², if lifestyle interventions alone are not effective in achieving the target weight.\(^9,38,39,44\)

Pharmacotherapy will be required in all patients categorized as stage 2 and above (BMI ≥25 and with one or more comorbidities). Bariatric surgery may be considered if patients categorized as stage 2 and above (BMI ≥25 and with one or more comorbidities). The use of appropriate staging pharmacologic agents, and long-term absence of comorbidities, available needs to be individualized, considering comorbidities. The treatment for obesity as a significant contributor to other conditions, such as the EOSS, after adapting it to outcomes. The use of appropriate staging criteria, such as the EOSS, after adapting it to the Indian population, can help optimize the treatment strategy and improve treatment outcomes.

**Acknowledgments**
We extend our heartfelt appreciation to Dr Ashok Kumar Das, Dr Mithun Bhartia, Dr Tejas Shah, Dr Supriyaa Bhakthavatchalam, Dr Arjun BS, Dr Pranjali Shah, Dr Abhijith Jawanjal, Dr Sagar Sourav, Dr Amit Basu, Dr Harshikesh Bora, Dr Sharad Bedi, Dr Sudharsan Narayanamoorthy, Dr Ranjit Mohan, Dr Anusha, Dr Sharath Hegde, Dr Vishnupriya Reddy, Dr Sagar Sourabh, Dr Karthik, Dr Abdul Raqeeb, Dr Srinath K Bhat, Dr Malay Parekh, Dr Kiran Deep Kamal, Dr S Pawan Kumar Sharma, Dr Amit Bhatnagar, Dr Meghana Reddy, and Dr Saran M S for their valuable contributions and unwavering support throughout this endeavor. We would also like to thank BioQuest Solutions for the editorial assistance.

**Author Contributions**
All authors have contributed equally to the conception, design drafting, review, and finalization of the manuscript.

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**Appendix**

**Appendix 1: Grade criteria**

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Level of evidence</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1a</td>
<td>Systematic review of (homogeneous) randomized controlled trials</td>
</tr>
<tr>
<td>A</td>
<td>1b</td>
<td>Individual randomized controlled trials (with narrow confidence intervals)</td>
</tr>
<tr>
<td>B</td>
<td>2a</td>
<td>Systematic review of (homogeneous) cohort studies of &quot;exposed&quot; and &quot;unexposed&quot; subjects</td>
</tr>
<tr>
<td>B</td>
<td>2b</td>
<td>Individual cohort study/low-quality randomized control studies</td>
</tr>
<tr>
<td>B</td>
<td>3a</td>
<td>Systematic review of (homogeneous) case-control studies</td>
</tr>
<tr>
<td>B</td>
<td>3b</td>
<td>Individuals case-control studies</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>Case series, low-quality cohort or case-control studies</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>Expert opinions based on non-systematic reviews of results or mechanistic studies</td>
</tr>
</tbody>
</table>

**References**


**Appendix**

- Endocrine evaluation tests (if applicable/ necessary in the particular case).
- Socioeconomic status.

Incidence of New-onset Hypertension and New-onset Type 2 Diabetes during or after SARS-CoV-2 Infection

Abhinav Gupta1*, Ranjana Duggal2

Received: 22 January 2023; Accepted: 03 May 2023

ABSTRACT

Background: Considering the potential clinical and therapeutic implications, there is a need to determine whether or not COVID infection induces or unmasks new-onset/newly diagnosed hypertension/diabetes during the acute phase and post-COVID-19.

Aim: In the current article, we discuss the current data at the intersection of COVID, hypertension, and COVID and diabetes, from prevalence, risk factors, and underlying mechanisms during an acute and post-COVID phase; focusing on new-onset hypertension and new onset type 2 diabetes.

Method: We have performed a literature search via online databases such as PubMed/MEDLINE and Google Scholar from December 2019-August 2022. The data from various studies and review articles have been included.

Results: Current evidence suggests the occurrence of new-onset hypertension and new onset type 2 diabetes in patients infected with the SARS-CoV-2 virus. Data also indicate a higher risk of negative outcomes in these patients.

Conclusions: It is evident that the tenacity of these new-onset diseases post-COVID-19 is likely to have huge implications in terms of unexpected morbidity. Therefore, screening and follow-up of these patients seems reasonable. Clinicians shall have to deal with this evolving challenge and adequately equip themselves to address this facet of COVID-19 as well. Further data from various follow-up studies and registries like the CovidDIAB Project is required to be better equipped to propose exact recommendations for patients with NOD. On the contrary, more evidence is required for incidence and long-term sequelae for patients with new-onset hypertension.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused havoc globally for nearly the past 3 years. It continues to create new challenges due to its association with its long-term risk of new-onset comorbidities. Initially, it was perceived that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the respiratory system. However, with increasing clarity on its pathophysiology and its effect on multiple organ systems, several underlying mechanisms are being identified.1 Considering the potential clinical and therapeutic implications, whether or not, COVID-19 infection induces or unmasks new-onset/newly diagnosed hypertension/diabetes during the acute phase and post-COVID-19 should be determined. These data would allow the development of appropriate recommendations for management during the acute phase as well as follow-up of patients’ post-COVID-19 infection.

In the current article, focusing on new-onset hypertension and type 2 diabetes, we discuss the current data at the intersection of COVID-19, hypertension, and COVID-19 and diabetes, from prevalence, risk factors, and underlying mechanisms during an acute and post-COVID-19 phase.

METHODS

We have performed a literature search via online databases such as PubMed/MEDLINE and Google Scholar by using the following keywords—acute phase COVID-19, post-COVID-19, new-onset hypertension, and new-onset type 2 diabetes in subjects aged ≥18 years from December 2019 to August 2022. The data from various studies and review articles have been included.

Incidence of New-onset Hypertension Associated with SARS-CoV-2 Infection

Few studies have reported the occurrence of new-onset hypertension in patients with COVID-19 infection during the acute and post-COVID-19 phases. These have been described in (Table 1).

Indirect Evidence

Two authors have also reported blood pressure-associated adverse event following immunizations following messenger ribonucleic acid (mRNA) COVID-19 vaccination. These include a case series of nine patients with stage 3 hypertension and two isolated cases of hypertension with intracranial hemorrhage postvaccination.6,7

Unlike the case series in which most have a history of hypertension, the blood pressure (BP) of an elderly female in the single case report was 110/70 mm Hg which increased to 210/110 mm Hg.

The rise in BP after COVID-19 is also indirectly supported by hypertension occurring after vaccination. More research is needed to confirm the occurrence of hypertension after mRNA-based vaccination and SARS-CoV-2 infection.8

Though limited these data show that newly diagnosed hypertension was present in a significant proportion of COVID-19 patients and suggests an association between COVID-19 infection and elevated BP.

Incidence of New-onset Type 2 Diabetes Associated with SARS-CoV-2 Infection

Several published studies listed in (Table 1) demonstrate the increased prospect of new-onset diabetes (NOD) during the acute phase of infection or just after recovering from infection SARS-CoV-2.14–36 A recent meta-analysis by Shrestha et al. found the pooled prevalence of COVID-19 associated diabetes mellitus (new-onset) to be 19.7%.9 Results from these studies are reinforced by the Mendelian randomization analysis creating an association between SARS-CoV-2 infection and NOD.10

The majority of these studies were retrospective observational studies that found a varying proportion of patients with NOD (Table 2). These included the previously undiagnosed along with new-onset ones. However, since hemoglobin A1c (HbA1c) was not performed for all the included patients a clear distinction between new-onset and previously undiagnosed was challenging.
Incidence of New-onset Hypertension and New-onset Type 2 Diabetes

Table 1: Studies reporting new-onset hypertension during the acute phase of SARS-CoV-2 infection

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al.</td>
<td>2021</td>
<td>China</td>
<td>Retrospective cohort</td>
<td>Analysis of electronic medical records data revealed that stage I chronic hypertension was present in only 37% of patients, while the prevalence of chronic hypertension stages II and III was nearly twice as high (61 and 70%, respectively). &gt;8.0% of patients had a major rise in SBP during hospitalization. When comparing the RAS activity between the normal and elevated BP groups, angiotensin-II levels were significantly higher in the latter group (median (IQR) — 169.25 (142.17–186.98) vs 137.12 (123.63–161.67) pg/mL, p = 0.020).</td>
</tr>
<tr>
<td>Akpek</td>
<td>2022</td>
<td>Turkey</td>
<td>Retrospective cohort</td>
<td>Elevated SBP (120.9 ± 7.2 vs 126.5 ± 15.0 mm Hg, p &lt; 0.001) and diastolic BP (78.5 ± 4.4 vs 81.8 ± 7.4 mm Hg, p &lt; 0.001) in the post-COVID-19 period (4-week follow-up) than at admission. New-onset hypertension was confirmed in 12% of patients at the end 4-week follow-up period. The proportion of patients with hypertension was significantly higher than at admission (12 vs 0%; <em>p &lt; 0.001) as per the Joint National Committee 8</em> and European Society of Cardiology** guidelines.</td>
</tr>
<tr>
<td>Mahmud et al.</td>
<td>2021</td>
<td>Bangladesh</td>
<td>Prospective cohort study</td>
<td>1.2% (2/162) developed new-onset hypertension, twice that of NOD 0.6% (1/162).</td>
</tr>
<tr>
<td>Xiong et al.</td>
<td>2021</td>
<td>China</td>
<td>Longitudinal study</td>
<td>The incidence of new-onset hypertension is 1.3% (7/538).</td>
</tr>
</tbody>
</table>

#IQR, interquartile range; **Eighth Joint National Committee; ***European Society of Cardiology

Table 2: Studies reporting NOD during the acute phase of SARS-CoV-2 infection

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>New-onset T2D% (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>2020</td>
<td>China</td>
<td>Retrospective cohort</td>
<td>27.5% (22/80)</td>
</tr>
<tr>
<td>Li et al.</td>
<td>2020</td>
<td>China</td>
<td>Retrospective</td>
<td>5.5% (25/453)</td>
</tr>
<tr>
<td>Previously undiagnosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clausen et al.</td>
<td>2022</td>
<td>Denmark</td>
<td>Multicenter observational cohort</td>
<td>11% (74/674)</td>
</tr>
<tr>
<td>Motavesa et al.</td>
<td>2022</td>
<td>Egypt</td>
<td>Case report</td>
<td></td>
</tr>
<tr>
<td>Smith et al.</td>
<td>2021</td>
<td>USA</td>
<td>Retrospective study</td>
<td>46.2% (85/184)</td>
</tr>
<tr>
<td>Sathish et al.</td>
<td>2021</td>
<td>India</td>
<td>Retrospective cohort</td>
<td>20.6% (21/102)</td>
</tr>
<tr>
<td>Li et al.</td>
<td>2020</td>
<td>China</td>
<td>Retrospective</td>
<td>8.4% (38/453)</td>
</tr>
<tr>
<td>Yi et al.</td>
<td>2020</td>
<td>China</td>
<td>Retrospective cohort</td>
<td>0.6% (3/521)</td>
</tr>
<tr>
<td>Yang et al.</td>
<td>2020</td>
<td>China</td>
<td>Retrospective case series</td>
<td>Critical 53.85% and moderate-severe 13.95%</td>
</tr>
<tr>
<td>Li et al.</td>
<td>2020</td>
<td>China</td>
<td>Retrospective</td>
<td>6.8% (31/453)</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>2020</td>
<td>Australia</td>
<td>Retrospective</td>
<td>3/8</td>
</tr>
<tr>
<td>New-onset and previously undiagnosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al.</td>
<td>2021</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>15.8% (29/184)</td>
</tr>
<tr>
<td>Fadini et al.</td>
<td>2020</td>
<td>Italy</td>
<td>Retrospective</td>
<td>5.08% (21/413)</td>
</tr>
<tr>
<td>Seigle et al.</td>
<td>2020</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>2.9% (13/450)</td>
</tr>
<tr>
<td>Lampasona et al.</td>
<td>2020</td>
<td>Italy</td>
<td>Retrospective cohort</td>
<td>9.6% (49/509)</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2020</td>
<td>China</td>
<td>Retrospective</td>
<td>16% (176/1101)</td>
</tr>
<tr>
<td>Case report/series</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suwanwongs and Shabarek</td>
<td>2021</td>
<td>USA</td>
<td>Case series</td>
<td>2</td>
</tr>
<tr>
<td>Ghosh et al.</td>
<td>2020</td>
<td>India</td>
<td>Case report</td>
<td>2</td>
</tr>
<tr>
<td>Chee et al.</td>
<td>2020</td>
<td>Singapore</td>
<td>Case report</td>
<td></td>
</tr>
<tr>
<td>Heaney et al.</td>
<td>2020</td>
<td>USA</td>
<td>Case report</td>
<td></td>
</tr>
<tr>
<td>Alsadhan et al.</td>
<td>2020</td>
<td>Saudi Arabia</td>
<td>Case report</td>
<td></td>
</tr>
<tr>
<td>Kuchay</td>
<td>2020</td>
<td>India</td>
<td>Case series</td>
<td>2</td>
</tr>
</tbody>
</table>

Newly diagnosed diabetes (NOD)—no prior history of diabetes with fasting plasma glucose (FPG) ≥7.0 mmol/L or random blood glucose (RBG) ≥11.1 mmol/L and HbA1c < 6.5%) or previously undiagnosed diabetes (FPG ≥7.0 mmol/L or RBG ≥11.1 mmol/L and HbA1c ≥ 6.5% or HbA1c ≥ 6.5% only
Growing evidence from the past 3 years also shows that NOD is detected in the postacute COVID-19 phase, also termed “long COVID-19” (Table 3).11,12


Inhibition of angiotensin-converting enzyme 2 (ACE2) and consequent increase in angiotensin-II due to the binding of SARS-CoV-2 to ACE2 may be the underlying mechanism of elevated blood pressure during infection. Overactivation of the renin--angiotensin system (RAS) supports an inflammatory response. Hyperactivation of RAS thus could be the predominant mechanism of COVID-19 infection and hypertension2 (Fig. 1). Thus, SARS-CoV-2 may be accompanied by spontaneous hypertension in patients during hospitalization and could become a sequela of SARS-CoV-2 infection, which may be associated with distinctly raised angiotensin-II levels.5

Potential mechanisms contributing to NOD in the acute and post-acute phase may include virus-induced β-cell cytotoxicity, insulin resistance, and dysregulation of the immune and RAS (Fig. 2).

Suggested mechanisms justifying the incidence of these new-onset diseases with SARS-CoV-2 infection may also include its effect on the hypothalamic-pituitary-adrenal and sympathoadrenal axes. These may lead to an increase in counter-regulatory hormones and activation of the RAS resulting in unimpeded detrimental actions of angiotensin-II.37

Risk Factors for New-onset Hypertension and Diabetes

No predictive risk factors at baseline have been identified in patients who developed new-onset hypertension or diabetes. Individuals hospitalized for COVID-19 had higher rates of multiorgan dysfunction compared with the anticipated risk in the general population postdischarge.32 The increase in risk was not restricted to any age group or ethnicity.32 Therefore, monitoring during the acute phase and follow-up may be the only approaches for patients infected with SARS-CoV-2.32

Screening and Post-COVID-19 Follow-up

Coronavirus disease 2019 (COVID-19) leads to an increase in both systolic and diastolic BP during the acute phase which is sustained in several patients and causes new-onset hypertension. Generally, BP is determined at presentation and during illness. However, given the potential risk for new-onset hypertension during the post-COVID-19 period, physicians should advise follow-up

Table 3: Studies reporting NOD during the post-COVID-19 phase of SARS-CoV-2 infection

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Follow-up</th>
<th>% NOD (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayoubkhani et al.</td>
<td>2021</td>
<td>England</td>
<td>Retrospective cohort</td>
<td>4.6 months</td>
<td>29 (95% CI, 26–32) per 1000 person-years</td>
</tr>
<tr>
<td>Daugherty</td>
<td>2021</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>2.9 months</td>
<td>NOD was the sixth most common postacute clinical sequelae</td>
</tr>
<tr>
<td>Montefusco et al.</td>
<td>2021</td>
<td>Italy</td>
<td>Prospective cohort</td>
<td>6 months</td>
<td>2% (5/253)</td>
</tr>
<tr>
<td>Farag et al.</td>
<td>2021</td>
<td>Egypt</td>
<td>Cross-sectional prospective</td>
<td>3 months</td>
<td>10.2% (58/570)</td>
</tr>
<tr>
<td>Cromer et al.</td>
<td>2022</td>
<td>USA</td>
<td>Retrospective</td>
<td>30 days</td>
<td>80.51% (62/77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>323 days (IQR* 205–385 days)</td>
<td>58.06% (36/62)</td>
</tr>
</tbody>
</table>

New-onset diabetes (NOD)—if the patient had no prior history of diabetes (based on self-reports or clinical notes), no HbA1c values ≥ 6.5%, no random blood glucose (RBG) values >200 mg/dL, and had never taken nonmetformin diabetes medications; *IQR, interquartile range

Fig. 1: Proposed mechanisms for SARS-CoV-2 infection-induced new-onset hypertension
of these patients. Early recognition may allow prompt treatment and avoid hypertension-associated complications.

There are comparatively more incidences of NOD reported than new-onset hypertension associated with COVID-19 infection. A recent meta-analysis of 128 studies has found that the mortality rate was highest among patients with NOD compared to those with preexisting T2D and those without T2D (24.96 vs 16.03 vs 9.26%). These data suggest that COVID-19 patients should be screened for NOD during the acute phase and post-COVID-19 phase.

It may be argued that these two diseases associated with COVID-19 infection could be stress-induced due to the current crisis with corticosteroids for treatment. In such cases, the patient’s blood pressure and blood glucose levels will normalize after recovery. It has been found that elevated systolic blood pressure (SBP) reverted to normal post-recovery in a few patients, for ensuring the same follow-up is required.

Several decades earlier infections have been identified as a risk factor for hypertension and T2D. Studies have shown chronic infections such as cytomegalovirus, human herpes virus 8, human immunodeficiency virus-1, and chronic hepatitis C virus increase the prevalence of these diseases, possibly via increased expression of renin. Indeed, the American Diabetes Association guidelines recommend screening for infection in newly diagnosed patients, particularly if blood glucose levels are very high. While data for the new-onset of hypertension with acute infections is still sparse, emerging studies have supported the risk of NOD with SARS-CoV-2 infection, hence the history of acute viral infection could be a risk factor for the development of diabetes.

**CONCLUSION**

Current evidence suggests the occurrence of new-onset hypertension and NOD in patients infected with the SARS-CoV-2 virus. Data also indicate a higher risk of negative outcomes in these patients. Thus, the tenacity of these new-onset diseases post-COVID-19 is likely to have huge implications in terms of unexpected morbidity, particularly if screening and follow-up of these patients are neglected. It seems reasonable to state that clinicians shall have to deal with this evolving challenge and adequately equip themselves to address this facet of COVID-19 as well. As further data accumulate from various follow-up studies and registries like the CoviDiab Project, we shall be better equipped to propose exact recommendations for patients with NOD. On the contrary, more evidence is required for incidence and long-term sequelae for patients with new-onset hypertension since ACE2 receptors which are receptors for SARS-CoV-2 are more closely associated with the maintenance of normal blood pressure.

**REFERENCES**


Digital Technology in Hospital Administration: A Strategic Choice

Dev Taneja1*, Shriram V Kulkarni2, Sagar Sinha3, Ramakrishnan N Dindigal4

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ABSTRACT

Digital technology has encompassed all aspects of healthcare. There are many international and national organizations, guidelines, and formats available in health information systems (HIS), but many are presently still not being used in India. The aim is to give a flawless, secure, and user-friendly health information technology (IT) system for Indian healthcare. We discuss the timeline of digital technology in hospital administration, administrative applications, and the importance of clinical quality in health. Clinical perspectives of clinical information systems (CIS), both in acute as well as chronic clinical care models. Cross-integration of healthcare in IT (HIT) in electronic health records (EHR) or electronic medical records (EMRs), in chronic disease management (CDM) systems, and in clinical decision support systems (CDSS) are elaborated. Also, practical strategic application methods are discussed. The limitations of the current HIS software in India are mostly used for transaction reporting, prescription, and administrative tools. They lack CIS and strategic business applications as compared to mature multinational company (MNC) HIS software. Along with this, various features and levels of HIS Software, challenges of HIT adoption, Indian health IT standards, and the future framework of IT in health in India are systematically analyzed. We aim at all physicians in India and at all levels of practice, from individuals, group practices, health institutes, or corporate hospitals, and to encourage them to make strategic use of CIS and strategic IT applications in their individual practice and hospital management. This will improve clinical outcomes, patient safety, practitioner performance, adherence to treatment guidelines, and reduction in medical errors, along with efficiency improvements and cost reductions.

INTRODUCTION AND HISTORICAL PERSPECTIVES

Technology touches every aspect of our lives and has played a huge role in healthcare over the years, paving the way for innovative medicines and procedures. Technology continues to revolutionize healthcare information technology, including facilitation from paper record systems to digital ones. Further transitioning includes additional complexities like protection of privacy and patient access. The healthcare system is represented by the frontline doctors and nurses working with the patients; however, the role of the healthcare administrators is paramount, who are responsible for the day-to-day operations of the organization. This has a lot of paperwork, but new software and technology have changed how healthcare administrators keep track of everyday tasks.

The Association of Record Librarians of North America was founded in 1928 by the American College of Surgeons to elevate the standards of clinical records in hospitals and other medical institutions.1 Its current form, the American Health Information Management Association and, later, a not-for-profit Health Information and Management Systems Society (HIMSS), are attempting to reform the global health ecosystem through the power of information technology. The HIMSS’ electronic medical record adoption model (EMRAM) measures clinical outcomes, patient engagement, and the clinical use of EMR technology to strengthen organizational performance and health outcomes across patient populations. A healthcare organization’s digital maturity is evaluated as per EMRAM adoption stages from 0 to 7.2

A health information system (HIS) refers to a system designed to manage healthcare data. This includes systems that collect, store, manage, and transmit a patient’s EMR, a hospital’s operational management system, or a system supporting healthcare policy decisions.

HEALTH MANAGEMENT AIMS

Key goals of every hospital management include (1) improvement of quality, cost-effectiveness, and efficiency of hospital services; (2) increase of patient/customer satisfaction; and (3) reduction in medical errors and promotion of medical safety. Besides direct benefits to the frontline healthcare provider (HCP), HIS can assist the management and administration in understanding the health of the organization, including continuous monitoring of clinical outcomes and business performance. The daily vital operational charts of clinical, operational, and financial performance indicators can guide the management, as illustrated in Table 1.

CURRENT INDIAN DIGITAL HEALTHCARE

Currently, in the Indian healthcare industry, hospital data is captured both manually and electronically. The healthcare industry globally has traditionally been a laggard in using HIS to improve efficiency, unlike mature industries like pharma, banking, etc. Strategic use of healthcare in information technology (HIT) is a proven and reliable productivity tool. Hospitals adopt a relatively large proportion of administrative information technology compared to clinical and strategic information technology.3 Most information technology applications are centered on administrative and financial transactions rather than on delivering clinical care.4 Going beyond transaction reporting, enterprise-level integration of processes, key result areas (KRAs), and key performance indicators (KPIs) for management information systems (MIS) are required to achieve the hospital’s desired goals, as illustrated in Table 2.

Health Information Systems (HIS) can be classified by provided solutions (e.g., service delivery or support services) or by core functions, like (1) patient management, (2) clinical services and support department management, (3) managerial applications for managing and control of clinical, operational, and financial performance, and...
Table 1: Health management indicators for clinical, operational, and financial performance

<table>
<thead>
<tr>
<th>Clinical indicators</th>
<th>Operational indicators</th>
<th>Financial indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical programs</td>
<td>Hospital occupancy</td>
<td>EBITDA</td>
</tr>
<tr>
<td>Physician performance</td>
<td>Department-wise utilization rates</td>
<td>Earning per bed per day</td>
</tr>
<tr>
<td>Clinical quality</td>
<td>Days in inventory</td>
<td>Current ratio</td>
</tr>
<tr>
<td>ALOS</td>
<td>Facility maintenance</td>
<td>DER</td>
</tr>
<tr>
<td>Mortality and morbidity</td>
<td>Employee attrition</td>
<td>Percentage salary to total expenses</td>
</tr>
<tr>
<td>OPD/IPD Census</td>
<td>Service excellence</td>
<td>Percentage consultant fee to total income</td>
</tr>
<tr>
<td>Clinical program marketing</td>
<td>Profit and cost center analysis</td>
<td>Percentage cash and credit business</td>
</tr>
<tr>
<td>Investigations—radiology/laboratory/others</td>
<td>MIS/HIS</td>
<td>Revenue cycle management</td>
</tr>
</tbody>
</table>

ALOS, average length of stay; DER, debt to equity ratio; EBITDA, earnings before interest, taxes, depreciation, and amortization; IPD, indoor patient department; MIS, management information software; OPD, outpatient department

Table 2: Health MIS—KRAs and KPIs

<table>
<thead>
<tr>
<th>Transaction data</th>
<th>Clinical data</th>
<th>Financial data</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT</td>
<td>Clinical quality</td>
<td>Resource utilization</td>
</tr>
<tr>
<td>RIS</td>
<td>Patient satisfaction</td>
<td>Service line efficiency</td>
</tr>
<tr>
<td>LIS</td>
<td>Clinical procedures</td>
<td>Risk management</td>
</tr>
<tr>
<td>Billing</td>
<td>Hospital departmental census</td>
<td>Trends</td>
</tr>
<tr>
<td>Stores</td>
<td>Mortality and morbidity</td>
<td>Forecasting</td>
</tr>
</tbody>
</table>

ADT, admission, discharge, and transfers; LIS, laboratory information system; RIS, radiology information system

Table 3: Common medical errors during delivery of clinical care

<table>
<thead>
<tr>
<th>Types of medical errors</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>Failure to employ indicated tests, Use of outmoded tests or therapy, Failure to act on results of monitoring or testing</td>
</tr>
<tr>
<td>Treatment</td>
<td>Error in the performance of an operation, procedure, or test, Error in administering the treatment, Error in dose or method of using the drug, Avoidable delay in treatment or in responding to abnormal test, Inappropriate (not indicated) care</td>
</tr>
<tr>
<td>Preventive</td>
<td>Failure to provide prophylactic treatment, Inadequate monitoring or follow-up of treatment</td>
</tr>
<tr>
<td>Others</td>
<td>Failure of communication, Equipment failure, Other’s system failure</td>
</tr>
</tbody>
</table>

Table 4: Medication errors and clinical process improvements to improve coordination of care

<table>
<thead>
<tr>
<th>Medication errors</th>
<th>Clinical care coordination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician ordering (56%)</td>
<td>Science of error reduction—continuous quality improvement (CQI)</td>
</tr>
<tr>
<td>Nursing medication administration (34%)</td>
<td>EMR</td>
</tr>
<tr>
<td>Secretarial medication transcription (6%)</td>
<td>Design around patients—disease management programs</td>
</tr>
<tr>
<td>Pharmacy medication dispensation (4%)</td>
<td>Research organizations—research, investigate, innovate and disseminate (RIID)</td>
</tr>
</tbody>
</table>

The Clinical Perspectives in Health IT

In India, we mostly use a transaction reporting system, whether in the hospitals or in the individual physician's office-based clinical practice management software. The potential of using clinical information systems (CISs) to improve clinical care, clinical quality, and clinical outcomes is still not being appreciated by the healthcare community. Furthermore, HIS applications in chronic disease management (CDM) and clinical decision support systems (CDSS) are rudimentary in India at present. One of the key reasons for this is that there is a huge variation in physician practices in the absence of defined national-level clinical protocols. Most clinical research is focused on new approaches for diagnosis and treatment. In contrast, relatively little effort has been targeted at the perfection of operational systems which are partly responsible for problems with medical safety.

Clinical Information Systems (CIS)

The publication of the report “To Err is Human: Building a Safer Health System” by the Institute of Medicine (IOM), United States of America (USA), in 1999 shocked the whole world, wherein it was revealed that between 44,000 to 98,000 people die in the USA annually as a result of medical errors. These “preventable errors” exceeded the deaths due to vehicular trauma, breast cancer, and acquired immune deficiency syndrome. There was disbelief, which was followed by a governmental response questioning the wisdom of leaving national healthcare to the fate of HCPs alone. Common errors during the delivery of clinical care were identified, as illustrated in Table 3. This led to further steps to improve coordination of clinical care delivery, as illustrated in Table 4. The IOM report shattered the belief that many
Digital Technology in Hospital Administration

Incorporating digital technology into hospital administration can significantly reduce errors and improve patient care. One such example is the implementation of a mandatory reporting system for hospitals in the USA. This system was found to be effective and reliable, leading to a reduction in medical errors and improved patient outcomes.

### Quality in Health and Accreditations

Joint Commission International accreditation, which earlier was mandatory for Medicare and Medicaid social health insurance programs, was made compulsory for all HCPs in the USA. This quality push was later followed across the whole world, where national health quality accreditations were introduced. In India, accreditations are provided by the National Accreditation Board for Hospitals and Healthcare Providers (NABH).

### Cross-integrations

**Importance of EMR and Personal Health Record (PHR)**

Electronic medical records (EMRs) address one of the greatest inefficiencies of healthcare, that is, the immobility of healthcare records. Timely availability of patient data can greatly help in the coordination of care, clinical decision-making process, and the significant reduction of medical errors.

In India, under the Ayushman Bharat Health Mission, now Ayushman Bharat Health Account (ABHA) numbers can be created for citizens and HCPs free of cost. Every citizen of India will have an Aadhaar card linked to a digital health card, which will have important medical records under this scheme. Henceforth, any registered HCP can access a patient’s medical history using his/her ABHA account/digital health card.

**Information Technology (IT) Enabled CDM System**

The medical community must appreciate that CDM means that the patient cannot be cured of his/her disease. As clinicians, we can, at best, help the patient maintain the near-normal health status of his/her ailment by using medications and advocating lifestyle changes. IT-enabled use of patients’ health data by the care team stakeholders can significantly improve CDM outcomes (Fig. 1). Currently, there is a dearth of coordinated care for CDM patients and a team approach to manage CDM for better health outcomes.

**Clinical Decision Support Software (CDSS)**

The main input for this system lies in the use of standardized clinical protocols nationally. Clinical pathways enable health providers to deliver evidence-based healthcare to patients, provide treatment guidance based on the latest research, and also support standardization of care. In India, the Indian Council of Medical Research has also come out with standard treatment workflows for various clinical specialties. Sooner than later, these clinical treatment workflows or protocols will be made mandatory for hospitals in India like NABH.

Clinical decision support software (CDSS) provides timely information, usually at the point of care, to help make informed decisions about a patient’s care. In conventional medical practice, there is a clinical presentation of the patient, followed by the clinician’s examination and judgment, which is followed by manual or electronic health records (EHR), eventually followed by decisions about the treatment. If the EHRs of the patients are available in the hospital system, then by using the rule-based algorithms or machine-learning algorithms, the clinical decision can be supported by the CDSS system’s inputs before making decisions about the treatment (Fig. 2). CDSS tools and systems help clinical teams by taking over routine tasks, giving warnings about potential problems, or providing suggestions for the clinical team and the patient to consider. CDSS has led to improved practitioner performance. An effective CDSS involves six levels of decision-making—alerting, interpreting, critiquing, assisting, diagnosing, and managing.

### Strategic Business Perspectives in Health IT

Healthcare is a capital-intensive and manpower-heavy industry, whether run by governmental funding as public health or by the private healthcare players where people pay for consuming health services either as out-of-pocket expenses or through private or social health insurance reimbursement. The current health insurance reimbursement reduction trends have forced hospitals to focus on providing high-quality care but also on cost containment.

**Levels of HISs**

In India, we mostly use basic HIS. Strategic upper-end solutions like enterprise resource planning (ERP) and business intelligence (BI) or health analytics level software usage are uncommon here (Fig. 3).

An additional layer of enterprise strategic management tools like Balanced Scorecard in healthcare is used by bigger healthcare systems. In India, the majority of health providers hardly use sophisticated financial modules for costing studies, utilization reviews, and financial controls and are happy using low-end financial software instead of...
Digital Technology in Hospital Administration

HMIS, ERP and BI: Advantages and limitations

| Modules mostly capture transactional data | HMIS | Limited applications for all support depts. |
| Modules cover transactions + support depts. But +/- clinical information systems | ERP | Static MIS dash boards. Limited analytical capability |
| Business intelligence/health analytics | Readymade role based actionable information available. No need to spend time for analyzing data | Interactive visualization of data to support decision making. Transformation of data to information to knowledge |

Fig. 3: Health information system (HIS) application levels—advantages and limitations; HMIS, health management information systems; ERP, enterprise resource planning

Table 5: Financial information systems maturity levels comparison—Indian vs MNC vendors

<table>
<thead>
<tr>
<th>MNC vendor’s financial modules offerings’ maturity level</th>
<th>Indian vendor’s financial modules offerings’ maturity level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced</td>
<td>Basic</td>
</tr>
<tr>
<td>Accounts payable</td>
<td>♦</td>
</tr>
<tr>
<td>Benefit administration</td>
<td>♦</td>
</tr>
<tr>
<td>Case mix management</td>
<td>♦</td>
</tr>
<tr>
<td>Cost accounting</td>
<td>♦</td>
</tr>
<tr>
<td>Electronic claims</td>
<td>♦</td>
</tr>
<tr>
<td>Executive information systems</td>
<td>♦</td>
</tr>
<tr>
<td>General ledger</td>
<td>♦</td>
</tr>
<tr>
<td>Materials management</td>
<td>♦</td>
</tr>
<tr>
<td>Patient billing</td>
<td>♦</td>
</tr>
<tr>
<td>Payroll</td>
<td>♦</td>
</tr>
<tr>
<td>Registration/admission-discharge-transfer</td>
<td>♦</td>
</tr>
<tr>
<td>NA, not available</td>
<td>♦</td>
</tr>
</tbody>
</table>

Table 6: Common HIS modules maturity levels comparison—Indian vs MNC vendors

<table>
<thead>
<tr>
<th>MNC vendor’s common HIS modules offerings’ maturity level</th>
<th>Indian vendor’s common HIS modules offerings’ maturity level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced</td>
<td>NA</td>
</tr>
<tr>
<td>Electronic medical history records</td>
<td>♦</td>
</tr>
<tr>
<td>Financial accounting and economics accounting</td>
<td>♦</td>
</tr>
<tr>
<td>Costing software</td>
<td>♦</td>
</tr>
<tr>
<td>Client relationship management system (CRMS)</td>
<td>♦</td>
</tr>
<tr>
<td>ERP</td>
<td>♦</td>
</tr>
<tr>
<td>HR management subsystem</td>
<td>♦</td>
</tr>
<tr>
<td>Logistic management subsystems</td>
<td>♦</td>
</tr>
<tr>
<td>Office automation</td>
<td>♦</td>
</tr>
<tr>
<td>CDM support systems</td>
<td>♦</td>
</tr>
<tr>
<td>Medical management and quality control systems</td>
<td>♦</td>
</tr>
<tr>
<td>Clinical data warehouse</td>
<td>♦</td>
</tr>
<tr>
<td>Remote medical service systems</td>
<td>♦</td>
</tr>
<tr>
<td>Patients inquiry terminal</td>
<td>♦</td>
</tr>
<tr>
<td>Knowledge management platform/BI</td>
<td>♦</td>
</tr>
<tr>
<td>Patient online service platform</td>
<td>♦</td>
</tr>
<tr>
<td>Institute and community HC interphase</td>
<td>♦</td>
</tr>
<tr>
<td>Patient card (intrahospital)</td>
<td>♦</td>
</tr>
<tr>
<td>Patient card (interhospital)</td>
<td>♦</td>
</tr>
<tr>
<td>Medical history, record, and statistics</td>
<td>♦</td>
</tr>
</tbody>
</table>

BI, business intelligence; CDM, chronic disease management; NA, not available

mature high-end multinational company (MNC) vendor software, as illustrated in Table 5.

Considering the maturity levels perspective of common HIS modules (Table 6) and CISs modules (Table 7), Indian HIS vendors will have to tread a steep learning curve to achieve the level of advanced offerings of various modules from mature MNC HIS vendors.

CHALLENGES OF IMPLEMENTATION OF DIGITAL TECHNOLOGY FOR HOSPITAL ADMINISTRATION

Health administrators and promoters must make strategic use of IT in healthcare for improvement in efficiency, clinical quality and safety, patient satisfaction, and overall business performance. In India, the level of health IT applications is directly proportional to the IT literacy and IT understanding of the top management of the hospitals and their promoters. Major HIT implementations are akin to major transformations in how an organization’s business will work in the future and, thereby, a need to implement resultant changes in business processes and employee-centered training and change management. This requires the active involvement of all stakeholders and the application of rigors of project management.

What we routinely encounter is a lack of the organization’s proper actual need assessment documentation. Also, there is an overemphasis on the purchase cost of IT hardware and mostly poor understanding of HIS software capabilities, and due to this, hospitals are reluctant to commit higher costs for good HIS software. Right software implementation is the core for enhancing organization capabilities. As a result, >90% of HIS software vendors in India provide low-end solutions, as it is too expensive to build and maintain upper-end HIS solutions for them.

Also, there is poor in-house stakeholder ownership in hospitals during new HIS implementations; a vendor’s standard HIS products are often implemented without proper customization of HCP’s actual requirements. This leads to frustrations at the operational level post new HIS implementation, which in turn leads to frequent change requests in HIS from the various stakeholders; for this, a totally preventable additional cost is incurred by the HCP.

The availability of healthcare IT professionals is an exception than a rule in India, both for the hospitals and the HIS vendors. The health IT work in India is mostly done by generalist IT professionals.
Professional healthcare IT training in India is rudimentary at present. The other major problem is the near absence of HIS application consultants to assist in choosing and guiding implementations of HIS software in the hospitals. This entails mapping the hospital’s standard operating protocols and, at times, using business process reengineering (BPR). The disappointing performance of health information technology can be largely attributed to several factors: sluggish adoption of HIT systems coupled with the choice of systems that are neither interoperable nor easy to use and the failure of health providers and institutions to reengineer care processes to reap full benefit for health IT. Providers must reengineer healthcare processes to take full advantage of efficiencies offered by health IT and also use change management’s systematic approach to dealing with the transition or transformation of an organization’s goals, processes, or technologies. This can be achieved by adopting strategies for efecting change, controlling change, and helping people to adapt to change. Typical challenges for health IT implementations are depicted in Table 8.

The Indian health IT Standards are a work in progress; however, they need to meet international standards for the exchange of data among systems, patient data privacy, etc., like the following:

- Systematized Nomenclature of Medicine—Clinical Terms is a systematically organized computer-processable collection of medical terms providing codes, terms, synonyms, and definitions used in clinical documentation and reporting of EHR systems, and logical observation identifiers names and codes is used for laboratory test orders and results.
- Health Level Seven for exchanging clinical and administrative data between systems.
- Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act of the USA for the privacy of personal health information.
- Standards for devices and software: US Food and Drug Administration/European Union certifications.

### Table 7: Clinical information systems (CIS) maturity levels comparison: Indian vs MNC vendors

<table>
<thead>
<tr>
<th>MNC vendor’s CIS modules offerings’ maturity level</th>
<th>Indian vendor’s CIS modules offerings’ maturity level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced</td>
<td>NA</td>
</tr>
<tr>
<td>Abstracting</td>
<td>Basic</td>
</tr>
<tr>
<td>Chart deficiency</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Chart tracking locator</td>
<td>Advanced</td>
</tr>
<tr>
<td>Clinical data repository</td>
<td></td>
</tr>
<tr>
<td>Clinical decision support</td>
<td></td>
</tr>
<tr>
<td>Enterprise EMR</td>
<td></td>
</tr>
<tr>
<td>Enterprise master patient index</td>
<td></td>
</tr>
<tr>
<td>LISs</td>
<td></td>
</tr>
<tr>
<td>Pharmacy MISs</td>
<td></td>
</tr>
<tr>
<td>Point of care</td>
<td></td>
</tr>
<tr>
<td>RISs</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
</tbody>
</table>

EMR, electronic medical records; NA, not available

### Table 8: Health information system (HIS)/ERP/BI implementation challenges

<table>
<thead>
<tr>
<th>Implementation phase</th>
<th>Activities</th>
<th>Challenges</th>
<th>Role of external consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIS</td>
<td>Repetitive transaction-based data gets captured at the unit/corporate level. Standard/generic module implementation by vendor with limited customization.</td>
<td>No process mapping. Limited Operations Departments’ ownership of implementation. Frequent change requests. Suboptimal customization. The organization still works simultaneously with both electronic and manual data.</td>
<td>Coordination between operations departments, in-house IT team, and software vendor. Assists in smooth HIS project implementation.</td>
</tr>
<tr>
<td>ERP</td>
<td>Enterprise-level integration of data. Role-based static dashboards are available. Limited analytical capability.</td>
<td>Limited in-house capabilities of enterprise-level systems and process thinking per business needs. It entails BPR and change management. Various departments need hand-holding in this phase. Continuous validation and support from the top management.</td>
<td>Coordinates with top management, IT, ERP implementation team, and ERP vendor. Assists in BPR/change management. Assist in project implementation and timely project closure.</td>
</tr>
<tr>
<td>BI/health analytics/ balanced scorecard</td>
<td>Data is converted into meaningful information. Availability of role-based actionable information at every level. Visualization and interaction with the dashboards for insights and decision-making. ± Enterprise balanced scorecard implementation.</td>
<td>Limited in-house capability of enterprise-level systems, processes, and information flows thinking per business requirements. Continuous involvement, validation, and support of top management.</td>
<td>Coordinates with top management, IT, and BI project teams to map enterprise-wide role-based information requirements. Assists in drawing metrics/dashboards. Assists in developing an organization-balanced scorecard. Once information framework is ready then, coordinate with BI vendor for the rollout of BI solutions.</td>
</tr>
</tbody>
</table>

BI, business intelligence; BPR, business process reengineering; ERP, enterprise resource planning; HIS, health information system
Digital Technology in Hospital Administration

**Future Framework of IT in Health in India**

National Institute for Transforming India Aayog serves as the apex public policy think tank of the Government of India, and in November 2019, they came up with a vision document to chart a roadmap for the complete transformation of India’s health system. The report charts a vision over the next 15 years to transform the delivery of health services in India titled “Health System for a New India: Building Blocks.” Chapter 5 of this report, “Reimagining India’s Health System for New India: Building Blocks,” wiring the Indian health sector sets a blueprint for using IT to improve the Health System for India in the 21st century. The national thrust for rapid digitization of India and the recent introduction of 5G technology will improve healthcare access through telemedicine, efficiency, productivity, and improved clinical outcomes.

Indian health universities must also take the lead in introducing interdisciplinary digital health modules for multidisciplinary streams of students, as India will need an army of health IT professionals down the line. The Indian Institute of Management, Raipur has pioneered a Certified Digital Health Professional course. A national health information exchange in the future can bring all stakeholders: patients, providers, payors, and public health applications on a single platform.

**Conclusion**

Likely, applications of digital health can be encapsulated, as shown in Figure 4. Indian HCPs must treat IT in health as a strategic resource for an organization, like important human resources and finance. They must make an informed strategic spending plan for IT. The up sides of using digital technology in hospital administration are immense and are cost-effective in the long run. There is enough evidence of the efficacy of IT in improving quality and efficiency and in reducing costs.

What we see in India at present is just the “tip of the iceberg” in the potential of health IT applications.

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13. ABHA number | ABDM: https://healthid.ndhm.gov.in/register

**Fig. 4:** Applications of digital health; mHealth, mobile health; EHR, electronic health records; AI, artificial intelligence; ML, machine learning; IOT, internet of things; CDM, chronic disease management, HTN, hypertension, DM, diabetes mellitus
Digital Nerve Care Forum: Innovative Healthcare Professionals Education on Neuropathy

Sanjay Kalra1*, Mangesh Tiwaskar2, Dina Shrestha3, Noel Somasundaram4, Sonali Gokhlay5

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ABSTRACT

Neuropathy is a common complication of diabetes, rarely detected on time, often deprioritized by treating physicians, and hence rarely managed in time, leading to avoidable complications which can be limb and life-threatening. Despite introducing new diagnostic tests, novel potential biomarkers, and a series of relatively small intervention studies utilizing detailed phenotypic profiling, the management of diabetic neuropathy (DN) and painful DN has remained unchanged due to misdiagnosis. The diagnostic complexity of diabetic peripheral neuropathy (DPN), variation in patient response to treatment, and regulatory pressures to meet data-driven quality metrics for diabetes management all likely contributes to the underdiagnosis and treatment of DPN in clinical practice. Educating the primary healthcare providers and diabetic trainers would help improve the number of diagnosed DPN cases as these practitioners lead public health literacy. The digital nerve care forum (NCF) is an educational initiative created by clinical experts and Procter and Gamble (P&G) health academy. Its primary aim is to generate awareness amongst healthcare practitioners (HCPs) about early diagnosis and timely management of DPN. Since its inception in October 2020, NCF has conducted 143 engagements; 39 neuropathy case puzzles, four interactive case-based discussions, two diagnostic workshops, four mentor-mentee nerve talk shows, two intercountry nerve talk shows, two global neuropathy awareness week initiatives, three nerves of steel (Women’s Day special engagements), and 17 NCF times (Newsletters).

This online forum is hosted on a global HCP education and upselling platform, Medisage, which offers these educational resources to HCPs worldwide for free. It has helped create a community of 254,714 HCPs from 86 countries across six continents supported by 30 neuropathy experts from seven countries. With a repeated viewership of 53% of HCPs engaging continuously, NCF empowers this community to improve diabetic patient care. Activities that increase disease awareness and highlight the importance of diabetic nerve health have been the key objectives behind the several educational programs on NCF: To drive this continuum, these digital programs are now becoming more phygital and impactful than ever. Therefore, earlier detection of DPN in at-risk individuals and those with prediabetes or type 2 diabetes is recommended for better management through optimal intervention and lifestyle changes and to prevent future complications of untreated DPN.

Introduction

Peripheral neuropathy (PN) alludes to the disease conditions characterized by damage to the peripheral nervous system, which serves as a communication link between the central nervous system and other body parts.1 PN is a common complication associated with diabetes mellitus (DM). According to the International Diabetes Federation 2021, it is estimated that 537 million people will have diabetes, which is projected to reach 643 million by 2030, and 783 million by 2045.2

The PN in people with diabetes can have life-altering effects. Diabetes is a primary cause of lower limb amputation and 50% of patients with diabetes will suffer a foot ulcer during their lifetime. In addition, neuropathic pain and loss of feeling can cause various adverse effects, such as falls, reduced quality of life, limitations on daily activities, and depression symptoms. Although persons without diabetes can develop peripheral neuropathy, glycemic control primarily focuses on the prevention and management of peripheral neuropathy in diabetes. Additionally, pain treatment is still crucial in managing diabetic neuropathy (DN) and lifestyle strategies like exercise and weight loss are becoming more popular.3 Several surveys have shown that around 50% of diabetic patients with PN are undiagnosed and every eighth patient has never reported their symptoms.4,5

Numerous acute, chronic, focal, and widespread neuropathy symptoms are brought on by diabetes; however, diabetic PN (DPN) makes up the vast majority of DN, comprising 75% of the total number. Other types of nerve damage include diabetic neuropathic cachexia, cranial neuropathy, diabetic autonomic neuropathy, mononeuritis multiplex, mononeuropathy, lumbosacral radiculoplexus neuropathies, and treatment-induced neuropathy in diabetes. A patient may experience different types of neuropathies.6 DPN’s pathophysiology still needs to be fully understood. Some academics suggest prolonged hyperglycemia exposure and cardiovascular risk factors can be linked to DPN. The current methods of evaluation and diagnosis, including flare reactions, skin biopsies, and nerve biopsies, are challenging to perform and unpopular with patients. Testing for laboratory indicators for DPN is crucial in clinical practice since it may identify the earliest stages of neuropathy, enabling early intervention, even though there are no medications that specifically target the underlying nerve damage.7

Given the epidemic explosion of diabetes worldwide, the high prevalence of associated complications, and its clinical and socioeconomic consequences, the need for effective therapeutic and preventive measures for DPN and DPN-related pain is paramount.8 Indeed, without the same established medical infrastructure and resources necessary for early detection, low and middle-income countries in the world may be characterized by a higher number of people diagnosed with diabetes after the onset of complications. The prevalence of DPN was 33.3%, of whom 52.2% were at risk of diabetic foot ulcer, and 53.6% were undiagnosed due to lack of awareness.9,10 Thus, better systems for screening that identify individuals with undiagnosed diabetes earlier in the disease process, thus allowing the opportunity for treatment, will reduce morbidity and mortality associated with this disease.10

The usage of digital media has grown at an alarming rate in the last few years in India.

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In a national survey conducted among Indian healthcare professionals (HCPs), it was found that the digital mode of engagement was the most accepted by HCPs. During the pandemic era, most physicians felt overwhelmed by a huge number of educational webinars. This has made the interactions between pharmaceutical firms and HCPs explore digital channels as medical representatives (MRs) were not able to efficiently reach the HCPs. As the growing incidence of neuropathy; hence, the forum has taken the initiative for Global Neuropathy Awareness.

Clinical Knowledge Pearls

The modern era’s digital advancement has revolutionized the world at our fingertips, especially in neuropathy and nerve care. In an effort to keep doctors informed, P&G Health and Medisage introduced NCF so that they could exchange their clinical knowledge pearls with the community.

Nerves of Steel Initiative

Nerves of steel was an initiative from medical & technical affairs (M&TA) during Women’s Day week aimed to focus on nerve health and women. This initiative includes a global interactive panel discussion with regional digital opinion leaders with curated content and sharing their insights on DPN in women.

Neuropathy Clinical Case Studies

Neuropathy is a complex condition that often presents a wide range of symptoms though early detection is key to effective management. Unfortunately, it is usually diagnosed too late and leads to several uncontrolled neurologic harms and severe pain. Therefore, the neuropathy clinical case program was launched to provide real-world cases emphasizing the adequate monitoring, diagnosis, and care of PN to promote a better understanding of early varied and unrecognized symptoms of PN. National neurology experts presented ten neurological case studies focused on PN. On the contrary, ten endocrinological case studies were presented on diabetes neuropathy by five national endo/diabetology experts. This program’s achievable targets were a preventive approach, myelin regeneration, and nerve protection.

Clinic: Gold for Postgraduate (PG) Students

This forum offers education to PG students for the early and timely diagnosis of neuropathy to alleviate the detrimental impact on quality of life. The PG Diagnostic workshop was launched in March 2022 exclusively for the 100 PG neurology students in person via telecast. It comprised 2 hour workshops with four experts, one chairperson, and one moderator. The program was aimed to educate and enhance awareness amongst PG students via one-on-one training on diagnostic tools for early and easy diagnosis of PN and DPN.

Diagnostic Workshops for Physicians

The NCF offers clinical insights to physicians for the adequate monitoring, diagnosis, and care of PN to improve the effectiveness of treatments and avoid long-term consequences.

Engagement of HCP Communities

The digital survey was undertaken to establish the number of HCPs engaged in multiple specialties, such as endocrinology, general practitioners, consulting physicians, neurology, medical students, and others. As a result, the highest viewership was successfully collected and reported.

Impact of NCF and Behavior Shift of Communities

The impact of NCF was calculated based on the robust audience and touchpoints in distinct nations to monitor the success of NCF within the community of HCPs in these countries. To tackle the satisfaction score and comprehension of topics covered in diagnosing and managing neuropathy, a behavioral shift was perceived.

Global Footprint of HCPs on NCF

The global footprint of HCPs engaged on life, and archived content across the globe, including Northern countries (United Kingdom, Russia), Southern countries (India, Sri Lanka, South Africa, Australia, Malaysia), Western countries (Canada, United States) and Eastern countries (Saudi Arabia, United Arab Emirates, Philippines) was assessed. However, few of them are documented in the present article.

RESULTS AND DISCUSSION

The present section deals with the comprehensive outcomes of the NCF.

The Nerve Stimulating Formats

Nerve gurus from the NCF provided advice on the PN in women on the occasion of Women’s Day. They suggested the following key insights:

- Do not neglect the sensory symptoms like tingling, numbness, burning feet, and pain.
- Prioritize your diet and avoid eating leftovers.
- It can affect the patient’s quality of life, so it is crucial to address the symptoms and prevent DNP by controlling blood glucose.
- Increase the uptake of micronutrients in daily diet.

The total number of NSF-encompassing microsites that features organized by P&G Health along with Medisage are represented in (Table 1).

![Table 1: Nerve stimulating formats](image)
**Clinical Knowledge Pearls**

Credible Neuropathy Cases

The nerve care folks discussed the rare clinical studies on the DNP and described its diagnosis and monitoring. For example, a 47-year-old female with severe ulceration on her footsole for 10 days presented decreased urine output. She was diagnosed with uncontrolled diabetes and septicemia with acute kidney injury. The patient was treated with intravenous (IV) antibiotics along with insulin. The ulcerations were appropriately dressed with local dressings. Unfortunately, it took 6 months for the healing of ulceration.

Some antituberculosis drugs, such as Isoniazid and ethambutol (damage to optic nerve), are likely to develop DPN in primary care. The experts provided some advice to prevent the DPN as follows:

- Patients were advised to inspect their feet daily.
- Wipe your feet dry after taking a bath with soft clothes.
- Maintain nail hygiene.
- Don’t walk with bare feet.
- Always wear cotton socks.
- Long-term treatment of pain modulators can lead to toxic effects.

**Diagnostic Workshops for Physicians**

Until now, two digital workshops have been conducted for physicians by P&G Health and Medisage on diagnosing and managing PN. However, patient history, examination, and investigation are essential tools for diagnosing PN effectively. Management of PN includes the LEMON phenomenon that is expressed below:

- L: Lifestyle modification.
- E: Endocrine optimization.
- M: Metabolic optimization.
- O: Orthopedic optimization.
- N: Nutritional optimization.

**Engagement of HCP Communities**

Pushing boundaries across the globe, P&G Health, in collaboration with Medisage, convened a digital forum featuring 86+ countries, 60+ engagements, 257,714 HCPs, 30 neuropathy experts, and 17 million touchpoints. The endocrinology community explored the largest proportion of viewers, followed by the other communities, with 53% repeat audience (Table 2).

**Impact of NCF and Behavior Shift on Communities**

The nerve care express, executed in two countries with a total online presence of 1113 and a 700+ physical audience, was indeed an achievement of a new “Phygital engagement” strategy. The overall audience satisfaction score after events was 4.09/5.00. Around 50% of the HCPs acknowledged the subjects covered helped them improve their understanding of diagnosing and managing neuropathy (Fig. 1).

**Global Footprint of HCPs on NCF**

The forum has 37,000+ HCPs engaged in live content and 200,000+ HCPs on archived content from across the globe, including Northern countries (UK, Russia), Southern countries (India, Sri Lanka, South Africa, Australia, Malaysia), Western countries (Canada, United States) and Eastern countries (Saudi Arabia, United Arab Emirates, Philippines) to name a few. A closer look at evidence-generation studies in these countries revealed that the diabetes prevalence ranged from 18.8 to 61.9% (India), 15.9% (Thailand), 44.4% (Nepal), 25.1% (Sri Lanka), and 63.5% (Indonesia), indicating that painful DPN is to be adequately addressed. Therefore, a maximum HCP engagement was observed from these countries in the NCF.

**Conclusion**

Given the epidemic explosion of diabetes worldwide, the high prevalence of this complication, and its clinical and socioeconomic consequences, effective therapeutic and preventive measures for DPN and DPN-related pain are paramount. A few decades ago, neuropathy was considered a “firefighting” condition since there were only fewer specialists who dealt with neuropathy. But, in today’s world, the underestimation of PN is mainly due to a lack of consensus guidance on routine screening, diagnosis and management. This lack of awareness and urgency in diagnosing leads to increased 5-year mortality in patients.

Also, DPN places a significant economic burden on people with type 2 DM and national healthcare systems. Due to the substantial impact that DPN has on patients’ health, quality of life, and healthcare costs, the American Diabetes Association currently recommends that screening for DPN may be performed in all adults at the time of diabetes diagnosis and annually after that to reduce the complications and health-related burden associated with the disease. Therefore, there is a need to amplify awareness and literacy among both physicians and patients to detect neuropathy early for quick intervention for a more promising outcome rather than the later stage complications.

A research study inferred that HCPs could be targeted through digital and social media platforms. To create awareness or inform HCPs on the most recent developments in healthcare and their areas of interest, e-learning is an emerging platform that is heavily employed with the right tools for gaining engagement and upskilling doctors in low and middle-income countries. A “phygital approach,” or a physical interaction with the HCPs through medical representatives (MRs) from the healthcare organizations followed by digital means of disseminating information (such as videos, podcasts, and QR codes), could be advised for healthcare organizations.
Hence, the NCF has aimed at revolutionary change from a focus on diagnosing, managing, and controlling DPN to a continual improvement of patient quality of life, from emphasizing learning and achievement to building knowledge that has a social value from predominantly HCPs communities. The comprehensive data obtained from the NCF explored that it can be a successful and effective platform to address the complications regarding the DPN.

**References**


Chlorthalidone vs Hydrochlorothiazide for Hypertension–CV Events: Did the Design Influence the Outcome?

Anil Pareek1,*, Franz H Messerli2, C Venkata S Ram3

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ABSTRACT

The Diuretic Comparison Project (DCP)1 was a real world study planned to evaluate in a pragmatic manner whether Chlorthalidone (CTD), as compared with Hydrochlorothiazide (HCTZ), would reduce the risk of major nonfatal cardiovascular disease outcomes in elderly hypertensive participants (≥65 years) who were receiving HCTZ (25 or 50 mg) at baseline. This study being a real world study lacks the robustness of a randomized controlled trial. The principle limitation being unequal exposure of the two diuretics, prolonged unknown duration of exposure to HCTZ vs a short exposure to CTD (Median 2.4 years). In the high risk population with history of MI/Stroke, CTD conferred a lower risk of primary outcome as compared to low risk population where no significant difference in outcome was seen in both diuretics. Other factors included, lack of established dose equivalency of the two diuretics and absence of use of 12.5 mg HCTZ in older hypertensives.

BACKGROUND

The DCP1 was a pragmatic real-world study done to compare CTD and HCTZ. The primary aim was to evaluate which of the two diuretics reduces the risk of major adverse CV events (MACE) in hypertensive patients above 65 years of age (older patients) who were taking HCTZ (25 or 50 mg) at baseline. The patients were randomly assigned to continue HCTZ or were switched to CTD at a dose of 12.5 or 25 mg.1 We think that this study has a few limitations in its design and dose used in the study population.

DOSEING CONSIDERATIONS

Equivalent daily doses in this study were 25 mg hydrochlorothiazide (HCTZ) and 12.5 mg chlorthalidone (CTD). However, the usual dose at which HCTZ should be started is 12.5 mg in older patients and 25 mg in younger patients. The usual dose at which CTD should be started is 6.25 mg in older patients and 12.5 mg in younger patients.2 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (BP) VI and the Canadian hypertension guidelines (1995) suggest that HCTZ be initiated at 12.5 mg daily. A 2018 meta-analysis found that the equivalent doses of HCTZ and CTD have a ratio of 3:1.3 An ambulatory BP monitoring study noted that 6.25 mg CTD produced a significant decrease in 24-hour and night-time BP than did 12.5 mg HCTZ.4 More hypokalemia in the CTD arm also indicates that CTD potency was more than two times higher than HCTZ.

DESIGN LIMITATIONS

This trial, in a pragmatic manner, aimed to answer a pertinent question. This trial had many flaws in the design, which included its open-label nature, which cannot match the accuracy of randomized controlled trials. In this study, 95% of all patients were taking HCTZ 25 mg before being randomized either to continued HCTZ or to CTD. Patients with a history of myocardial infarction (MI) and/or stroke comprised 10.8% of participants in the CTD group and 10.7% of participants in the HCTZ group. In this high-risk population, CTD conferred a lower risk of primary outcome than HCTZ [hazard ratio (HR) 0.73; 95% confidence interval (CI), 0.57–0.94; p = 0.013]. In turn, no major difference in HR for the primary outcome was found between CTD and HCTZ participants who had no history of MI and stroke (HR 1.12; 95% CI, 1.00–1.26; p = 0.054). As all the patients were taking HCTZ for an unknown period before randomization, shifting to CTD for a mere median duration of 2.4 years was not sufficient to make a difference in the low-risk population. However, in the high-risk population, such short exposure to CTD did achieve clinically meaningful differences between the two drugs. This seems to indicate that the unequal exposure to the two thiazides before randomization was a critical issue.

CONCLUSION

In the study of Ishani et al.,1 the following appear to be the study limitations:

- There was unequal exposure to the two thiazides.
- Lack of established dose equivalency in the two thiazides.
- Absence of commonly used dose of 12.5 mg HCTZ in older hypertensives.
- Open-label nature of the study.

Thus, the authors’ conclusion that “participants who received CTD did not have a lower occurrence of major adverse cardiovascular (CV) events (MACE) than patients who received HCTZ” is questionable. This illustrates the design limitations of conclusions drawn on pragmatic studies in comparison to randomized controlled trial (RCTs). Hence RCTs remain the gold standard for comparison of time-tested drugs.

REFERENCES


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A Case of Refractory Anemia in Patient of Chronic Kidney Disease and the Challenges in its Management

Komal Gade1, Charulata Londhe2, Sangeeta Pednekar3, Dharmendra Pandey4, Namita Padwal5, Ashish Agrwal6

Received: 17 April 2023; Accepted: 08 May 2023

ABSTRACT
Anemia is a common complication of chronic kidney disease (CKD) that has been classically attributed to inadequate production of endogenous erythropoietin.1 Though there are many other common causes of refractory anemia in CKD like iron deficiency, vitamin B12, and folic acid deficiency, noncompliance to dialysis and erythropoietin therapy are rare causes like blood loss, bone marrow failure, infections causing aplastic crisis like CMV, parvovirus B19 should be ruled out. Parvovirus has an extreme tropism for erythroid cells and is an uncommon cause of anemia in patients with CKD on maintenance dialysis (MHD) and on erythropoietin.2 Here we are reporting a rare case of refractory anemia in a patient of CKD on MHD secondary to parvovirus-related aplastic crisis.

INTRODUCTION
In immunocompetent hosts acute parvovirus B19 infection is mild and associated with transient anemia, arthritis, and rash.3 Patients with renal failure on dialysis have disruptions in their immune system due to the immunosuppressive effect of uremia. Therefore dialysis patients have increased susceptibility to acute and chronic anemia after B19 infection. Moreover, B19 infection can induce aplastic crisis in these patients.4

CASE REPORT
A 45-year-old female with hypertension and chronic kidney disease (CKD) on regular maintenance hemodialysis for the last 10 years was admitted with complaints of generalized weakness, easy fatigability, and dyspnea on exertion. On examination, there was pallor without icterus and pedal edema. All other systemic examinations were within normal limits.

Laboratory tests revealed hemoglobin 4.9 gm/dL with total leukocytes of 3600 and platelets 35000 with mean corpuscular volume 92.2 fl, mean corpuscular hemoglobin concentration 28.2 pg. Peripheral smear showed anisocytosis with normochromic normocytic anemia. The reticulocyte count showed anisocytosis with normochromic normocytic anemia. The reticulocyte count was 2.6 with a reticulocyte production index of 0.4. Iron studies were within normal limits. Biochemical analysis revealed creatinine of 5.5 with normal liver function tests. Serum B12, folic acid were within normal range. Viral markers like human immunodeficiency virus (HIV), hepatitis B surface antigen, and hepatitis C virus were negative. Tests for malaria, and leptospirosis were negative.

The patient has been compliant with dialysis and erythropoietin treatment for the last 10 years and never received a blood transfusion in the past. During this admission, the patient received four units of packed red cell transfusions and was discharged on persistent request with hemoglobin of 8.8 gm/dL. She was advised for optimum compliance with dialysis and erythropoietin therapy. Around 1 month after discharge she was again readmitted with similar complaints with hemoglobin of 5.9 total leukocytes of 3400 and platelets of 1 lac in spite of being on regular dialysis and proper erythropoietin therapy. Again she has transfused two units of packed red cells to build up hemoglobin to 8 gm/dL. We did her bone marrow biopsy in view of pancytopenia which was suggestive of hypocellular bone marrow with suppressed erythroid lineage. In background knowledge of CKD being an immunocompromized state, we suspected aplastic crisis secondary to parvovirus B19 as a cause of refractory anemia in our patient. Her parvovirus polymerase chain reaction (PCR) was done which came positive.

The patient started on intravenous immunoglobulin therapy (IVIg) which was administered on alternate days after dialysis at a minimum infusion rate of 0.5 mL/kg/hour with frequent monitoring of pulse, blood pressure, oxygen saturation, and signs of fluid overload. However, after three doses of IVIg patient had an acute rise in BP with convulsions. There were no focal neurological deficits. Computed tomography (CT) brain showed posterior reversible encephalopathy syndrome (PRES). CT brain venography was normal.

The patient improved after control of BP. We terminated IVIg therapy after three doses. Subsequently, her hemoglobin level was stabilized and no further drop was noted. After two months her hemoglobin was stable at 8 gm/dL.

Hematological parameters of the patient:

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>After 2 weeks</th>
<th>After 1 month</th>
<th>After 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>4.9</td>
<td>8.8</td>
<td>5.9</td>
<td>8</td>
</tr>
<tr>
<td>TLC</td>
<td>3600</td>
<td>4200</td>
<td>3400</td>
<td>4600</td>
</tr>
<tr>
<td>Platelets</td>
<td>35000</td>
<td>1.1 lac</td>
<td>1 lac</td>
<td>1.23 lac</td>
</tr>
</tbody>
</table>

DISCUSSION
Parvovirus B19 is a small nonenveloped single-stranded DNA virus belonging to the Paroviridae family.5 This virus has severe manifestations in immunocompromised patients. Anemia is present in around 99% of patients of parvovirus B19 with immunocompromised state and is often associated with erythropoietin resistance. Parvovirus B19 (PVB19) infection should be suspected early in cases of anemia in immunocompromised patients, including transplant patients, and prompt evaluation should be initiated. Viral detection in clinical specimens is important for the diagnosis of PVB19 infection.

Causes of poor response to erythropoietin therapy in CKD patients:

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Uncommon causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Iron deficiency</td>
<td>1. Blood loss</td>
</tr>
<tr>
<td>2. Infection</td>
<td>2. Bone marrow failure due to myelofibrosis secondary to hyperparathyroidism</td>
</tr>
<tr>
<td>3. Inadequate dialysis</td>
<td></td>
</tr>
<tr>
<td>4. Vitamin B12 and folic acid deficiency</td>
<td></td>
</tr>
<tr>
<td>5. Poor compliance to erythropoietin therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Aplastic crisis due to infections like CMV, parvovirus B19, and HIV</td>
</tr>
</tbody>
</table>

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Our patient presented with anemia inspite of erythropoietin therapy and regular dialysis. We suspected parvovirus B19 associated aplastic crisis as no other cause of anemia was found on laboratory work and her parvovirus B19 PCR came positive.

The IVlg is the mainstay therapy for PVB19-associated pure red cell aplasia, and it is a widely used regimen, with a total dose of 2 gm/kg over 2–5 days, although the daily dose and duration of therapy may vary according to centers.

Unfortunately, our patient could only receive three doses as she had IVlg-induced PRES which is a rare side effect of IVlg therapy but she responded IVlg well to treatment and currently not requiring any blood transfusion. IVlg also can cause anaphylaxis, volume overload, thromboembolism, and acute kidney injury. Hence IVlg should be administered cautiously specially in renal failure patients.

**Conclusion**

Anemia in CKD patients requires a thorough workup to ensure a correct diagnosis and therapeutic approach. Although anemia secondary to parvovirus B19 infection is uncommon it must be considered in the differential diagnosis of refractory anemia with resistance to erythropoietin therapy in CKD patients as they are immunocompromized hosts and prone to such infections. It responds to IVlg treatment very well.

**References**

Atorvastatin-induced Myositis and Drug-induced Liver Injury

Kritartha Kashyap, Khushboo Bisht, Minakshi Dhar, Kartik Mittal

Received: 03 February 2023; Accepted: 27 April 2023

ABSTRACT

Statins are drugs for preventing cardiac events in the elderly population. Statins are well tolerated with a lower reported incidence of serious side effects (<0.15%) like myopathy and elevated transaminases (>3× upper limit of normal (ULN)). Serious adverse effects of statins like statin-associated myopathy range from mild muscle pain to rhabdomyolysis. Drug-induced liver injury (DILI) is another adverse effect of statin use, typically presenting with an acute hepatocellular liver injury pattern as mixed or cholestatic injury. Symptoms usually disappear after 3 months of discontinuation of statins. Some patients require immunosuppression with steroids, intravenous immunoglobulin, or rituximab for management of rhabdomyolysis. DILI can be rapidly reversed by the stoppage of the statins if the enzyme elevation is more than twice the normal. Elderly patients are particularly at increased risk of such adverse effects, emphasizing a need for rational prescription of statins in older adults and close monitoring. We report a case of an elderly presenting with paraparesis and later diagnosed to be a case of statin-induced myositis that significantly improved with prompt management.

INTRODUCTION

More than 100 million prescriptions of statins are written for the management of hypercholesterolemia every year. Although statins are well tolerated with a lower incidence of serious side effects (<0.15%) like myopathy and increased transaminase levels (more than three times the upper limit of normal (ULN)). A meta-analysis of 21 clinical trials with 180,000 person-years of follow-up defined statin-induced myopathy based on muscle symptoms and creatine kinase (CK) levels (>10-fold ULN), that occurred in five patients per 100,000 person-years. Grades I and II myositis is defined by muscle symptoms with CK levels less than four times UNL, whereas grades III and IV have CK levels between four and 10 times UNL, respectively. Rhabdomyolysis following statin use is usually associated with renal dysfunction due to myoglobinuria. Immune-mediated statin myopathy is another entity associated with increased anti-3-hydroxyl-3-methylglutaryl-coenzyme A reductase autoantibody and Human Leukocyte Antigen associations. Clinically important drug-induced liver injury (DILI) is very rare with statin use. DILI from statins typically presents with an acute hepatocellular liver injury pattern, although mixed or cholestatic injury patterns have also been reported.

Elderly people are at particularly increased risk of these adverse effects due to their advancing age. Multimorbidity and organ dysfunctions like renal insufficiency, hepatic dysfunction, and hypothyroidism are present and, polypharmacy further increases the risk of adverse events. Thus, the rational use of statins while prescribing them to elderly patients is of utmost importance. This is a case of a 68-year-old patient who was admitted with complaints of paraparesis and was eventually diagnosed to be a case of statin-induced myositis with DILI.

CASE SUMMARY

A 68-year-old patient who was a known case of coronary artery disease (anterior wall myocardial infarction) with 30% left ventricular ejection fraction underwent percutaneous transluminal coronary angiography twice. The patient was on atorvastatin (80 mg) and aspirin (75 mg) for 8 months and presented with complaints of acute onset weakness in bilateral lower limbs for 20 days. The patient felt a sudden difficulty in getting up from the toilet seat, even with support and had to be carried by the son to the bed. Weakness gradually progressed in terms of difficulty in standing from sitting or lying down. For the next 10 days, the patient started experiencing difficulty in taking turns in bed while lying. However, there were no complaints of any difficulty in wearing slippers, or slippage of sandals from the toes. Simultaneously progressive yellowish discoloration of eyes, without any associated change in his urine or stool color, pain or distension of the abdomen, melena, hematemesis, hematuria, and altered talk was noticed by patients and caregivers. The patient also reported pain along the anterolateral portion of the bilateral thigh, for 15 days which was insidious in onset, dull aching, moderate to severe intensity, pain that aggravated while walking or moving the limbs (hip flexion or extension), with no significant relieving factors. Also, there was mild difficulty in combing hair or lifting the mug while bathing for 7–8 days. There was no difficulty in buttoning the shirt or while eating. There is no history of any radicular pain, back pain, trauma, tingling or numbness over the body, any loss of sensation, loss of appetite or loss of weight, or any bowel or bladder incontinence.

Physical examination revealed icterus and wasting of his proximal muscle groups of both lower limbs. A focused neurological examination showed wasting, significantly diminished power (two-fifths in all flexors, extensors, abductors, and adductors) and tone in proximal muscle groups of lower limbs. The deep tendon reflexes in the lower limbs were absent. Tenderness was present along the anterolateral group of muscles of bilateral thighs. The sensory system and upper limbs and the rest of the examination were unremarkable. Given the history, clinical examination possibilities kept were statin-induced myopathy, polymyositis, or immune-mediated necrotizing myopathy (IMNM).

Hemogram, renal profile, and serum electrolytes were within normal limits. Liver function profile was deranged, aspartate transaminase (AST)—1590 U/L and alanine transaminase (ALT)—1301 U/L, along with an increased total and direct bilirubin (13.1 and 6.7 mg/dL, respectively). N-acetyl cysteine-activated creatine phosphokinase (CPK-NAC level was 21,650 U/L, lactate dehydrogenase was 3,618 U/L. Magnetic resonance imaging (MRI) of both thighs showed heterogeneous T2/Transverse relaxation time (T2 FS) hyperintensity in muscle fibers of the bilateral adductor group of muscles and muscles of the bilateral anterior compartment of the thigh, bilateral obturator externus and internus,
gluteus maximus, semitendinosus and semimembranosus, suggesting the possibility of inflammatory myopathy (Figs 1 and 2).

Urine color was found to be highly concentrated and urine for myoglobin was negative. An EMG was ordered which showed positive sharp waves in the bilateral vastus lateralis and rectus femoris indicating some amount of muscle damage. A muscle biopsy was done to rule out the possibility of IMNM or polymyositis along with a myositis panel. The myositis panel came negative, a biopsy was suggestive of inflammatory myopathy (Fig. 3). Considering the duration of symptoms and the clinical profile of the patient, statins were stopped. After stopping statins, the patient gradually started showing improvement in his muscle power and pain by the 5th day. A repeat AST/ALT and CPK-NAC levels showed 363 U/L, 118 U/L, and 2309 U/L respectively. Bilirubin levels were decreased (total and direct bilirubin—5.91 mg/dL and 5.3 mg/dL, respectively). Clinically jaundice improved.

In light of the clinical history and laboratory findings and observations, we finally diagnosed it to be a case of statin-associated myopathy with DILI. On subsequent follow-up, his power had further improved with a decrease in CPK-NAC levels.

**Discussion**

The incidence of statin-induced myopathy is estimated to be nearly about 0.1–0.5% and rhabdomyolysis to be 0.02–0.04% when the patient is on statin monotherapy.\(^2\) Symptoms vary from mild muscle aches to fatal rhabdomyolysis and acute renal failure. They began to occur within a few weeks of starting statin, and sometimes up to a few years...
Atorvastatin-induced Myositis and Drug-induced Liver Injury

Atorvastatin (atorvastatin, lovastatin) more often cause musculoskeletal side effects than hydrophilic statins (pravastatin, rosuvastatin, and fluvastatin) due to their better penetration into myocytes enhancing their myotoxic effects. Kashani et al. collated results of 21 studies of 48,138 patients concluding that only atorvastatin had a significantly higher risk difference per 1,000 patients for myopathy when compared to placebo.

Clinically apparent DILI has been rarely reported with statins. From previous studies published on the statin-induced liver, we know that it could range from an acute hepatocellular to the cholestatic or mixed pattern, to autoimmune hepatitis-like phenotypic manifestations. Overall, statin-induced liver injury is usually mild-to-moderate in severity and rapidly reversible in most cases once the agent is stopped.

**CONCLUSION**

Discontinuation of statin use in patients with inflammation and elevated CK levels is the currently accepted mode of treatment of statin-myopathy. In patients with liver injury, a different statin can be reinstated with careful and frequent monitoring. Currently, statins are one of the most prescribed medications worldwide, hence the risk of these side effects and their proper management should be kept in mind and patients should be monitored with more vigilance. Further studies on myotoxicity will enhance our understanding of these mechanisms and help in preventing myopathy and in the discovery of lipid-lowering agents free of such adverse effects.

**REFERENCES**


**ANNOUNCEMENT**

ASSOCIATION OF PHYSICIANS OF INDIA
TRIPURA STATE BRANCH

We are proud to announce that the 23rd Annual State Conference of Association of Physicians of India, Tripura State Branch (TAPICON-23) will be held on 13th and 14th January, 2024 (Saturday and Sunday) at Agartala, Tripura.

**Theme:** Applied Science in Pursuance of Excellence.

For further information please contact:

Prof. (Dr.) Pradip Bhaumik, National Governing Body Member, API.

and

Dr. Saumen Chaudhuri, Hony. General Secretary, API-TSB.

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Contact no: 9436120250, 9436120497, 07005649529.
An 18-year-old girl presented with multiple painless large subcutaneous swelling on the gluteal-sacral (Fig. 1A) and elbow region (Fig. 1B). She also had swelling over the metatarsal joints of the foot (Fig. 1C) and interphalangeal joints of the fingers (Fig. 1D) since childhood. There was no family history of similar illness, premature coronary events, or death. Because of the cosmetic disfigurement, she had multiple excisions of gluteal xanthomas. Her total cholesterol was 921 mg/dL (optimal below 200 mg/dL), low-density lipoprotein cholesterol (LDLc) 755 mg/dL (optimal below 100 mg/dL), high-density lipoprotein cholesterol (HDL) 125 mg/dL (optimal >60 mg/dL), and very low-density cholesterol 40.5 mg/dL (optimal below 30 mg/dL). The calculated total cholesterol and LDL ratio was 7.3 (normally <3.3). A clinical diagnosis of familial hypercholesterolemia (FH) was made based on the Simon Broome criteria.

Xanthomas are subcutaneous and tendinous cholesterol deposition within macrophages of the extracellular matrix inside the tendons or the skin. They have a predilection for elbows, knees, tendons, joints, hands, feet, and buttocks. FH is a common genetic cause of premature cardiovascular disease (CVD) and is due to a defect in the LDL receptor (LDLR) or low uptake of LDL by the liver. Homozygous FH results in markedly high total cholesterol levels, 3–6-fold higher than normal, usually with >600 mg/dL. The estimated risk of premature CVD is 20-fold higher in FH as compared to that of the general population. There are significant gaps in knowledge regarding the life course of FH and the benefits of existing therapy including proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors.

PCSK9 inhibitors block the LDLR recycling by clathrin-mediated endocytosis and subsequently lysosomal degradation of LDL-receptors. Alirocumab and evolocumab (subcutaneous injection administered every 2 and 4 weeks, respectively) are the two most common PCSK9 inhibitors commonly used recently. In refractory cases, plasma exchange and lipoprotein apheresis have been tried.

The FH is an under-recognized and rare entity in India, appropriate clinical diagnosis is required to avoid inadvertent surgery, which had happened in the present case. Our patient was treated with 80 mg of atorvastatin and 10 mg of ezetimibe. She followed up for a period of 6 months. Her xanthomatosis did not improve despite of 50% reduction in LDL cholesterol. Thereafter she was lost to follow-up.

**References**


Figs 1A to D: (A) Huge xanthomas in sacral area over both buttocks; (B) Elbow xanthomatosis; (C) Metatarsal xanthomas; (D) Interphalangeal xanthomas in hands
A 53-year-old male, known diabetic and hypertensive with coronary artery disease, presented with acute onset quadriaparesis, unsteadiness of gait, and dysphagia. On examination, he had slurred speech, bilateral horizontal gaze-evoked nystagmus, symmetrical quadriaparesis involving both proximal and distal equally, preserved deep tendon reflexes, bilateral plantar extensor, and truncal ataxia. Magnetic resonance imaging (MRI) of the brain (1.5 Tesla) (Figs 1 to 3) showed T2 and fluid-attenuated inversion recovery (FLAIR) heart-shaped hyperintensity on both sides of the ventral medulla, which showed diffusion restriction and was suggestive of an acute bilateral medial medullary infarct. Magnetic resonance angiography (MRA) was normal. He was treated with antiplatelets, statins, and physiotherapy. His weakness and ataxia started improving gradually over the weeks, and he is on regular follow-up.

Medial medullary infarct (MMI) is a rare cause of stroke syndrome. MMI was first described by Spiller in the 19th century. It accounts for <1% of all cases of brain infarction. MMI presents as a triad of ipsilateral hypoglossal paralysis, contralateral hemiparesis sparing the face, and contralateral loss of deep sensation. Bilateral MMI (BMMI) is still more uncommon than MMI; the exact incidence is not known. Bilateral MMI commonly presents as quadriplegia, dysphagia, speech difficulties, and bilateral loss of deep sensations. Isolated hemiparesis, facial nerve palsy, ataxia, vertigo, nystagmus, and respiratory failure do occur. Most common etiology of BMMI syndrome is arterial occlusion, whereas brainstem encephalitis and Guillain–Barré syndrome can also present with similar features.

According to vascular supply, the medulla oblongata is divided into anteromedial, anterolateral, lateral, and posterior territories. The medial medullary territory (anteromedial territory and anterior-lateral) is supplied by penetrating arteries from the anterior spinal artery and vertebral artery. Infarction involving bilateral anterior-medial territory and the anterior-lateral territory can result in a "heart appearance" sign. The etiological mechanism of bilateral MMI is commonly due to vertebral artery atherosclerosis, atheromatous branch occlusion, cardioembolism, and dissection of the vertebral artery. The occurrence of a simultaneous bilateral MMI occurs due to the occlusion of anatomic variability branches originating from a vertebral artery that supplies both sides of the medullary.

So, it is important that this syndrome should be kept in mind in cases of hyperacute onset quadriaparesis with associated long tract signs or lower cranial nerve involvement, particularly in patients with underlying comorbid conditions because MRI will reveal a crystal-clear diagnosis. Earlier confirmatory imaging findings will avoid unnecessary delays in treatment initiation and a large battery of investigations.

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The Big picture of diabetes management across a broad patient population

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John Michael Bishop (1936)—American virologist graduated from Gettysburg College, Pennsylvania in 1957 and from Harvard Medical School in 1962. After spending residency at Massachusetts General Hospital, Boston, he became a researcher in virology at the National Institutes of Health, Bethesda, Maryland in 1968. He joined the faculty of the University of California Medical Center in San Francisco, becoming a full professor in 1972. In 1998 Bishop was elected chancellor of the University of California, a post, he held until 2009.

In 1970, Bishop teamed up with Varmus and they set out working with the Rous Sarcoma Virus, known to cause cancer in chickens. They found that a gene similar to the cancer-causing gene within the virus was also present in healthy cells. In 1976, Bishop and Varmus, together with colleagues published their findings, concluding that the virus had taken up the gene responsible for the cancer from a normal cell. The duo showed that such genes can be converted by certain chemical carcinogens into a form that allows uncontrolled cellular growth.

Harold Varmus (1939)—American virologist Varmus graduated from Amherst College in 1961; obtained MA from Harvard University in 1962, and MD from Columbia University, New York in 1966. He then joined the National Cancer Institute in Bethesda, Maryland. In 1970, he went to the University of California, San Francisco, as a postdoctoral fellow. There, Varmus joined Bishop. The findings of their research as already stated earlier that cancer is caused by viral genes (oncogenes), distinct from a cell’s normal genetic material, which lie dormant in body cells until activated by carcinogens.

Varmus was director of the National Institutes of Health from 1993 to 1999, during which time he significantly increased the budget provided for research. Varmus was appointed president of Sloan Kettering Cancer Center in New York in January 2000 and became director of the National Cancer Institute in 2010, where he served until 2015.

Because the mechanism described by Bishop and Varmus seemed common to all forms of cancer, their work proved invaluable to cancer research. Today it is suspected that nearly 1% of the human genome, which contains an estimated 20,000–25,000 genes, is made up of proto-oncogenes. The discovery of oncogenes and tumor suppressor genes, both, in the mutant forms of normal cellular genes, are in the process of revolutionizing the understanding of cancer.

Bishop and Varmus received the Nobel Prize for Physiology or Medicine in 1989 “for their discovery of the cellular origin of retroviral oncogenes” or achievements in clarifying the origins of cancer.

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Not all that Wheezes is Asthma

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Sir,

We want to highlight the presentation of a 75-year-old female who was initially managed as asthma and subsequently diagnosed with concurrent excessive dynamic airway collapse (EDAC).

Excessive dynamic airway collapse (EDAC) is a relatively new disease entity defined as the pathological narrowing and collapse of the airway lumen by >50% which results from a laxity and bulging of the posterior tracheal wall membrane during expiration with maintained structural integrity of the cartilaginous rings. This disorder is different from tracheobronchomalacia, which is characterized by loss of structural integrity of the cartilaginous rings.1

This disease is underdiagnosed or diagnosed incidentally as its symptoms mimic those of poorly controlled asthma or severe chronic obstructive pulmonary disease and often obtain the label of “difficult to treat” asthma.

Patients may remain asymptomatic for a long time however the pathological progressive airway weakening can also lead to dynamic airflow obstruction causing persistent breathlessness, wheezing, recurrent respiratory infections, severe intractable cough, difficulties in weaning or unexplained extubation failure.2

EDAC may present as a cough and wheeze that is resistant to corticosteroid and bronchodilator therapy.

We present a case of a 75-year-old female, nonsmoker, and retired school teacher who was admitted with an intractable cough accompanied by severe wheezing. She was a physician diagnosed- “difficult-to-control” asthma with an exacerbation rate of 3–5 times a year.

She complained of paroxysmal cough and wheezing for the past 2 years. A mild relief of these exacerbations was achieved by frequent oral steroids and antibiotics.

She was on regular inhaled bronchodilators and oral corticosteroids which did not provide much relief and the audible wheezing was heard continuously. The inhaler usage technique as assessed on admission, was correct. Past medical history included hypertension and there was no family history of bronchial asthma as well.

Previous pulmonary function tests were not available.

At lung auscultation, she presented with significant wheezing, dominant over central airways. Ear, nose, and throat examination revealed signs of laryngopharyngeal reflux. Pulmonary function tests were normal (Fig. 1). Serum immunoglobulin E (IgE) and absolute eosinophil counts were within normal limits. High-resolution computed tomography (CT) thorax showed focal peribronchial thickening with small nodular opacities in the posterior segment of the right upper lobe (Fig. 2).

She was managed with antibiotics, oral and inhaled corticosteroids, inhaled bronchodilators, leukotriene inhibitors, antiallergics, proton pump inhibitors, and cough suppressants.

She only had a mild improvement in symptoms and wheezing was continuing as before.

A bronchoscopy was conducted under conscious sedation and there was a near-total collapse of the posterior membrane of the trachea and right main bronchus during expiration (Fig. 3).

Figs 3A and B: (A) Trachea in full inspiration; (B) Collapsed trachea in expiration

Fig. 1: Normal spirometry

Fig. 2: Focal peribronchial thickening with small nodular opacities in the posterior segment of right upper lobe
Moderate amounts of purulent sputum were collected from beyond the area of excess airway collapse. Bronchial washing cultures, including those for tuberculosis, were negative. The patient was diagnosed with EDAC.

Her bronchodilators were reduced, she was trained during hospitalization in assisted cough, administered proton pump inhibitors and started on continuous positive airway pressure (CPAP) therapy. During a follow-up, she reported a significant reduction in cough and wheezing.

It has been postulated to be caused due to chronic coughing, reflux gastric aspiration, repeated lung infections, and smoking which leads to atrophy of the elastic fibers of the posterior membrane of the trachea.

The pathogenesis of EDAC has been attributed to two mechanisms mainly age-related weakness of the tone of smooth muscles of the posterior membrane and a decrease in luminal pressures of tapering airways coupled with reduced elastic recoil causing greater stenosis and large transmural pressure gradient.

Our patient had a history of chronic cough, probably being gastric reflux related which would have resulted in the laxity of the airway membrane.

The EDAC can be recognized during a dynamic bronchoscopy done under conscious sedation or even radiologic imaging using a dynamic CT.

The management depends upon the severity of symptoms and the degree of airway collapse. Many patients of EDAC remain asymptomatic and are not to be treated.

Usual treatment strategies include conservative therapy using noninvasive positive pressure ventilation, high-flow nasal oxygen therapy, airway stenting, and surgical therapy like tracheobronchoplasty, tracheostomy, airway splinting, or tracheal resection.

EDAC was considered for this patient due to the minimal improvement in an escalation of asthma treatment, normal spirometry, and persistent wheezing.

We hereby conclude that EDAC should be considered if poorly controlled asthma is not responding to standardized treatment. A dynamic CT or bronchoscopy under conscious sedation should be considered in the evaluation of a patient with difficult-to-control asthma after ruling out other possibilities like acid reflux, sinusitis, and nonasthmatic eosinophilic bronchitis.

**References**


5. It has long been understood that using addictive substances also results in higher infection rates. For instance, tuberculosis (TB) is a common source of opportunistic infections in this setting because HIV patients are more likely to contract the disease due to the abuse of drugs. There is currently a serious threat from drug-resistant TB. India, China, and Russia together account for 62% of the world’s drug-resistant TB burden.

**Materials and Methods**

Between April 2021 and March 2022, a prospective study on the prevalence of substance abuse in antiretroviral therapy (ART)—naive HIV patients older than 12-year-old was carried out at the ART Center, Khagaria. A questionnaire covering substance type, use frequency, and length of addiction was created. For the purpose of identifying opportunistic infections, clinical examinations, and tests, such as complete blood count/bronchus carotica resection (CBC/CXR) cartridge-based nucleic acid amplification test (CBNAAT) of sputum for *Mycobacterium tuberculosis* with other pertinent testing, were performed.

**Results and Discussion**

Eligible patients (n = 201) with age (mean –33.34, standard deviation, 11.33) and gender identity, 116, 84, 1 (male, female, and transgender) were studied. Alcohol, marijuana, crack cocaine, and tobacco were among the substances used by 20% of HIV patients. In HIV patients with...
Correspondence

substance use disorders, the percentage incidence of opportunistic infections is 46%, which is significantly higher than the 15% rate in HIV patients without a history of substance use. Incidence of opportunistic infections was compared between the two groups (Fig. 1). Chi-squared test −18.67 and degree of freedom-1 indicated that the p-value was highly significant (p-0.00001). Of 39 opportunistic coinfection in HIV patients, 26 cases have drug-sensitive TB, two cases have drug-resistant TB, seven had extrapulmonary TB, and four cases had other than tuberculosis.

Human immunodeficiency virus (HIV)—infected drug users who also have latent TB develop the disease as a result of increased immunosuppression, increased transmission from crowded areas, and latent TB infection. These substances immunomodulate the immune system by influencing T-helper 1 and 2 response.³

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