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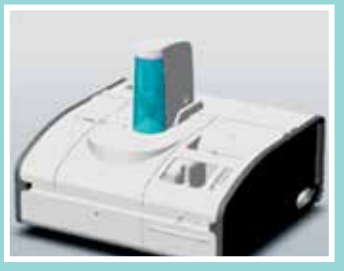

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**Indian Journal of Clinical Practice**, Vol. 32, No. 4, September 2021

**Dr KK Aggarwal**
5th September 1958 - 17th May 2021

# HCFI Round Table on Environment "Consensus Statement on Eco-restoration of Lakes/Ponds/Water Bodies"

**4TH, 11TH AND 18TH JULY, 2021 (12 NOON-1 PM)**

## KEY POINTS FROM THE DISCUSSION

- There are four major sources of pollutants in lakes/ponds/water bodies: domestic sewage, industrial effluents, accidental release of chemicals (point sources) and throwing of all kinds of debris, including all kinds of solid, hazardous and bio-medical wastes.
- There are other non-point sources, such as agricultural run-off, natural/man-made calamities and other human/animal activities which are not being managed properly, like non-availability of sanitation services in the surrounding areas.
- Restoration and conservation of lakes/ponds/water bodies include:
  - Prevention of pollution from point sources by intercepting/diverting/treating the pollution loads entering the lakes/ponds/water bodies.
  - Prevention of pollution from non-point sources by providing low-cost sanitation.
  - *In situ* measures of lake cleaning such as cleaning of lake/pond/water body, de-silting of the water body/ponds/lakes, de-weeding, bioremediation, aeration, bio-manipulation, withdrawal of anoxic hypolimnion, utilization of treated wastewater, constructed wetland approach or any other successfully tested eco-technologies, etc., depending on site conditions.
  - Catchment area treatment, including affo-restation, storm water drainage, silt traps, etc.
  - Strengthening of bund, lake fencing, shoreline development, etc.
  - Lake front eco-development including public interface.
  - The Cogent facilitating activities: public awareness and public participation, capacity building, training and research in the area of lakes/ponds/water bodies conservation.
- The PWD, Village Panchayat, Horticulture Department, Irrigation Department, District Administration and other stakeholders need to be involved in the project. Synergy of all departments/ stakeholders involved is very essential.
- The aim of ecological restoration needs to be defined which may be fully restoring the components and processes of a damaged site or ecosystem to a previous historical state, to a contemporary standard, or towards a desired future condition. Therefore, appropriate goals to be set up as a critical step in the development of an effective restoration project.

- High priority restoration needs to be identified based on available and survey information on restoration priorities including Coarse and Fine Restoration Plans.

## PROPOSED RECOMMENDATIONS/SUGGESTIONS FOR ECO-RESTORATION OF LAKES/PONDS/WATER BODIES

- Identification/Delineating of catchment area and zone of influence of lake/pond/water body.
- Removal of sludge/silt from the water holding area of the lake/pond/water body and deepen it for holding maximum water.
- Removal of all encroachment/waste material dumped around the lake/pond/water body.
- Creation of strong bund/fencing to make the lake/pond/water body safer and clean.
- Trapping of rain water/treated wastewater to rejuvenate the lake/pond/water body.
- The treatment of wastewater may be done through constructed wetland, which has a very low maintenance and very low energy requirements.
- Creation of enhanced capacity of the lake/pond/water body to hold monsoon flows.
- Restoration and reconnection of the larger catchment to the lake/pond/water body to increase collection of storm water.
- Checking of water quality so that it meets the standards prescribed by the Water Quality Assessment Authority, Government of India.
- Creation of bathing Ghats in an environmental-friendly manner, wherever appropriate.
- Creation of ecologically designed easy-to-maintain landscapes like chairs, sitting boards, canopy, kiosks, etc., with eco-friendly products for public use.
- Logistical tips on items like permissions, safety and project timing to be included in the implementation plan.
- For successful restoration projects, consider future maintenance requirements, monitoring and responsible stakeholder.
- Put in place management regimes that are sustainable for the long-term by involving the community and other key stakeholders, particularly, PWD, Village Panchayat, Horticulture Department, Irrigation Department, District Administration as synergy of all departments involved is very essential.
- Actively involve the community and educate them with:
  - the objective of the project and its benefits.
  - the process of trapping and treating wastewater inlets.
  - the need to prevent further inlets from going directly into the water body.
  - use of water resources and landscape area of lake/pond/water body and their maintenance issues.

*Based on presentations by Mr Anand Malligavad (Lake expert from Bangalore), Dr RN Jindal (Ex-Director, MoEF&CC GOI), Dr M Dwarakanath (Ex-MS, Puducherry Pollution Control Committee-PPCC), Prof. Meenakshi Dhote (School of Planning and Architecture) and Mr RS Tyagi (Ex-Member, Drainage - Delhi Jal Board)*

**Participants:** Mr Vivek Kumar, Dr Anil Kumar, Mr Anand Malligavad, Dr M Dwarkanath, Dr SK Gupta, Mr Ankit Sethi, Dr Dipankar Saha, Mr Raghav Khemka, Mr Mukul Chand, Mr Varun Singh, Mr MR Chauhan, Dr SK Tyagi, Mr Pradeep Khandelwal, Mr Neeraj Tyagi, Mr Sanjiv Kumar, Mr Ashu Dhingra, Mr RN Jindal, Mr RS Tyagi, Mr Vikas Singhal, Mr RS Verma, Ms Meenakshi Dhote, Ms Ira Gupta, Dr S Sharma

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Indian Journal of Clinical Practice, Vol. 32, No. 4, September 2021

# Pyrogenic Cytokines Mediated Pathophysiology of Fever and Role of Mefenamic Acid in Pediatric Practice

AJAY GAMBHIR*, SUCHIT TAMBOLI†, SM PRASAD‡, NUSRAT RAHIM INAMDAR#


## ABSTRACT

While fever in most cases represents a normal physiological response to illness, many times it is a presenting sign of a more serious underlying condition. Hence, it is important to assess a child who may be suffering with a serious condition and may require treatment in terms of antipyretic agents. The use of antipyretic agents is usually guided by the degree of fever, and the discomfort caused by fever and associated pain. Paracetamol and, more recently, ibuprofen are the generally used over-the-counter drugs for antipyresis. However, of late, there is a trend of increased use of mefenamic acid as antipyretic. Mefenamic acid has shown better efficacy and tolerability as compared to the other nonsteroidal anti-inflammatory drugs (NSAIDs) in use. In this review, authors have assessed the existing literature on the role of mefenamic acid in pediatric fever. They have highlighted the role of mefenamic acid in pediatric febrile illness in terms of clinical uses, efficacy, comparison with other NSAIDs and its safety in pediatric patients. Its probable action in inflammatory fever and febrile seizure due to its inhibitory action on the NLRP3 inflammasome and potential antiviral actions in viral infections are also highlighted, respectively.


**Keywords:** Pediatric fever, febrile illness, anti-inflammatory, antipyretic, mefenamic acid, fenamates

Fever is one of the most common reasons for visits to doctor in children, contributing to 15-25% of primary care and emergency consultations.[1-3] It is defined as, "a physiologic response characterized by an elevation of body temperature above normal daily variation."[1] Pediatricians frequently prescribe mefenamic acid as an antipyretic and anti-inflammatory drug. It is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, analgesic and anti-inflammatory activity which is reported to be highly effective in reducing fever.[4]

*Head - Neonatology and Pediatrics
Saroj Hospital & Heart Institute, Fortis Hospital, Shalimar Bagh, Delhi
†Consultant Pediatrician
Chiranjiv Clinic, Ahmednagar, Maharashtra
E-mail: tamboli.k@gmail.com
‡Professor, Dept. of Pediatrics
Dr BR Ambedkar Medical College, KG Halli, Bangalore, Karnataka
#Associate Professor
HBT Medical College and Dr RN Cooper Hospital, Mumbai, Maharashtra
**Address for correspondence**
Dr Ajay Gambhir
Head - Neonatology and Pediatrics
Saroj Hospital & Heart Institute, Fortis Hospital, Shalimar Bagh, Delhi
E-mail: drajaygambhir@rediffmail.com

The evidence that NLRP3 inflammasome has a role in the pathophysiology of febrile seizures and mefenamic acid can inhibit this NLRP3 inflammasome, meaning it probably can alleviate the levels of pro-inflammatory cytokines responsible for febrile seizure.[5]

In this article, the authors have explored the evidence available on mefenamic acid, enumerate its role and significance, clinical safety and efficacy in pediatric febrile illness. The role of mefenamic acid as an antiviral agent in febrile illness of viral origin is also highlighted.

## METHODOLOGY

To locate evidence on mefenamic acid, the authors conducted a literature search on medical database including PubMed and Google Scholar. The MESH terms used in the search were **((“Mefenamic Acid” [Mesh]) AND “Anti-Inflammatory Agents, Nonsteroidal” [Pharmacological Action]) AND “Fever of Unknown Origin” [Mesh] AND “Fever” AND “Pyrexia” [Mesh]**. The search duration was June 2010 to June 2021. The inclusion criterion of the articles was all articles in English language, articles mentioning the use of mefenamic acid in treating febrile illness. The articles that were excluded from the search were the articles in

any language other than English. The types of articles searched for the present study were clinical trials, systematic reviews and meta-analyses, case reports, case series and narrative reviews.

The abstracts of the searched articles were scanned, and then final articles were identified and selected. Using a backward chronological search method, other relevant articles from the selected articles were also searched and selected if found relevant to the objectives of the present review. Owing to the heterogeneity of the articles available and the time gap between them, a narrative review was developed based on themes that were identified as a result of analysis of the selected articles.

## RESULTS AND DISCUSSION

Based on the search methodology, 46 articles were selected. The themes that emerged as a result of the analysis of the selected literature included information on fever, pathophysiology, assessment, treatment of fever, use of antipyretics and the place and value of mefenamic acid in treatment strategy of pediatric febrile illness.

### Fever

Fever is the most frequent reason for visit to the doctor in pediatric clinical practice and emergency department.[6] Fever is an abnormal rise in the body temperature occurring as a result of a biologic response managed and controlled by the central nervous system (CNS). It is dependent on the age of the child and the clinical circumstances.[7-10] Fever is a controlled physiologic phenomenon, owing to protective mechanisms in the thermoregulatory centers; however, adverse events after a febrile illness are many times related to neural immaturity and the underlying disease.[1] Table 1 depicts the temperature elevation that is considered abnormal in children.

The most common causes of fever in children are:[1,6]

- Infections
- Noninfectious causes – immune-mediated, inflammatory and neoplastic conditions
- Fever of unknown origin – cannot be identified by history and physical examination.

### Thermoregulation

Current evidence suggests that the core body temperature is controlled by several independent thermoeffector loops with their own efferent and afferent shoots. This led to the conclusion that the regulation of body temperature is dependent on a thermoregulatory circuitry. The anterior hypothalamus is the major thermoregulatory center in the CNS, where both the peripherally and centrally generated temperature signals converge and diverge. Heat sensitive neurons form the preoptic regions which are stimulated or blocked in response to the alterations in temperature. A sensitive balance between heat loss and heat gain regulates the body temperature to optimum limits. An early rapid phase (peripheral prostaglandin E2 [PGE2]-dependent) and a delayed late phase (central PGE2) mark the febrile response. As a result, while peripheral PGE2 may act to initiate the febrile response, central PGE2 may be mostly involved in its maintenance.[11]

The second humoral pathway is directed by circulating pyrogenic cytokines (IL-1β, IL-6, tumor necrosis factor [TNF]-$\alpha$). They send fever indicators to the thermoregulatory network through indirect and direct routes. The indirect pathway includes the binding of cytokines outside the brain and stimulating the cytokine receptors located on capillaries of the circumventricular organ resulting in PGE2 release. The direct pathway involves disruption of the blood-brain barrier by the circulating cytokines giving direct access to cytokine receptors present on vascular, glial and neuronal structures of the brain. While PGE2 is essential in the febrile response, certain cytokines such as IL-6 may also trigger the febrile response independent of PGE2.[11] In fact, it has been reported that the centrally produced IL-1β may act as a pro-epileptic agent and

**Table 1.** Fever of Concern as per Age and Clinical Circumstance

| Age | Fever of concern | Clinical circumstance |
|---|---|---|
| **Infant younger than 3 months of age** | Rectal temperature ≥38.0°C (100.4°F) | Otherwise, healthy |
| **Children 3-36 months** | Rectal temperature ≥39.0°C (102.2°F) | No focus of infection on examination |
| **Older children** | Oral temperature ≥39.5°C (103.1°F) | |

**The temperature thresholds of concern for children with underlying conditions like sickle cell diseases, neutropenia are different.**

**Table 2.** Humoral and Neural Pathways of Fever

| | Humoral pathway | Neural pathway |
|---|---|---|
| **Fever signals** | Carried by pathogen-associated molecular patterns (PAMPs) and pyrogenic cytokines | Peripheral nerves such as cutaneous sensory nerves and the vagus nerve. |
| **Mechanism** | 1. Circulating PAMP lead to release of PGE2 from the arachidonic acid pathway.<br>PGE2 diffuses across the blood-brain barrier, binds to specific PGE2 receptors (EP3 receptor) in the preoptic area activating thermal neurons to a higher thermal balance point.<br>Early phase: dependent on PGE2 synthesis<br>Second phase: dependent on centrally synthesized PGE2<br>Peripheral PGE2 initiate fever, while central PGE2 maintains it. | 1. Localized PGE2 synthesized at inflammation sites may activate cold-sensitive cutaneous nerves, transmitting fever signals to the brain. |
| | 2. Second pathway is guided by circulating pyrogenic cytokines as explained earlier. | 2. Circulating pyrogens stimulate liver to produce endogenous mediators like pyrogenic cytokines. These cytokines activate the hepatic arm of the vagus nerve within the nucleus of tractus solitarius from where the signal is transmitted to the preoptic and hypothalamic regions through the ventral noradrenergic bundle stimulating release of norepinephrine.<br>Norepinephrine activates the vagal pathway by triggering rise of core body temperature mediated by $\alpha_1$-adrenoceptor and dependent on PGE2. |

hence linked with the development of febrile seizures in children.[12]

Table 2 gives an overview of the humoral and neural pathways of fever.

## Pathophysiology of Fever

Fever can be described as a hallmark of infectious and inflammatory diseases.[13] There are three pathophysiologic bases of fever: 1) Fever due to the rise of the hypothalamic set point in the CNS, 2) fever due to heat production exceeding heat loss, and 3) fever caused by defective heat loss. The first type of fever can be reduced with the help of antipyretics and physical removal of the heat.[14] Fever is the result of a physiological process triggered by an external stimulus. Pyrogens are substances which may be infectious microorganisms, toxins released by microorganisms or pyrogenic cytokines that prompt fever.[15]

## Exogenous Pyrogens

Infectious microorganisms such as bacteria, virus, fungi or toxins are exogenous pyrogens (ExP) that incite fever, often within 2 hours of exposure. The ExP interact with macrophages or monocytes triggering the cytokine induction. Several other mechanisms may also be involved in the development of fever, including: (a) Bacterial endotoxins, acting directly on the hypothalamus to change the set point; (b) Lymphocyte activation by ExP; (c) Release of IL-1 via release of lymphokines activated by bacterial endotoxins. Some pyrogens are nonmicrobial in nature such as antigen-antibody complexes, steroids, some hormones, drugs and intracranial lesions such as bleeding and thrombosis. In blood transfusion reactions and immune hemolytic anemia, phagocytosis is the main mechanism behind causing fever.[15]

## Endogenous Pyrogens

Exogenous pyrogens including microbial pyrogens-bacteria, virus, and fungi and nonmicrobial pyrogens start the cycle by stimulating host cells, especially macrophages, to produce and release endogenous pyrogens like IL-1. Endogenous pyrogens trigger the synthesis of prostaglandins (PGE2) via the mediation of CNS, which raise the thermostatic set point to initiate the febrile response. PGE2 is the most important prostaglandin involved in the heat production. IL-1 also activates T-lymphocytes to produce various factors, such as INF and IL-2, important for immune response.[15]

The major fever causing cytokines are IL-1β, IL-1α, IL-6, TNF-α and INF-α. These cytokines can be produced in the periphery and brain and have pyrogenic effect directly affecting the production of PGE2 from the hypothalamus which resets the thermoregulatory set point. As a management approach, if the pyrogenic cytokines disappear from the circulating blood or cyclooxygenase (COX) is inhibited, the hypothalamus is again reset downward, thereby triggering the heat dissipation process and temperature reduction via vasodilation and sweating. NSAIDs such as mefenamic acid can lower the cytokines from circulation, thereby reducing fever.[16]

## ROLE OF ANTIPYRETICS IN MANAGING FEVER

Not only is fever one of the most troublesome symptoms for parents and caregivers as well as healthcare providers, but it also raises the concern that if untreated, it may progress to brain damage, seizures and death, even though there are no definitive evidence to prove this. Fever management differs in specific clinical situations. Fever may increase metabolic and oxygen consumption; hence, aggressive treatment may sometimes be needed.[1]

In a febrile illness, discomfort is usually due to an associated pain, such as myalgia, a sore throat or a headache. Antipyretic medications are required to improve comfort, along with improvements in eating, feeling of irritability, and providing pain relief and reduce chances of dehydration.[17] Besides, parents have also reported issues in giving medicines to a sick child. In a survey, it was reported that 85% of parents has to wake their children to give antipyretics.[18]

In a clinical report from the American Academy of Pediatrics, it has been suggested that the primary aim of offering treatment for a febrile child should be to improve the wholesome comfort level of the child and not just reduce the temperature.[19] A long-acting antipyretic will offer a long-lasting reduction of body temperature and provide the necessary comfort. Physical treatments like tepid sponging or cold baths are not recommended due to modest efficacy.[1]

Majority of healthcare workers believe that the risk of heat-related adverse outcomes is increased with temperature above 40°C (104°F) and almost 90% of health practitioners prescribe antipyretic therapy at temperatures >39°C.[20,21] In a large UK pediatric study in ICU patients, it was shown that the threshold for treatment of fever is still 38°C and 58% of caregivers in the study reported a fever of 39°C to be unacceptable.[22]

Febrile seizures is the most common type of acute seizure, affecting approximately 2-14% of children aged 6 months to 5 years worldwide. The pro-inflammatory cytokines viz. IL-1β, IL-6, TNF-α have been implicated in fever with IL-1β as central to initiation and regulation of inflammation which is released by activation of NLRP3 inflammasome. A significant increase of NLRP3 inflammasome expression is evident in children with febrile seizure as compared to controls.[23] The most commonly used antipyretics are NSAIDs with significant analgesic effect, thus promoting the feeling of well-being. There is a lot of variance among pediatricians prescribing antipyretic medicines for children.[16]

Presently, paracetamol, mefenamic acid and ibuprofen are the antipyretics of choice used to treat fever in kids.[24] Among individuals with normal renal function with no other risk factors, such as dehydration, for an acute renal hemodynamic effect, there is no risk associated with the use of NSAIDs.[25]

### Adverse Events Associated with Antipyretics

Paracetamol can be prescribed to infants from birth. However, paracetamol has a narrow therapeutic index and infants and children are at increased risk of overdose. Children aged under 5 years who are acutely unwell are particularly vulnerable to paracetamol toxicity, which can lead to liver failure and death.[26]

While paracetamol has the ability to reduce fever and pain, it lacks the anti-inflammatory activity that might be fundamental in containing exacerbation of diseases having inflammatory origin. It has been argued that preferential use of paracetamol may lead to an oxidative imbalance, deteriorating the clinical outcomes in a coronavirus disease 2019 (COVID-19) patient.[27]

Paracetamol may also lead to adverse effects in the presence of risk factors, such as dehydration, and in the case of medication errors such as overdosing or too frequent adminsitration.[26,28] Acetaminophen is associated with hepatic injury[29] while ibuprofen is linked with gastrointestinal bleeding and both have an increased risk of asthma in early childhood.[1,30,31]

## MEFENAMIC ACID

### Role of Mefenamic Acid in Fever

Mefenamic acid exerts central and peripheral actions in prostaglandin inhibition. It also blocks the E-type prostanoid (EP) receptors, thus inhibiting the pre-formed prostaglandins. Hence, it has a prominent action on all the fever producing pathways. Due to its dual action,

it can significantly reduce the inflammatory cytokines thereby improving sleep, and other symptoms such as myalgia and arthralgia associated with fever.[5]

Mefenamic acid exerts its action by blocking the COX enzyme or prostaglandin H synthase (PGHS), thus disrupting the conversion of arachidonic acid to its metabolites, including prostaglandins, prostacyclin and thromboxane. By being a preferential COX-2 selective inhibitor, mefenamic acid not only leads to an antipyretic, anti-inflammatory and analgesic effect, but it improves effectiveness without inducing significant gastrointestinal side-effects.[5]

Clinical studies suggest safe use of mefenamic acid above 6 months at 4-6.5 mg/kg/dose as antipyretic. In general, for children above 6 months the dose suggested is 25 mg/kg/day in three divided dosages.[16,32]

## Clinical Evidence

A study compared the ability of mefenamic acid with that of acetylsalicylic acid, paracetamol and aminophenazone, in reducing fever in children. In this study, a series of cases including 71 patients (age 3 months to 15 years with rectal temperature above 38.5°C) were observed and the antipyretic effect of mefenamic acid in a dose of 4 mg/kg was optimum. The effect was reported to be 2.5 times that of paracetamol and at par with that of aminophenazone. The study concluded that the antipyretic effect of mefenamic acid was stronger than its anti-inflammatory and analgesic properties.[33]

In a study comparing the relative efficacy of 3 anti-pyretics-mefenamic acid, ibuprofen and paracetamol, the results showed that mefenamic acid group with 29 patients demonstrated a fall of 3.5°F at the conclusion of 4 hours compared with the paracetamol group (29 patients) that showed a fall of 2.44°F at the end of 4 hours and ibuprofen group (20 patients) showing a fall of 2.79°F. The results of this comparative study have shown that mefenamic acid showed significantly better antipyretic activity compared to paracetamol ($p < 0.05$) over 4 hours and ibuprofen ($p < 0.05$) in the 2- to 4-hour range. In fact, it was suggested that mefenamic acid displayed a persistent activity even at the end of 4 hours compared to paracetamol and ibuprofen.[34]

In another study conducted to compare the antipyretic effect of paracetamol and mefenamic acid in pediatric patients, it was suggested that mefenamic acid has more efficacy and equal tolerability compared with paracetamol as an antipyretic in pediatric patients with fever. The antipyretic efficacy of mefenamic acid was reported to be higher than paracetamol ($p < 0.05$). The researchers have suggested mefenamic acid as the best alternative to paracetamol.[16]

In a randomized, open-label study, it was shown that mefenamic acid has faster onset of action. Its efficacy at the end of 6 hours is maximum as compared to paracetamol and ibuprofen. Mefenamic acid, at the end of 24 hours, demonstrated highest reduction in the baseline mean temperature among the three study groups, including mefenamic acid, paracetamol and ibuprofen groups. The study authors concluded that mefenamic acid is a better antipyretic compared to paracetamol and ibuprofen in terms of faster onset of action and prolonged effect.[24] Besides, it also gives comfort to parents with 'fever phobia'[18] who do not need to disrupt their child's comfort by awakening them from sleeping.

It is an established fact that febrile seizures are the most common convulsions in childhood, which is believed to be activated by IL-1β. In a recent study, it has been reported that NLRP3 protein was considerably increased in children with typical febrile seizure compared to in fever only controls. Increased NLRP3 can mediate the release of IL-1β which is responsible for febrile seizures in children.[23,35]

Mefenamic acid inhibits the NLRP3 inflammasome and the release of IL-1β by blocking the membrane volume regulated anion channel and volume-modulated transient receptor protein channels. It acts independently of its COX-mediated anti-inflammatory activity.[5] The NLRP3 inflammasome inhibitory activity of mefenamic acid can be a promising potential therapy in the prevention and/or management of febrile seizures in children. This further broadens the scope of mefenamic acid use in children with febrile illness.

Mefenamic acid is also approved for use as an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis, osteoarthritis and pain including muscular, traumatic, dental pain and pyrexia in children. It is also used for primary dysmenorrhea in older children and adolescents.[36] Mefenamic acid is one of the prescribed antipyretic medications for the treatment of fever. Mefenamic acid, the potent COX inhibitor, has both central and peripheral action and is recommended to be used in a dose of 4-6.5 mg/kg/dose.[16,36] It is also included in the National Formulary of India for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, mild to moderate pain, inflammation, fever, and dental pain.[37]

In a study, it was demonstrated that mefenamic acid and doxycycline, when used together, led to significant inhibition of DENV2 NS2B-NS3pro resulting in significant reduction of viral load. In the study, mefenamic acid depicted better selectivity against dengue virus replication *in vitro* compared to doxycycline. Hence, the anti-dengue and anti-inflammatory properties of mefenamic acid can be a promising therapy in the management of dengue.[38]

In another study, mefenamic acid and meclofenamic acid demonstrated significant antiviral activity against viral replication either alone or in combination with another antiviral drug, ribavirin, besides leading to significant reduction of pathological signs. The results of the study led to the possibility of further expansion of the clinical spectrum of mefenamic acid.[39]

### Mefenamic Acid vs. Other Antipyretics

Paracetamol has been used as an antipyretic for a long time and it exerts its effect by reducing prostaglandin synthesis in the brain. However, paracetamol does not inhibit the synthesis of prostaglandins in the periphery unlike mefenamic acid.[36] There have been some reports of failure of antipyretic drugs such as paracetamol in controlling fever, giving rise to use of mefenamic acid as an antipyretic. While paracetamol has only central action with weak anti-inflammatory action, mefenamic acid, on the other hand, has central and peripheral action with significant anti-inflammatory effect, with better antipyresis at 1 hour.[16]

Mefenamic acid has demonstrated similar analgesic and anti-inflammatory effect compared with ibuprofen in a study. The study also revealed similar side effect profiles for the two drugs except for drowsiness seen in 6 cases with ibuprofen and 2 cases with mefenamic acid.[40] In a case series and reports, it has been suggested that mefenamic acid may have a beneficial effect in patients with bronchial asthma,[41,42] whereas ibuprofen and paracetamol have been associated with increased risk of asthma.[30,31]As previously mentioned, it has been shown that mefenamic acid has better efficacy and tolerability compared with paracetamol and ibuprofen.[24]

Nimesulide is an NSAID with anti-inflammatory, analgesic and antipyretic properties, with efficacy at par with naproxen, acetylsalicylic acid, mefenamic acid and paracetamol. However, nimesulide may cause fulminant hepatitis. On the other hand, mefenamic acid is an NSAID with dual activity - central as well as peripheral analgesic action.[16] The Government of India as well as many other countries like Switzerland, Spain, and the United States have banned nimesulide for pediatric use in common fever and pain because of its detrimental effects on the liver.[43] Additionally, as shown above, the unique inhibitory action of mefenamic acid on NLRP3 inflammasome may assist in attenuating fever and inflammation effectively.

### Pediatric Safety and Efficacy

In a clinical trial including 87 children, mefenamic acid showed optimum fever control at a dose of 4 mg/kg. Its antipyretic activity was reportedly higher than the antirheumatic effects.[44] Mefenamic acid has comparatively better efficacy and tolerability than other NSAIDs (ibuprofen) or paracetamol.[24] The results of a clinical trial have demonstrated that there were no hypersensitivity or intolerance events associated with the use of mefenamic acid. Besides, no side effect from the short-term therapy in children for fever was observed.[45]

The safety of mefenamic acid has been established from the various clinical studies as published. It has been used for closure of symptomatic patent ductus arteriosus in preterm infants (2 mg/kg once in 24 hrs), especially in those patients where intolerance to indomethacin is seen or minute titration of dosage is not possible.[46]

Mefenamic acid is considered to be one of the safest drugs in terms of safety outcome and is registered for use since 6 months of age in children with fever.[17] As per the official journal of the American Academy of Pediatrics, mefenamic acid can be safely used in breastfeeding mothers.[5]

## CONCLUSION

Even though there are variances among clinical judgments, many pediatricians routinely prescribe antipyretic agents to treat fever. These antipyretics belong to NSAIDs, with paracetamol, mefenamic acid and ibuprofen being the current choices of drugs. The dual action of mefenamic acid (central and peripheral), and COX enzyme inhibition and blocking of EP receptor, makes it a unique entity in the landscape of fever management. The novel actions (NLRP3 inflammasome inhibition and potential antiviral action) as evident from literature makes it stand out in comparison with other NSAID options. It has a longer duration of antipyretic action and also possesses proven anti-inflammatory and analgesic actions. Many studies have shown that mefenamic acid has better efficacy as an antipyretic

agent compared to paracetamol in pediatric patients. The comparable safety profile of mefenamic acid is also superior to other drugs in the same category used for treating fever.

However, the authors would like to state that more extensive studies comparing the efficacies, safety and multifactorial use of NSAIDs as an antipyretic, anti-inflammatory and analgesic agent must be conducted in pediatric patients for an informed clinical decision on their utility in children with febrile illness. Future clinical studies to explore the role of mefenamic acid in conditions of febrile seizures or febrile infection-related epilepsy syndrome (FIRES) are also recommended.

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# The Glycemic Efficacy and Safety Profile of Gliptins: Updated Data in 2020

PARMINDER SINGH*, SUYOG J DOSHI†, SUJA P SUKUMAR‡, CHITRA SELVAN#, GURURAJ RAO¥


## ABSTRACT

**Background:** The earlier update on the safety of gliptins published in 2018 showed that dipeptidyl peptidase-4 (DPP-4) inhibitors have good tolerance and safety profile even in susceptible populations. This review provides recent updates (2018-2020) on the glycemic efficacy and safety profile of gliptins, cardiovascualr safety of gliptins, and their role when used early in diabetes therapy. **Summary:** DPP-4 inhibitors or gliptins is an established class of oral antidiabetic agents in the management of type 2 diabetes with proven efficacy and safety profiles in adults, elderly and young patients. The excellent safety and efficacy of DPP-4 inhibitors are established in type 2 diabetes management even in fragile populations and individuals with varying degrees of renal dysfunction. DPP-4 inhibitors are associated with a good tolerability profile and reduced risk of hypoglycemia. Studies have not shown the involvement of gliptins in cardiovascular adverse events and are considered to be safe for use in terms of cardiovascular events.


**Keywords:** DPP-4 inhibitors, vildagliptin, alogliptin, cardiovascular benefits, safety and efficacy

Dipeptidyl peptidase-4 (DPP-4) inhibitors or gliptins are antidiabetic agents which act by binding to the enzyme DPP-4 to inhibit the degradation of the incretin, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), with a primary role in glucose homeostasis and glycemic control. DPP-4 inhibitors prolong the activity of endogenous GLP-1 and GIP and may improve postprandial hyperglycemia, without inducing hypoglycemia, in patients with type 2 diabetes mellitus (T2DM).[1]

In the previous update on the safety of gliptins published in 2018, it was suggested that the DPP-4 inhibitors possess good tolerance/safety profile even in the more fragile populations with no gastrointestinal adverse events and minimal chances of hypoglycemia. The review mentioned the occurrence of new adverse event arthralgia; however, until now, there is no definitive evidence about the causality of the relationship.[2]

This comprehensive review aims at discussing the recent updates on the glycemic efficacy and safety profile of gliptins, including their glycemic variability, adverse events and role of gliptins when used early in diabetes therapy.

## METHODOLOGY

Authors conducted a review of published literature to assess the glycemic efficacy and safety profile of DPP-4 inhibitors in the treatment of T2DM patients. The search was primarily conducted on PubMed and Google Scholar. In an attempt to identify relevant studies, an extensive literature search of PubMed was performed from January 2018 to July 2020, with the MeSH terms [(((((DPP-4 inhibitors) OR (Gliptins)) OR (DPP-4 inhibitors)) AND (Safety)) AND (tolerance)], (DPP-4 inhibitors) AND (Adverse events), and (((DPP-4 inhibitors) OR (Gliptins)) OR (DPP-4 inhibitors)) AND (glycemic variability), including randomized controlled trials (RCTs), clinical studies, systematic reviews and meta-analyses. In a backward chronological search, the reference lists of all relevant articles were checked for citations that could not be detected in the primary search. A total of 63 articles were selected for the development of the review.

*HoD, Dept. of Endocrinology, Dayanand Medical College, Ludhiana, Punjab
†Consultant Physician, FEACD, Niron Hospital, Santacruz East, Mumbai, Maharashtra
‡Endocrinologist, Renai Medicity Hospital, Kerala
#Consultant Endocrinologist, Bengaluru, Karnataka
¥Endocrinologist, Arogya Clinic, Mangalore, Karnataka
**Address for correspondence**
Dr Parminder Singh
Dept. of Endocrinology
Dayanand Medical College
Civil Lines, Tagore Nagar, Ludhiana, Punjab - 141001
E-mail: pam.endo@yahoo.co.in

## GLYCEMIC EFFICACY AND SAFETY PROFILE

The DPP-4 inhibitors are oral hypoglycemic agents generally considered to be effective in lowering glucose levels and possess no gastrointestinal adverse effects and minimal risk of hypoglycemia.[2]

A network meta-analysis including data till 2018 compared and evaluated the efficacy and safety of different DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin and alogliptin) compared with placebo and against each other. The results indicated that except alogliptin, all DPP-4 inhibitors led to a decrease of glycated hemoglobin (HbA1c) when compared with placebo. When evaluated for body mass index (BMI) and body weight, it was found that vildagliptin 5 once daily (QD) and linagliptin 5 QD was best placed in reducing the BMI and body weight, respectively.[3]

The EVOLUTION INDIA study assessed the efficacy and safety of evogliptin versus sitagliptin, added to background metformin therapy in Indian patients with uncontrolled T2DM. The study findings demonstrated that mean reduction in HbA1c at 12 weeks in evogliptin and sitagliptin-treated patients were -0.37 (1.06) and -0.32 (1.14), respectively. The results from the study led to the conclusion that evogliptin was noninferior to sitagliptin in HbA1c reduction. It effectively improved glycemic control and was well-tolerated in T2DM patients whose blood glucose was not managed by the use of metformin alone.[4]

A head-to-head prospective, open-label, randomized, active-control trial comparing teneligliptin with sitagliptin as an add-on to metformin and/or sulfonylurea in patients with T2DM was conducted. It was suggested that teneligliptin provided similar glycemic control as compared to sitagliptin and reduced HbA1c, fasting blood glucose (FBG) and postprandial blood glucose (PPBG) values significantly within 12 weeks of treatment. The results showed that at the end of 12 weeks, statistically significant lowering was seen in both teneligliptin and sitagliptin arms in HbA1c (-1.19 ± 1.16% $p < 0.0001$ and -0.92 ± 0.95%, $p < 0.0001$), FBG (-28.3 ± 63.0 mg/dL, $p = 0.01$ and 022.9 ± 47.4 mg/dL, $p < 0.006$) and PPBG (-41.3 ± 85.4 mg/dL, $p = 0.006$ and -54.7 ± 85.6 mg/dL, $p = 0.0005$). According to the results, both gliptins were found to be safe and well-tolerated with no differences in the adverse events rate in Indian patients with T2DM. However, post-hoc comparisons have shown that the percentage of patients reaching the target HbA1c <7% after 12 weeks of treatment was in favor of teneligliptin compared with sitagliptin.[5]

Another phase 4, randomized, placebo-controlled national study was conducted in Japan over 52 weeks in 102 patients (≥60 years) on stable treatment with basal insulin and metformin or $\alpha$-glucosidase inhibitors. The participants were randomized (1:1) to be administered linagliptin 5 mg QD or placebo with the primary endpoint being the change in HbA1c after 24 weeks of treatment. The findings of the study showed that significant HbA1c reductions with linagliptin versus placebo were observed in elderly patients at 24 weeks (95% confidence interval [CI] -0.96, -0.45, $p < 0.0001$) and maintained at 52 weeks. Linagliptin was effective in improving glucose control in Japanese patients aged ≥60 years with T2DM on stable glucose-lowering therapy with basal insulin and was well-tolerated in elderly patients with no adverse events reported.[6]

In a study comprising of 458 participants who were not at HbA1c goal on a submaximal dose of metformin, when a DPP-4 inhibitor like sitagliptin was added while metformin dose was being increased, the intervention resulted in improved glycemic response. The findings of the study showed that following 20 weeks of treatment, the least-squares mean changes from baseline in HbA1c were -12.1 mmol/mol (-14.0, -10.1) (-1.10% [-1.28, -0.93]) and -7.6 mmol/mol (-9.6, -5.6) (-0.69% [-0.88, -0.51]) with sitagliptin and placebo, respectively. The between-group differences in the least-squares mean changes from baseline HbA1c was -4.5 mmol/mol (-6.5, -2.5) (-0.41% [-0.59, -0.23]); $p < 0.001$. These findings suggested that the use of sitagliptin led to the achievement of HbA1c target with similar safety and tolerability as compared to increasing metformin dose alone.[7]

Similar results were obtained in a study which analyzed pooled data from two 52-week Phase III studies assessing the efficacy and safety of once daily combinations of empagliflozin/linagliptin as exclusive therapy or add-on to metformin in patients with T2DM. Adverse events were evaluated descriptively in patients who took ≥1 dose of the study drug. The findings showed that empagliflozin or linagliptin as monotherapy or add-on to metformin for 52 weeks was well-tolerated in T2DM patients, with a safety profile similar to individual components, including a low risk of hypoglycemia. The percentage of patients with confirmed hypoglycemic adverse events was low in all groups (1.1-2.2%); however, no patient required any assistance. Events consistent with urinary tract infection were described in a similar percentage of patients in all groups (11.4-13.8%); events consistent with genital infection were stated in increased proportions of patients on empagliflozin/linagliptin or

empagliflozin (4.0-6.5%) than linagliptin 5 mg (2.6%). Also, the risks of hypersensitivity reactions and adverse events related to loss of volume were low across all treatment groups.[8]

The results of a double-blind, randomized, controlled parallel-group study comparing 1 and 5 mg doses of a DPP-4 inhibitor (linagliptin) demonstrated similar clinical efficacy and safety profile of the drug in young patients equivalent to adult patients. The DPP-4 inhibitor was well-tolerated and led to a dose-dependent DPP-4 inhibition accompanied by the corresponding lowering of the HbA1c and fasting plasma glucose (FPG) levels in young people with T2DM. The higher dose was favored over lower dose in terms of efficacy and safety profile.[9]

The DPP-4 inhibitors are also considered to be both efficacious and well-tolerated across a wide range of renal function; however, sometimes, dose adjustment may be needed to control drug exposure.[10] The CompoSIT-R study was a prospective, randomized clinical trial comparing the efficacy and safety of the DPP-4 inhibitor sitagliptin with the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin in patients with T2DM and mild renal insufficiency. The findings showed that in T2DM patients with mild renal insufficiency, sitagliptin optimized blood glucose management to a greater extent than dapagliflozin. After 24 weeks, the between-group difference in the least square mean (95% CI) changes from baseline in HbA1c was -0.15% (-0.26, -0.04) (-1.67 mmol/mol [-2.86, -0.48]), p = 0.006, meeting the prespecified criteria for declaring both noninferiority and superiority of sitagliptin versus dapagliflozin. This study provided concrete evidence based on which clinicians could take informed patient-centered decisions for the treatment of T2DM patients. DPP-4 inhibitors are preferred choice in patients with T2DM and renal disease owing to their efficacy and good tolerability across the renal disease spectrum. In T2DM patients with mild renal insufficiency who were poorly controlled on metformin ± sulfonylureas, treatment with sitagliptin compared with dapagliflozin demonstrated enhanced glycemic efficacy and increased percentage of patients achieving the glycemic goal and a good safety profile.[11]

When compared with other treatments, DPP-4 inhibitors were linked with a larger variation in HbA1c level, and a higher response rate of patients achieving the HbA1c goal of <7%. The occurrence of adverse events in the two groups did not differ significantly, and DPP-4 inhibitors did not lead to an increased rate of hypoglycemia.[12] DPP-4 inhibitors significantly reduce HbA1c levels in T2DM patients with moderate-to-severe renal injury. It has been established that DPP-4 inhibitors did not increase the risk of hypoglycemia and adverse events.[13]

A systematic review and meta-analysis of 15 RCTs to assess ethnic differences in efficacy and safety of a potent DPP-4 inhibitor alogliptin concluded that it is more effective in improving glycemic levels in Asian population as compared to other ethnic populations. It was hypothesized that BMI value was a primary contributor to the differential glycemic effects of DPP-4 inhibitors. The studies with Asian population were on lower-BMI groups as compared with those of non-Asian population.[14] The results of a meta-analysis previously had shown that in some cases, the baseline BMI was significantly linked with HbA1c-reducing efficacy in patients being given DPP-4 inhibitors.[15] It has been proven that DPP-4 adipokine is significantly present in the visceral fat of obese people, and its release into circulation is also increased. Hence, DPP-4 activity is raised in obese individuals. As it is evident that the circulating DPP-4 level and activity are increased in obese individuals, the efficacy of DPP-4 inhibitors in non-Asian patients with high BMI should be lower than in Asian patients, which has also been proven in various studies.[14]

The results of the SUPER study, evaluating the efficacy of a DPP-4 inhibitor as add-on treatment in Chinese T2DM patients inadequately controlled by insulin ± metformin, showed that add on DPP-4 inhibitor, saxagliptin 5 mg QD, led to a substantial improvement in glycemic control without increasing the risk of hypoglycemia and was also well-tolerated in Chinese patients with T2DM uncontrolled by insulin and/or metformin.[16] Cumulative evidence from 30 RCTs concluded that saxagliptin has similar efficacy compared with most oral antidiabetic drugs and may be more effective than acarbose and may also have a better safety profile than both acarbose and sulfonylureas. The results of the study showed that compared with placebo, saxagliptin reduced HbA1c (weight mean difference [WMD] -0.52%, 95% CI -0.60 to -0.44) and FPG (WMD -13.78 mg/dL, 95% CI -15.31 to -12.25), and increased the proportion of patients achieving HbA1c <7% (risk ratio [RR] 1.64, 95% CI 1.53-1.75). Saxagliptin was also similar to other DPP-4 inhibitors but inferior to liraglutide and dapagliflozin on glycemic control. It significantly reduced the occurrence of overall adverse events compared with acarbose (RR 0.71, 95% CI 0.57-0.89) and liraglutide (RR 0.41, 95% CI 0.24-0.71) when added to metformin. Another advantage was that saxagliptin did not increase the risk of arthralgia, heart failure, pancreatitis and other adverse events.[17]

Another open-label, phase 3 exploratory study evaluated the efficacy and safety of a once-weekly novel DPP-4 inhibitor, trelagliptin, in Japanese T2DM patients when switched over from once daily sitagliptin therapy. Of the 14 patients receiving the study drug, the blood glucose did not show any marked changes from baseline at major assessment points in the meal tolerance test, and a reduction in blood glucose was seen at several other assessment points. Mild-to-moderate adverse events were reported in approximately 43% of the patients, and most were not related to the study drug. It was indicated that it is possible to transition from a once daily DPP-4 inhibitor to trelagliptin in T2DM patients with stable glycemic control in combination with diet and exercise therapy without any significant influences on glycemic control or safety.[18]

When used as monotherapy, the efficacy and safety of once-weekly DPP-4 inhibitor omarigliptin can improve glycemic control over 54 weeks. A study was conducted among people with T2DM not on glucose-lowering medications, or who were washed off monotherapy or low-dose dual therapy. The results showed that from a mean baseline HbA1c of 8.0-8.1%, the least-squares mean (95% CI) change from baseline in HbA1c at Week 24 (primary endpoint) was -0.49% (-0.73, -0.24) in the omarigliptin group and -0.10% (-0.34, 0.14) in the placebo group, for a between-group difference of -0.39% (0.59, -0.19) ($p < 0.001$).[19]

A systematic review and meta-analysis, including 11 clinical trials, offered a conclusion based on a subgroup analysis that omarigliptin possessed homologous efficacy and safety compared to other antihyperglycemic agents. It revealed that omarigliptin had a favorable efficacy and safety as monotherapy or added on to other antihyperglycemic agents. The results of the meta-analysis showed that in comparison with the control group, omarigliptin was linked with a considerably stronger reduction in HbA1c and FPG. The study findings did not reveal any significant differences in adverse events, serious adverse events, hypoglycemic events between omarigliptin and control group.[20]

In a systematic review and meta-analysis, the results of the 6-minute walk test and peak oxygen consumption suggested that DPP-4 inhibitors or GLP-1 receptor agonists improved patients' exercise tolerance and did not reduce patients' quality of life, with high heterogeneity among the results. The authors have concluded that DPP-4 inhibitors or GLP-1 receptor agonists can improve exercise tolerance in heart failure patients, and do not appear to increase the incidence of all-cause death or severe adverse events and do not decrease health-related quality of life.[21] It has been revealed in many studies that GLP-1 can use microvasculature and stimulate mitochondrial activity in muscle.[22-24] During exercise, microvasculature plays a crucial role in ensuring an adequate supply of oxygen and nutrients so that adenosine triphosphate (ATP) is generated in the mitochondria.[25] When DPP-4 GLP-1 pathway is targeted, an increase in GLP-1 levels ensures oxygen and nutrient supply to the muscles further stimulating mitochondrial activity. With improved microvasculature function, oxygen consumption is also improved. These cascading events may be potentially responsible for improved oxygen tolerance.[21] Another study has also shown that exercise tolerance is also improved as DPP-4 inhibitors activate the GLP-1 receptor signalling.[24] A systematic review and meta-analysis conducted to evaluate safety and tolerability profile of DPP-4 inhibitors versus sulfonylurea treatment in adult T2DM patients suggested a better safety profile for DPP-4 inhibitors than sulfonylureas and the effect was better for treatment regimens including metformin. The findings of the meta-analysis reported that DPP-4 inhibitors in combination with metformin reduced global adverse events (RR: 0.90; 95% CI, 0.86-0.94; $p < 0.0001$; $I^2 = 83\%$; 17 studies), cardiovascular events (RR: 0.54; 95% CI, 0.37-0.79; $p = 0.002$; $I^2 = 0\%$; 6 studies), hypoglycemia (RR: 0.17; 95% CI, 0.13-0.22; $p < 0.00001$; $I^2 = 76\%$; 17 studies) and severe hypoglycemic events (RR: 0.10; 95% CI, 0.05-0.19; $p < 0.00001$; $I^2 = 0\%$; 12 studies). The mean difference of the weight shift was 1.92 kg in favor of DPP-4 inhibitors in combination with metformin compared with sulfonylureas in combination with metformin. Besides, monotherapy with DPP-4 inhibitors also reduced the rates of hypoglycemia (RR: 0.31; 95% CI, 0.24-0.41; $p < 0.00001$; $I^2 = 0\%$) and severe hypoglycemic events (RR: 0.26; 95% CI, 0.10-0.66; $p = 0.004$; $I^2 = 0\%$) and patients did not gain weight.[26]

A novel xanthine DPP-4 inhibitor, yogliptin, targeting type 2 diabetes was assessed in a randomized, double-blind, parallel, placebo-controlled phase I single-dose escalation and the findings showed that it was well-tolerated in healthy participants, with no dose-limiting toxicity observed in the range from 2.5 to 600 mg. Additionally, yogliptin also exhibited plasma DPP-4 inhibitory activity for 3 days when given in a single dose of 25-200 mg and for 1 week when given in a single dose of 400 mg. Hence, it was suggested that once-weekly dosing of yogliptin was possible in T2DM patients.[27]

PREFERENCE 4 study was conducted to compare treatment satisfaction of four classes of oral hypoglycemic agents including DPP-4 inhibitors,

α-glucosidase inhibitors, biguanides and sulfonylureas. The DPP-4 inhibitor was the most preferred option in terms of treatment satisfaction. In this study, the mean total and the three subscale scores at Week 4 suggested that patients were most satisfied with the DPP-4 inhibitor treatment. Furthermore, increased satisfaction sustained with high adherence, HbA1c improvement and few adverse events over 12 weeks gave a good indication of the popularity of DPP-4 inhibitors for their ability to restore β-cell dysfunction with limited risk of hypoglycemia. The PREFERENCE 4 study provided a ground for basing clinical judgments in optimal drug selection for patients with T2DM.[28] The TRINITY trial assessed the patient preference for treatment with the oral once-weekly DPP-4 inhibitor, trelagliptin and oral once daily alogliptin given for 8 weeks each in patients with T2DM. The findings suggested that patients preferred once-daily alogliptin compared with once-weekly trelagliptin even though patient satisfaction and HbA1c levels were similar across treatments. However, both the treatments demonstrated favorable safety and tolerability profiles.[29] When 10 clinical trials were systematically reviewed and underwent analysis, it was concluded that DPP-4 inhibitor teneligliptin improved blood glucose levels and β-cell function with low risks of hypoglycemia in T2DM patients.[30]

## EARLY INITIATION THERAPY WITH GLIPTIN

Early treatment intensification is linked with sustained glucose management and delayed diabetes complications. The current guidelines for the management of hyperglycemia in T2DM recommend the use of metformin as first-line therapy with further intensification and second-line therapy only when glycemic control is not achieved.[31,32] However, frequently the treatment intensification is delayed, which may be the reason for the loss of glycemic control and exposure to avoidable hyperglycemia.[33] In the UK Prospective Diabetes Study, it was established that early treatment to reduce glycemia using metformin was linked with lowering of myocardial infarction, diabetes-related deaths and all-cause mortality and long-term continued benefit following 10 years of treatment.[34] Some other studies have also highlighted the significance of attaining early blood glucose control in the first 12 months of diagnosis as an approach towards improving long-term glycemic durability and lowering of complications associated with diabetes.[35]

Existing evidence has suggested that the combination therapy, including DPP-4 inhibitor and other antidiabetes drugs, showed a significant decrease in HbA1c ($p < 0.001$) and a similar risk of hypoglycemia ($p > 0.05$). When compared with monotherapy, initial combination therapy including DPP-4 inhibitors also resulted in significant HbA1c reductions, a similar risk of hypoglycemia and similar risks of other adverse events.[36]

Administering two or more agents in combination therapy is a critical approach. In a randomized, double-blind, parallel-group study of newly diagnosed patients with T2DM (VERIFY), it was seen that early intervention with combination therapy of vildagliptin + metformin provides more significant and sustainable long-term benefits compared with the current standard-of-care initial metformin monotherapy.[37]

## GLYCEMIC VARIABILITY

Glycemic variability is an essential aspect of blood glucose management, and DPP-4 inhibitors have been reported to have the ability to improve glycemic control and to reduce glucose fluctuations, by increasing active serum GLP-1 and GIP concentrations through a glucose-dependent insulin secretion.[38]

DPP-4 inhibitors are potential therapeutic agents for use in combination with metformin as they complement each other's mechanism of action. In a pilot study, a comparison of glycemic variability with high metformin dose versus low metformin dose and DPP-4 inhibitor combination was conducted in Japanese T2DM patients with inadequate glucose control despite the low-dose metformin monotherapy. The results indicated that low metformin + DPP-4 inhibitor might reduce post-breakfast glycemic variability to a more considerable extent than high metformin in T2DM patients receiving low-dose metformin monotherapy. The study results suggested that the combination of metformin and DPP-4 inhibitor has a better effect on improving post-breakfast glycemic excursions.[39]

An open-label, parallel-group, exploratory study examining the effects of two DPP-4 inhibitors on glycemic variability in patients with type 2 diabetes recommended that once-weekly trelagliptin and once-daily alogliptin improved glycemic control and reduced glycemic variability without inducing hypoglycemia.[38] An open-label, randomized study conducted among women with T2DM, suggested that both vildagliptin and gliclazide modified release similarly lowered the mean amplitude of glycemic excursions in them after 24 weeks of treatment.[40] However, in a trial including 20 T1DM patients, the findings showed that DPP-4 inhibitor (linagliptin) was not effective in reducing HbA1c and glycemic variability in relatively well-controlled type 1 diabetes.[41]

Following Roux-en-Y gastric bypass surgery (RYGB), in patients with diabetes and mild hyperglycemia a short course of DPP-4 inhibitor such as sitagliptin was found to provide small but significant glucose-lowering effect, with no identified improvement in β-cell function in a 4-week randomized trial.[42] In a randomized crossover study, 11 women who had undergone RYGB and had documented hypoglycemia were evaluated to investigate the effects of acarbose, sitagliptin, verapamil, liraglutide and pasireotide on post-bariatric hypoglycemia after the bypass. It was found that sitagliptin lowered nadir glucose values while acarbose and pasireotide reduced post-bariatric hypoglycemia.[43]

In a study assessing the efficacy of vildagliptin as add-on therapy to short-term continuous subcutaneous insulin infusion (CSII) with CSII monotherapy, the findings showed that the mean blood glucose (BG) concentrations during the whole treatment period were less and the time to attain target blood glucose levels was reduced in the CSII + vildagliptin group compared with the CSII group (9.89 ± 3.37 vs. 9.46 ± 3.23 mmol/L, $p < 0.01$; 129 ± 4 vs. 94 ± 5 h, $p < 0.01$, respectively). The authors concluded that short-term CSII with vildagliptin as add-on therapy might be a potentially beneficial alternative regimen for the management of uncontrolled blood glucose in T2DM patients.[44]

## EFFECTS ON CARDIOVASCULAR OUTCOME

Type 2 diabetes mellitus heightens the risk of major cardiovascular complications by two-folds in patients without pre-existing cardiovascular disease, often resulting in fatal outcomes. Even though it has been established that improved glycemic control leads to a reduction in microvascular diabetic complications, ambiguity about the role of a specific glucose-lowering approach or a specific medicinal agent in terms of cardiovascular safety persists.[45]

Cardiovascular adverse events following the use of DPP-4 inhibitors have been suspected since DPP-4 inhibitors were launched in 2006. However, in a study, cardiovascular events after taking DPP-4 inhibitors were detected in only 1% of total 307 adverse event reports. An analysis of spontaneous adverse drug reports data did not reach any conclusive association between DPP-4 inhibitors and cardiovascular adverse events, owing to a small number of cardiovascular adverse events reports.[46]

The CARdiovascular Outcome study of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA) trial compared the effect of linagliptin and glimepiride on major cardiovascular events in patients with relatively early T2DM and increased cardiovascular risk. The findings showed that the primary outcome (time to the first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) occurred in 356 of total 3,023 (11.8%) patients in the linagliptin group and 362 of 3,010 (12.0%) in the glimepiride group (hazard ratio [HR], 0.98 [95.47%, CI, 0.84-1.14]; $p < 0.001$ for noninferiority), meeting the noninferiority criterion but not superiority ($p = 0.76$). The results indicated that among adults with relatively early type 2 diabetes and increased cardiovascular risk, the use of linagliptin is of comparable efficacy and safety as compared with glimepiride.[47]

In a randomized noninferiority trial (CARMELINA trial) including 6,979 patients comparing the effect of linagliptin versus placebo, the findings showed that among patients with T2DM and high cardiovascular risk, linagliptin, compared with placebo, demonstrated noninferiority concerning the risk of major cardiovascular events over 2.2 years.[48] A network meta-analysis of 9 large trials showed that the DPP-4 inhibitors do not pose any additional cardiovascular risk.[49]

The EXAMINE trial randomized 5,380 patients who were 15 to 90 days post-acute coronary syndrome to the DPP-4 inhibitor alogliptin versus placebo and the results showed that DPP-4 inhibition with alogliptin was safe even in the high-risk period after acute coronary syndrome.[50] However, another systematic review and meta-analysis showed DPP-4 inhibitors to have a neutral effect on cardiovascular risk.[51]

A study was conducted to characterize all-cause mortality and major adverse cardiovascular events (MACE) in patients treated with metformin in combination with either sulfonylurea or a DPP-4 inhibitor using data from routine primary care in the UK. The findings showed that combination therapy with metformin + sulfonylurea was linked with a substantially increased risk of all-cause mortality of 36-85% compared with therapies combining metformin and DPP-4 inhibitors. It was also suggested that it might be possible for DPP-4 inhibitors to have a beneficial effect on cardiovascular outcomes beyond their antihyperglycemic properties.[52]

Because of the above discussion, it becomes clear that an oral hypoglycemic agent must be selected after metformin based on its cardiovascular safety and benefits. Based on the inputs from various existing trials, it has been established that DPP-4 inhibitors do not play any substantial role in increasing cardiovascular

outcomes in patients with T2DM suggesting them to be safe to use in terms of cardiovascular events.[53]

## ADVERSE EVENTS ASSOCIATED WITH DPP-4 INHIBITOR USE

Frequently occurring adverse effects related to the use of DPP-4 inhibitors occur in 5% of patients who receive them.[54] Three most frequently reported adverse reactions in clinical trials were nasopharyngitis, upper respiratory tract infection (URTI) and headache.[55] URTI, nasopharyngitis and headache with sitagliptin and URTI, urinary tract infection and headache with saxagliptin have been reported.[54] An analysis of 16 studies has shown that DPP-4 inhibitor linagliptin related adverse events have diverse incidence and frequency, ranging from mild-to-moderate intensity. The most frequent adverse event reports were nasopharyngitis with monotherapy at 5 mg and 10 mg dose (31.6% and 29.6%, respectively), gastrointestinal events (>10.0%) with linagliptin in combination.[56]

### Genitourinary Infection

A meta-analysis of RCTs and in an extensive pharmacovigilance database, it was shown that combination therapy with a DPP-4 inhibitor appears to reduce the frequency of genitourinary tract infections associated with SGLT2 inhibitors. The findings showed that the frequency of genitourinary infection in the patients on DPP-4 inhibitors/SGLT2 inhibitor combination therapy versus those on SGLT2 inhibitor monotherapy was 0.51 (95% CI 0.28-0.92). An explanation for genitourinary infection protection is both DPP-4 inhibitors and SGLT2 inhibitors may interact as proteins at the membrane level. DPP-4 activity is also present in some yeasts, moulds and bacteria and its inhibition by DPP-4 inhibitors may lead to an alteration of micro-organismal function.[57]

### Bone Health and Risk of Fracture

Cumulative evidence from RCTs has demonstrated that the use of DPP-4 inhibitors may not affect the risk of fracture. Similarly, in a meta-analysis based on real-world data, the use of DPP-4 inhibitors was not associated with the risk of fracture.[58] There is evidence to suggest that DPP-4 inhibitors may have beneficial effects on bone health while SGLT2 inhibitors may harm bone health.[59-61] This finding has significant clinical implications as many commonly prescribed second- and third-line glucose-lowering medications such as sulfonylureas, thiazolidinediones and insulin have been directly or indirectly linked with a higher risk of fracture. Hence, DPP-4 inhibitors may be considered as an alternative to those medications.[58]

### Inflammatory Bowel Disease

Despite DPP-4 inhibitors being a popular second-line treatment for T2DM, there have been conflicting reports about their risk of developing inflammatory bowel disease. The results of a meta-analysis based on a conservative random-effect analysis showed that DPP-4 inhibitors do not appear to increase the risk of developing inflammatory bowel disease.[62]

### Pancreatitis and Pancreatic Cancer

The results of a meta-analysis of randomized clinical trials indicated that no association between DPP-4 inhibitors with pancreatitis or pancreatic cancer was found. However, it has been stated that the risk of pancreatitis cannot be excluded in patients not at risk of pancreatic cancer. It has also been suggested that DPP-4 inhibitors could be capable of inducing pancreatitis in patients at elevated risk such as those with a history of pancreatitis, alcohol abuse, hypertriglyceridemia, but not in patients at low risk.[63]

A network meta-analysis conducted by Ling et al showed that there existed no significant variations in the incidence of diarrhea, renal and hepatic toxicity and hypersensitivity reaction between different DPP-4 inhibitors. However, it showed that the vildagliptin 100 QD, linagliptin 5 QD and linagliptin 0.5 QD had the least chances of reducing the incidence of diarrhea, renal and hepatic toxicity and hypersensitivity reactions, respectively. Amongst all the DPP-4 inhibitors, sitagliptin 100 QD had the lowest chance of reducing the incidence of URTI.[3]

## CONCLUSION

DPP-4 inhibitors have been proven to be safe and efficacious in patients across different age groups and individuals with renal disorders. Early combination therapy with DPP-4 inhibitors and metformin has shown durable glycemic control in patients with T2DM. Through various clinical studies and meta-analyses, it has been shown that DPP-4 inhibitors have no causal association with the development of cardiovascular events. Additionally, the DPP-4 inhibitors are not reported to be associated with adverse events such as bone fracture, inflammatory bowel disease, pancreatitis and pancreatic cancer.

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# Effect of Alcohol on Clinical Outcomes and Its Relationship with Semen Parameters

SUNITA CHANDRA*, SUHANI CHANDRA†, MAYANK SHARMA‡


## ABSTRACT

**Background:** The incidence of infertility is 10-15% globally and this has risen in recent years. Alcohol has been consumed in India for centuries, both in rural and urban areas, with prevalence rates ranging from 20% to 38% in males, according to various reports. Studies in northern India found the 1 year prevalence of alcohol use to be between 25% and 40%. In southern India, the prevalence of current alcohol use varies between 33% and 50%, with a higher prevalence among the lesser educated and the poor. **Aim:** To determine the effect of alcohol on seminal parameters. **Design:** Retrospective study. **Setting:** Morpheus Lucknow Fertility Center, Lucknow, Uttar Pradesh. **Time duration:** From January 2017 to December 2020. **Sample size:** Total 130 patients consisting of 57 patients as nonalcoholic control and 73 patients as alcoholic. **Main outcome measure(s):** The outcome of interest was seminal parameters, including count, motility, volume and morphology. **Method:** The study included two subject groups, controls and alcoholics. Subjects in the control group were volunteers who were free from any disease and who had never consumed alcoholic drinks and who had never smoked. Subjects in the alcoholic group were nonsmokers who had consumed a minimum of 180 mL of alcohol (brandy and whisky, both 40-50% alcohol content) per day for a minimum of 5 days per week in the past year. Semen samples were collected after at least 48 hours but no more than 7 days of sexual abstinence. Semen parameters - volume, count, motility and morphology - were analyzed. **Results:** In the alcoholic group, volume ($p < 0.005$), count ($p < 0.005$), percentage of rapid progressively motile sperm ($p < 0.005$), were statistically significantly decreased, while percentage of nonprogressive sperm and percentage of immotile sperm ($p < 0.005$) were statistically significantly increased, compared with the control group. The percentages of slow progressively motile sperm and morphology were not statistically significant. **Conclusions:** The present study found statistically significant results that chronic alcoholism suppresses semen quality, at the seminiferous tubular level. Alcohol decreases semen volume, total sperm concentration, motility of sperm and viability of sperm. This study has proved beyond doubt that chronic alcohol consumption has a detrimental effect on the quality of semen, which in turn, may have effect on their reproductive outcomes.


**Keywords:** Alcohol, semen, sperm, semen quality, volume, count, motility

Infertility affects about 15% of the general population, where male infertility appears to play a role in up to 30% of cases.[1] Men's reproductive health has been known to be influenced by lifestyle and environmental factors, such as eating patterns, obesity, cigarette smoking, alcohol intake, substance abuse and exposure to environmental toxins.[2] Although the evidence for a causal correlation between environmental factors and male infertility is still inconclusive.

*Chairperson and Director
†Consultant
‡Senior Embryologist
Rajendra Nagar Hospital & IVF Centre, Lucknow, Uttar Pradesh
Morpheus Lucknow Fertility Center, Lucknow, Uttar Pradesh
**Address for correspondence**
Dr Sunita Chandra
74, Second Street, Rajendra Nagar, Lucknow - 226 004, Uttar Pradesh
E-mail: drschandra50@gmail.com

Alcohol has been consumed in India for centuries. A number of mythological and religious books have highlighted the role it played in society. The pattern of drinking in India has undergone a change from occasional and ritualistic use to being a social event. Alcohol consumption is widespread in India, both in rural and urban areas, with prevalence rates ranging from 20% to 38% in males, according to various reports. Studies conducted in northern India reported the 1 year prevalence of alcohol use to be 25-40%, while in southern India, the prevalence of current alcohol use has been reported to range from 33% to 50%. The prevalence has been reported to be higher among the lesser educated and the poor.[3]

Excessive alcohol consumption (more than 3 days a week for more than a year) has been shown to have a negative effect on health. Alcohol reduces the amount of spermatozoa with regular morphology and increases the number of permanent tail defects.[4] Evidence suggests

that ethanol is a Leydig cell toxin,[5] although dose-dependent effects of alcohol on human spermatogenesis are not well-known. Seminiferous tubules in alcohol users mostly contain degenerated spermatids with a consequent azoospermia.[6]

Table 1 outlines the mechanisms underlying the connection between alcohol intake and reduced sperm content, which have been linked to a direct negative impact on testosterone metabolism and spermatogenesis. Alcohol consumption alters the ratio of free estradiol to free testosterone, and spermatogenetic arrest and Sertoli-cell-only syndrome are more commonly associated with heavy drinking.

Alcohol appears to have a dual impact on the hypothalamic-pituitary-gonadal axis, preventing the release of luteinizing hormone (LH)-releasing hormone/LH from the hypothalamic-pituitary axis and inhibiting testicular steroidogenesis. Moderate alcohol intake has been linked to a lower risk of mortality and morbidity, but not always. Excessive alcohol consumption, on the other hand, is harmful to one's health (e.g., coronary heart disease, stroke and liver disease). Some studies have also indicated a connection between alcohol consumption and sperm quality, but others have not confirmed these findings.

The areas of interest regarding the use of alcohol and its effects on fertility are described in Figure 1.[7] Men who drink too much alcohol can have problems conceiving. Reduced gonadotropin release, testicular atrophy, and decreased testosterone and sperm output have all been identified in studies of long-term, heavy alcohol use. Other studies of men who drink excessively have found increased gonadotropins and estradiol levels in the absence of liver disease, as well as reduced testosterone.

**Table 1.** Alcohol Intake and Male Reproductive Function

| Level of alcohol consumption | Effect on male reproduction |
|---|---|
| Moderate alcohol consumption | No effect on fecundability |
| | No increased subfecundity |
| | No effect on any semen parameters or pregnancy rate |
| | No difference in any semen parameters |
| Excessive alcohol intake | Increased serum free testosterone (19.7-24.6 pmol/L higher) and total testosterone (0.9-1.0 nmol/L higher) |

Although most studies found that the semen characteristics were lower at higher levels of recent alcohol intake; however, there was no statistically significant dose-response association. The hormonal changes observed in men with a high alcohol intake may, overtime, lead to adverse effects on semen quality. More longitudinal studies are needed to verify these results. Hence, the aim of this study is to find the relationship between alcohol intake and the semen characteristics.

## MATERIAL AND METHODS

### Subjects

This study was conducted at the Morpheus Lucknow Fertility Center, Lucknow, Uttar Pradesh, India. We screened a total of 73 alcoholics who had reported to the Morpheus Fertility Center and 57 nonalcoholic nonsmoking volunteers (as controls) from Lucknow city. The study population consisted of 66 nonsmoking alcoholics, aged 36.6 ± 5.7 years (mean ± SD). Alcoholics consuming drugs like diazepam, pethidine, cannabis and marijuana along with alcohol were excluded from the study. The control population consisted of 30 normal healthy persons aged 35.0 ± 6.1 years.

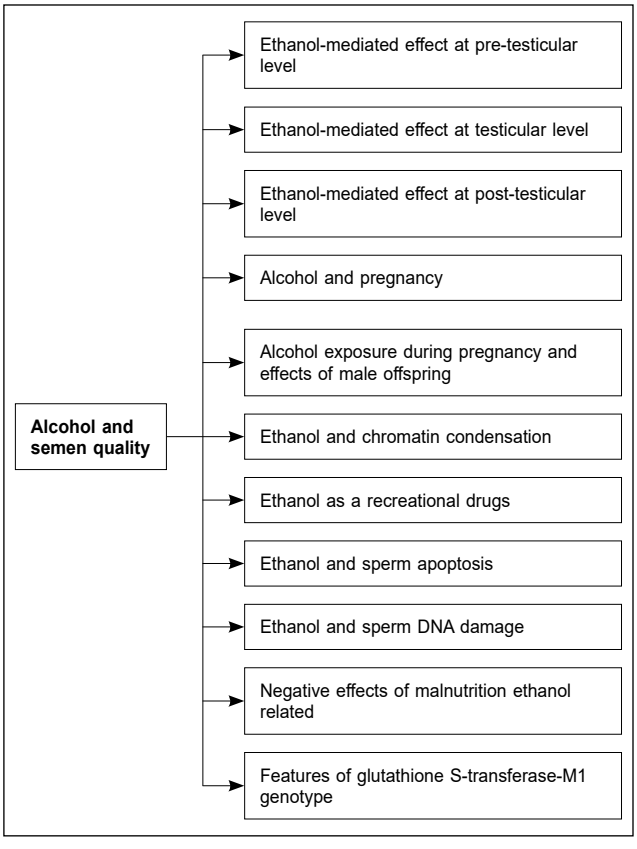


**Figure 1.** Main areas of interest regarding the use of alcohol and its effects on fertility (adapted from Condorelli et al, 2015).

The subjects were examined by a physician before inclusion in the study. Personal interviews were conducted with all alcoholic and control subjects to obtain relevant clinical data: age, sex, domicile (urban vs. rural dwelling), marital status, diet, history of alcohol consumption, infertility status, past medical illness and treatment, history of smoking, sexual urgency and frequency and premarital and extramarital sexual history. Sexual function (e.g., erectile function, libido potency, frequency of ejaculation) was also noted in the questionnaire.

### Experimental Design

The study included two subject groups - controls and alcoholics. Subjects in the control group were volunteers who were free from any disease and who had never consumed alcoholic drinks and who had never smoked. Subjects in the alcoholic group were nonsmokers who had consumed a minimum of 180 mL of alcohol (brandy and whisky, both 40-50% alcohol content) per day for a minimum of 5 days per week in the past year.

### Semen Collection

The participant was asked to collect semen in the collection room near to the laboratory in order to limit the exposure of the semen to fluctuations in temperature and the time between the collection and analysis was maintained. The sample was collected with minimum 2 days and maximum 7 days of sexual abstinence.

Before collection, partner was given clear instruction concerning the collection of semen sample as the semen sample should be complete and there should be no loss of any fraction of the sample. The sample was obtained by masturbation and was ejaculated into a clean wide-mouthed plastic container. Container should not be touched on the inner surface with wet hands was instructed to the participant. After collection, sample was stored at 37°C. It was left for liquefaction for 30 minutes at 37°C in incubator. If it was not liquefied, then needling was done with (18G) needle attached to 2 cc syringe.

### Semen Analysis

Semen analysis was performed prior to semen processing. Semen analysis mainly accounted for sperm count and sperm motility and values were evaluated in reference of World Health Organization (WHO) manual 2010.

### Sperm Count

Sperm count was performed using a hemocytometer having two chambers, and each chamber has a microscopic grid attached to the glass surface. The chambers are overlaid with a special heavy glass cover slip that stays on pillars exactly 0.1 mm above the chamber floor. The main divisions separate the grid into 9 squares. Each square has a surface area of 1 $mm^2$, a depth of 0.1 mm and a total volume of 0.1 $mm^3$ or $10^{-4}$ $cm^3$. The central square consists of 25 large squares, and each of these contains 16 smallest squares. Each horizontal and vertical count was taken for 10 consecutive boxes and average was taken in count.

### Sperm Motility

The collected sample was allowed to liquefy and a wet preparation was made using counting chamber. The chambers were overlaid with a special heavy glass cover slip that rests on pillars exactly 0.1 mm above the chamber floor. The slide was examined with phase-contrast optics at x200 or x400 magnification. At least 100 sperms for different categories of motility were counted.

### Sperm Morphology

Diff-Quik staining was performed according to strict criteria; the length of the head should be 4.0-5.0 μm and the width should be 2.5-3.5 μm with a length/width ratio of 1.50 to 1.75. There should be a well dense acrosomal region which comprises of 40-70% of the head area. The mid-piece should be slender, <1 μm wide, about 1.5 times the length of the head and attached axially. Cytoplasmic droplets should be less than half the size of a normal head. The tail should be straight (uncoiled), thinner than the mid-piece and approximately 45 μm long. For a spermatozoon to be considered normal, the head, neck, mid-piece and tail should all be normal. At least 100 sperms were counted.

### Seminal Parameters

Semen samples were collected after at least 48 hours but no more than 7 days of sexual abstinence. The semen sample was collected by masturbation and delivered to the laboratory within ½ hour from the time of collection. After liquefaction, semen appearance, volume, consistency, pH, fructose and sperm motility, concentration, viability and morphology were analyzed as per the criteria of the WHO manual 2010. Motility was expressed as percentages of rapid progressively motile, slow or sluggishly motile, nonprogressive motile and immotile sperm. Sperm viability was expressed as percentages of live and dead sperm, and sperm morphology.

## STATISTICAL ANALYSIS

The patients were recruited into two groups namely, Group 1 Nonalcoholics (n = 57) and Group 2 Alcoholics (n = 73). Descriptive statistics was done using tables, columns, charts and measure of central tendency and dispersion was also calculated. The results for both groups are expressed as mean ± SD. The results were analyzed statistically with commercial software (SPSS for Windows 7.5.1; SPSS, Chicago, IL). Student's-test was used to determine the degree of significance for the various mean variables obtained. $P < 0.05$ was considered as statistically significant.

## RESULTS

A total of 130 patients was recruited in the study, containing 57 nonalcoholics and 73 alcoholics. Table 2

**Table 2.** The Descriptive Statistics of All Seminal Parameters in Alcoholics and Control Group

| Group Statistics | | | | | |
|---|---|---|---|---|---|
| | **Group** | **N** | **Mean** | **SD** | **SE Mean** |
| Volume | Nonalcoholics | 57 | 2.7895 | 0.99187 | 0.13138 |
| | Alcoholics | 73 | 1.5767 | 0.56900 | 0.06660 |
| Count | Nonalcoholics | 57 | 117.5789 | 48.23638 | 6.38906 |
| | Alcoholics | 73 | 48.7534 | 18.48857 | 2.16392 |
| Rapid progressive motility | Nonalcoholics | 57 | 56.1579 | 6.25582 | 0.82860 |
| | Alcoholics | 73 | 14.9041 | 7.54462 | 0.88303 |
| Slow progressive motility | Nonalcoholics | 57 | 21.4912 | 2.67343 | 0.35410 |
| | Alcoholics | 73 | 23.9863 | 6.41286 | 0.75057 |
| Nonprogressive motility | Nonalcoholics | 57 | 2.9474 | 1.04234 | 0.13806 |
| | Alcoholics | 73 | 27.7123 | 7.66391 | 0.89699 |
| Immotile | Nonalcoholics | 57 | 20.2807 | 4.00337 | 0.53026 |
| | Alcoholics | 73 | 33.3973 | 13.26518 | 1.55257 |
| Morphology | Nonalcoholics | 57 | 5.9649 | 1.68994 | 0.22384 |
| | Alcoholics | 73 | 5.1096 | 2.21461 | 0.25920 |

**Table 3.** The Seminal Parameter Value in Nonalcoholics and Alcoholics

| Seminal parameter | Nonalcoholics (57) | Alcoholics (73) | 't' value |
|---|---|---|---|
| Semen volume (mL) | 2.789 ± 0.991 | 1.576 ± 0.569 | 8.234[a] |
| Sperm count (10^6/mL) | 117.578 ± 48.236 | 48.753 ± 18.488 | 10.203[a] |
| Rapid progressively motile sperm (%) | 56.157 ± 6.255 | 14.904 ± 7.544 | 34.068[a] |
| Slow progressively motile sperm (%) | 21.491 ± 2.673 | 23.986 ± 6.412 | -2.754649[NS] |
| Nonprogressively motile sperm (%) | 2.947 ± 1.042 | 27.7123 + 7.663 | -24.202[a] |
| Immotile sperm (%) | 20.281 ± 4.003 | 33.397 ± 13.265 | -7.994850[a] |
| Morphologically normal sperm (%) | 5.9649 ± 1.689 | 5.109 ± 2.214 | 2.417026[NS] |

Note: Values are expressed as mean ± SD. NS = Nonsignificant.

[a]$P < 0.05$

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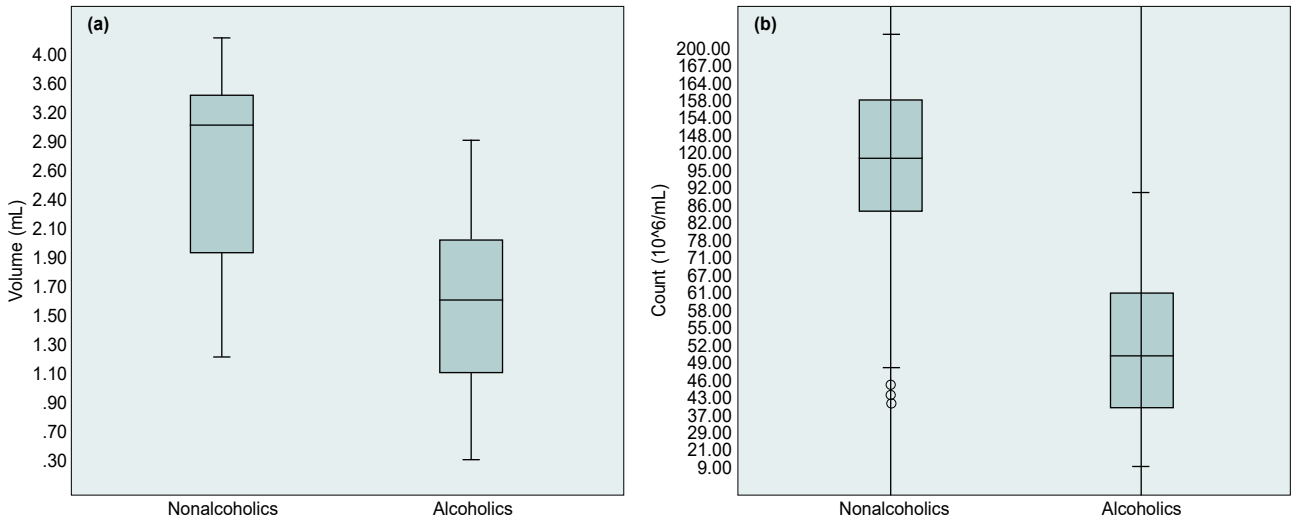


**Figure 2 a)** Box chart of volume in alcoholics and nonalcoholics, **(b)** Box chart of count in alcoholics and nonalcoholics.

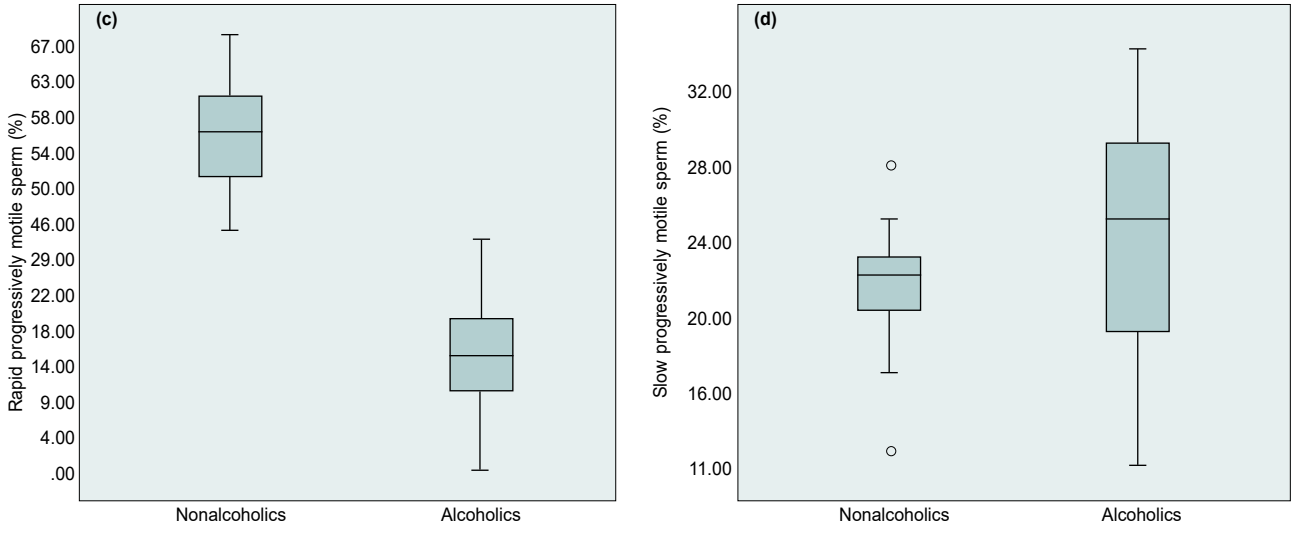


**Figure 2 c)** Box chart of rapid progressive motility in alcoholics and nonalcoholics, **(d)** Box chart of slow progressive motility in alcoholics and nonalcoholics.

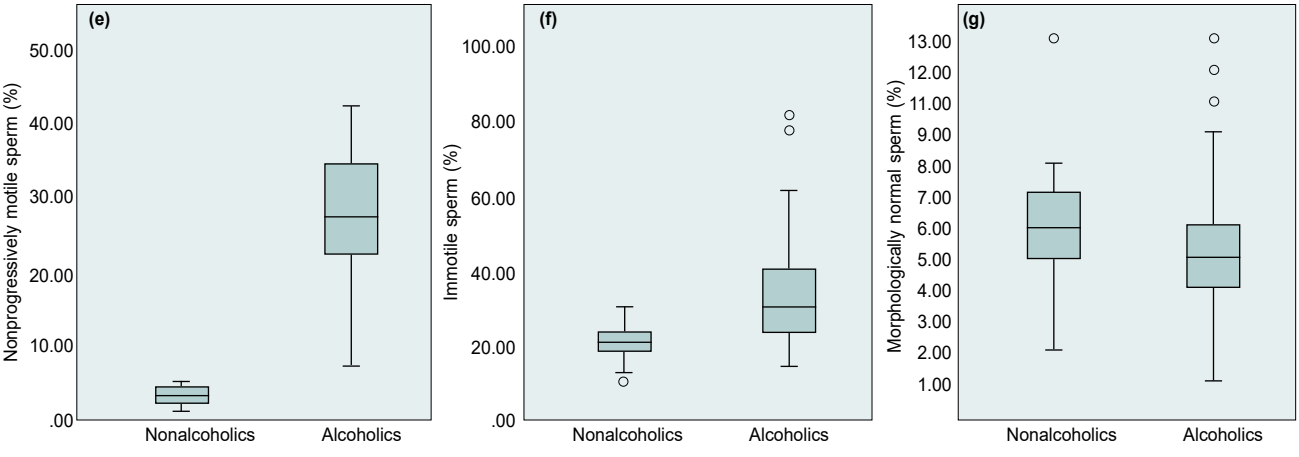


**Figure 2 e)** Box chart of nonprogressive motility in alcoholics and nonalcoholics, **(f)** Box chart of immotile sperms in alcoholics and nonalcoholics, **(g)** Box chart of morphology in alcoholics and nonalcoholics.

shows the descriptive statistics of seminal parameters in controls and alcoholics. Total average volume in alcoholics and nonalcoholics was 1.576 ± 0.569 and 2.789 ± 0.991, respectively; average count in alcoholics and nonalcoholics was 48.753 ± 18.488 and 117.578 ± 48.236, respectively. Average rapid progressive motility, average slow progressive motility, average nonprogressive motility, immotile sperm and average morphology are also presented in Table 2.

In the alcoholic group, volume ($p < 0.005$), count ($p < 0.005$), percentage of rapid progressively motile sperm ($p < 0.005$), were statistically significantly decreased, while percentage of nonprogressive sperm and percentage of immotile sperm ($p < 0.005$) were statistically significantly increased, compared with the control group (Table 3). The percentages of slow progressively motile sperm and morphology were not statistically significant. Figure 2 a-g depict the seminal parameters as box charts.

## DISCUSSION

In this study, where 130 patients were recruited, including 57 nonalcoholics and 73 alcoholics, there was a statistically significant association in the semen parameters where the alcoholics (>180 mL of alcohol 5 times a week) had a reduced semen volume, count, rapid motile sperms and increased nonprogressive motile sperms and immobility. However, in terms of morphology and slow progressive motility, the results were not statistically significant.

Previous studies on alcohol intake and semen quality have shown inconsistent results,[8-19] but most have been conducted among patients attending andrology or infertility clinics. Infertile men may have changed their drinking habits as a consequence of the infertility. Only four studies were conducted among unselected men, similar to our study, and they also found no association between semen quality and moderate or high alcohol intake or any statistically significant dose-response association.[11,15,17,19] We found no association between beer, wine or liquor consumption and semen quality.

The duration of human spermatogenesis is approximately 72 days,[20] and the time window of alcohol exposure in this study was the last 5 days prior to semen sampling. Since, alcohol habits often follow long time trends, the recorded exposure is expected to correlate with exposure during spermatogenesis. Alcohol exposure during the late stages of spermatogenesis may disturb maturation of spermatozoa during epididymal transfer, which in particular can affect sperm motility and morphology. Continued alcohol exposure throughout spermatogenesis could affect the other semen characteristics as well. However, we found no tendency towards sperm morphology and slow progressive motility.

Sex hormone-binding globulin (SHBG) is the key carrier protein of testosterone and estradiol. It is produced in the liver, and the levels and regulation depend on diet, age and body mass index (BMI).[21] The association between alcohol intake and SHBG is not clear. Considering the fact that SHBG affects free nonbound testosterone and estradiol, the observed rise in free testosterone and estradiol in the study by Hansen et al[17] appears to be likely guided by changes in SHBG. The study revealed that increasing recent alcohol exposure was associated with lower SHBG levels and higher testosterone levels. Similar findings were reported from the cross-sectional Third National Health and Nutrition Examination Survey (NHANES III) study conducted on healthy nonalcoholic men.[22] Studies conducted among men with chronic alcoholism and fatty liver point to a significant rise in SHBG levels with increasing alcohol exposure.[23] A detoxification study on alcoholics revealed a positive link between testosterone and SHBG, thus indicating SHBG regulation may be different in men with a high alcohol intake.[24]

The present study affirmed that there is decline in seminal parameters in alcohol-dependent patients, who consumed minimum of 180 mL of alcohol (5 times/week). There was a decline in count, volume, and motility. This finding has implications for clinical practice. There were certain limitations of this study. The study was carried out in a small sample of clinic-based population, and hence the findings could not be generalized to other population groups.

Future studies should try to overcome these limitations. In addition, future research should focus on alcohol consumption in a dose-dependent manner and its effects on the seminal parameters, on structured assessment of sexual dysfunction in partners of alcohol-dependent men. If the patient has a history of alcohol and drug use/abuse/dependence, efforts must be made to delineate the relationship of sexual dysfunction with the alcohol use and efforts must be made to achieve abstinence.

## CONCLUSION

In conclusion, the present study found statistically significant results that chronic alcoholism suppresses semen quality, at the seminiferous tubular level. Alcohol

decreases semen volume, total sperm concentration, motility of sperm and viability of sperm. This study has proved beyond doubt that chronic alcohol consumption has a detrimental effect on the quality of semen, which in turn, may have effect on their reproductive outcomes.

Hence, men are advised to refrain from chronic alcohol consumption if they want to procreate and lead a normal sexual life.

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# Congenital Toxoplasmosis with Aplastic Anemia: A Rare Association

MAHESH DAVE*, MANASVIN SAREEN†, RAHUL GANGODA‡, RANJANA VEERWAL#, NAGARAJ T GONCHIKAR†


## ABSTRACT

Congenital toxoplasmosis is caused by transmission of an intracellular obligate coccidian protozoan (*Toxoplasma gondii*) via vertical transmission during pregnancy. The clinical manifestations are wide ranging from asymptomatic to intracranial calcifications, seizures, developmental delay, chorioretinal lesions and even fetal death. Aplastic anemia is one of the rare presentations of congenital toxoplasmosis. Hence, we are reporting a case of a 23-year-old male who presented to us with aplastic anemia due to congenital toxoplasmosis. Thus, congenital toxoplasmosis should always be considered as a cause when evaluating a case of aplastic anemia.


**Keywords:** Aplastic anemia, congenital toxoplasmosis, *Toxoplasma gondii*

Toxoplasmosis is a parasitic disease caused by *Toxoplasma gondii*, an intracellular obligate coccidian protozoan. It usually spreads by eating poorly cooked food that contains cysts, exposure to infected cat feces or from infected mother to baby during pregnancy. It rarely spreads through blood transfusion.[1] Toxoplasmosis is a disease having worldwide distribution. In United States, 13.2% of individuals greater than 6 years of age had serological evidence of exposure, as per data from a 2009-10 survey.[2] The exact incidence of toxoplasmosis in India is not yet documented but few studies have shown prevalence rate of 22.4% among women of childbearing age (8.8-37.3%).[3]

Toxoplasmosis may present clinically with different presentations like acute toxoplasmosis and congenital toxoplasmosis. Acute toxoplasmosis is usually asymptomatic and self-limited and remains unrecognized in 80-90% adults; whereas the clinical manifestations of congenital toxoplasmosis are wide ranging from asymptomatic to intracranial calcifications, seizures, developmental delay, chorioretinal lesions, hematological complications and even fetal death.[1] Maternal infection is by far the most common in third trimester; however, more serious infectious sequelae occur with first and second trimester infection. If prenatal infection is severe, it may cause multi-organ dysfunction and intrauterine fetal deaths.

Aplastic anemia is a potentially fatal bone marrow failure disorder, and if left untreated, it is associated with high mortality. It appears to be 2- to 3-times more common in Asia compared to Europe.[4] Congenital toxoplasmosis is usually associated with hemolytic anemia, but in our case, it was associated with aplastic anemia and therefore, we are reporting this case.

## CASE REPORT

A 23-year-old male presented to us with complaints of easy fatigability and shortness of breath on exertion for past 3-4 months. He also had 1 episode of gum bleeding 4 months back. He had history of repeated blood transfusions (5 units whole blood in last 10 months). He had no history of any addiction and consumed a mixed diet. He also had no history of reddish or yellowish discoloration of urine, drug or toxin ingestion and radiation exposure. On general physical examination, patient was conscious, poorly nourished (body mass index [BMI] 17.5 kg/m$^2$), anemic and had mild pedal edema. He had nonparalytic squint (concomitant)

*Senior Professor and Unit Head
†Junior Resident (3rd Year)
‡Junior Resident (2nd Year)
#Senior Resident
Dept. of General Medicine, RNT Medical College, Udaipur, Rajasthan
**Address for correspondence**
Dr Manasvin Sareen
Junior Resident (3rd Year)
Dept. of General Medicine
RNT Medical College, Udaipur - 313 001, Rajasthan
E-mail: manasvinsareen7@gmail.com

in right eye. There was no lymphadenopathy and icterus. On per abdomen examination, there was mild hepatomegaly but no splenomegaly.

On cardiac auscultation, there was loud first heart sound and hemic murmur was heard. On neurological examination, mental function of the patient was normal but there was decreased distant vision (was able to do finger counting only from 1 meter distance) and decreased color vision (primary colors) in both eyes. Nystagmus was present bilaterally in horizontal gaze. The motor, sensory and cerebellar system examination did not reveal any abnormality and there were no signs of meningeal irritation. For further evaluation, ophthalmologist reference was taken and they found bilateral macular scarring along with few Roth spots on fundus examination, suggestive of congenital toxoplasmosis as shown in Figure 1.

On the basis of history and clinical examination including fundus finding, we made our provisional diagnosis of anemia with congenital toxoplasmosis.

For confirmation of above diagnosis, patient was thoroughly investigated and the following results were found: Complete blood count (hemoglobin [Hb] - 2.1 g/dL, total leukocyte count [TLC] - 1.96 × $10^3$/uL, platelet count - 14 × $10^3$/uL). Differential leukocyte count (DLC) was neutrophils - 22.9%, lymphocytes - 65%, monocytes - 9.2%, eosinophils - 0.4% and basophils - 4.5%. Mean corpuscular volume (MCV) - 95.7 fL, mean corpuscular hemoglobin (MCH) - 30.2 pg, MCH concentration - 31.5 g/dL, hematocrit - 6.1%. Peripheral blood film (PBF) showed normocytic normochromic red cells; leukopenia with neutropenia and no immature cells seen; thrombocytopenia with platelet morphology normal. Reticulocyte count was 0.30%, thus making reticulocyte production index = 0.02%; which reflects hypoproliferative anemia. On further investigation, iron profile, vitamin B12, thyroid profile, Coombs test, renal and liver function tests, lactate dehydrogenase, urine examination and autoimmune profile were all normal. Patient was also tested for human immunodeficiency virus (HIV), hepatitis B, C and E virus and was found negative. USG abdomen showed mild hepatomegaly. So, the next step in the algorithm was to perform bone marrow aspiration, which showed hypoplastic bone marrow with normal morphology, thus making the diagnosis as aplastic anemia. Various causes of aplastic anemia were ruled out like drugs and radiation exposure, infections like HIV and hepatitis E, autoimmune conditions and paroxysmal nocturnal hemoglobinuria (PNH). The most likely cause for aplastic anemia was toxoplasmosis; which was further confirmed by serology testing for toxoplasma IgG, which came out to be positive. On further enquiring, it was found that patient's family had cats as pet for past 25-30 years, which could be the source of toxoplasmosis.

Patient underwent 3 units whole blood transfusion and was treated with tablet sulfadoxine-pyrimethamine combination (800/160) b.i.d. and tablet folic acid 5 mg o.d., which will be continued for 1 year as per the

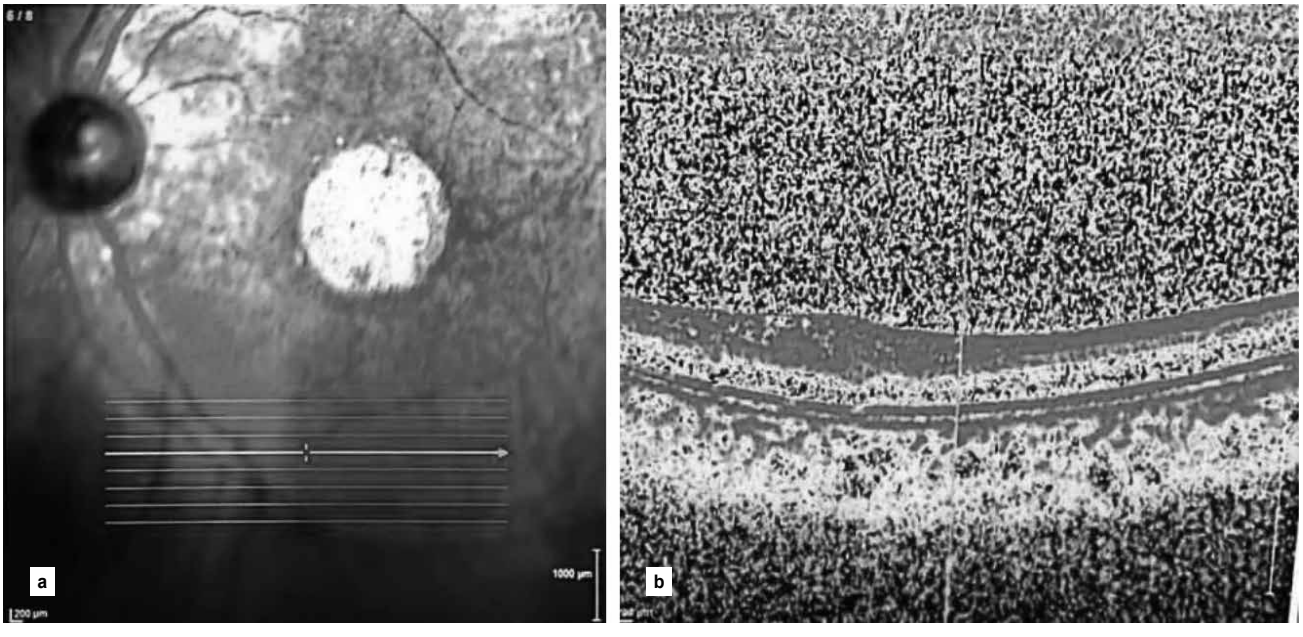


**Figure 1.** Macular scarring near the optic disc on fundus examination **(a)**; thinning of fovea on optical coherence tomography of the patient **(b)**.

guidelines. He was discharged from the hospital and advised regular follow-up.

## DISCUSSION

Toxoplasmosis is caused by a coccidian parasite, *T. gondii*. The disease is primarily spread through exposure to oocysts present in contaminated water, food or soil or by ingesting cysts from undercooked meat. There is also transplacental route of transmission. There are 3 stages of the parasite: tachyzoite, bradyzoite and sporozoite. Tachyzoites are seen in the acute infectious form of the disease, while bradyzoites are periodic acid-Schiff (PAS) positive dormant cyst stage awaiting reactivation as the host gets immunocompromised. Sporozoites exist within oocyst and are the form in which the parasite is spread through the environment.[1] Although most congenitally-infected children are asymptomatic at birth, they may develop some symptoms later in life. Loss of vision is the most frequently observed sequelae in congenitally-infected children. Hydrocephalus, chorioretinitis, psychomotor retardation, intracerebral calcifications, loss of hearing and death (very rarely) may occur.[5] Ocular toxoplasmosis can be a prodrome to central nervous system (CNS) toxoplasmosis.

There have been cases reported by Rawat et al[6] and Nelson et al[7] in which toxoplasmosis has presented with hemolytic anemia and hepatosplenomegaly.

Aplastic anemia is pancytopenia with hypocellular bone marrow. There is biphasic age of distribution, with a major peak in teenage and the twenties and a second surge in older adults. Men and women are equally affected.[8] The incidence of aplastic anemia is reported to be higher in Asia than in the Western countries. The exact incidence in India is not known because of a lack of epidemiological studies. About 20-40% of pancytopenic patients in referral centers have aplastic anemia.[9] The clinical presentation of aplastic anemia is usually lassitude, weakness, shortness of breath and bleeding. Lymphadenopathy and splenomegaly are highly atypical of aplastic anemia. There are various causes of aplastic anemia like constitutional, radiation and drug exposure, viruses (Hepatitis E, HIV, Epstein-Barr virus), immune diseases, paroxysmal nocturnal hemoglobinuria and pregnancy. Congenital toxoplasmosis is not a documented cause of aplastic anemia but in our case, it is the probable cause of aplastic anemia.

Congenital toxoplasmosis is a fatal disease that can be prevented and treated. Spiramycin is the drug of choice for preventing transplacental transmission of the parasite.[10] Most experts use spiramycin to treat pregnant females who have acute toxoplasmosis early in the pregnancy and pyrimethamine/sulfadiazine/folinic acid to treat women who seroconvert after 18 weeks of pregnancy or in cases of documented fetal infection. Congenitally-infected neonates are treated with daily oral pyrimethamine (1 mg/kg) and sulfadiazine (100 mg/kg) along with folinic acid for 1 year.

Since there is no effective vaccine against toxoplasmosis, the only option is to prevent the disease by not eating undercooked meat and avoiding oocyst contaminated material (cat's litter box). Litter boxes should be changed every day as freshly excreted oocysts will not be infectious. Also, these should be changed by HIV negative and nonpregnant persons preferably. Thorough washing of hands should be practiced after changing litter boxes and further it is advisable that all pregnant women should be screened for toxoplasmosis during antenatal period, so to treat and prevent transplacental transmission to fetus.

## CONCLUSION

Congenital toxoplasmosis can have various clinical presentations, including aplastic anemia. Hence, whenever a patient presents with recurrent anemia despite repeated blood transfusions, especially aplastic anemia, we should search for congenital toxoplasmosis as a cause and treat it.

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## ARTICLE RETRACTION

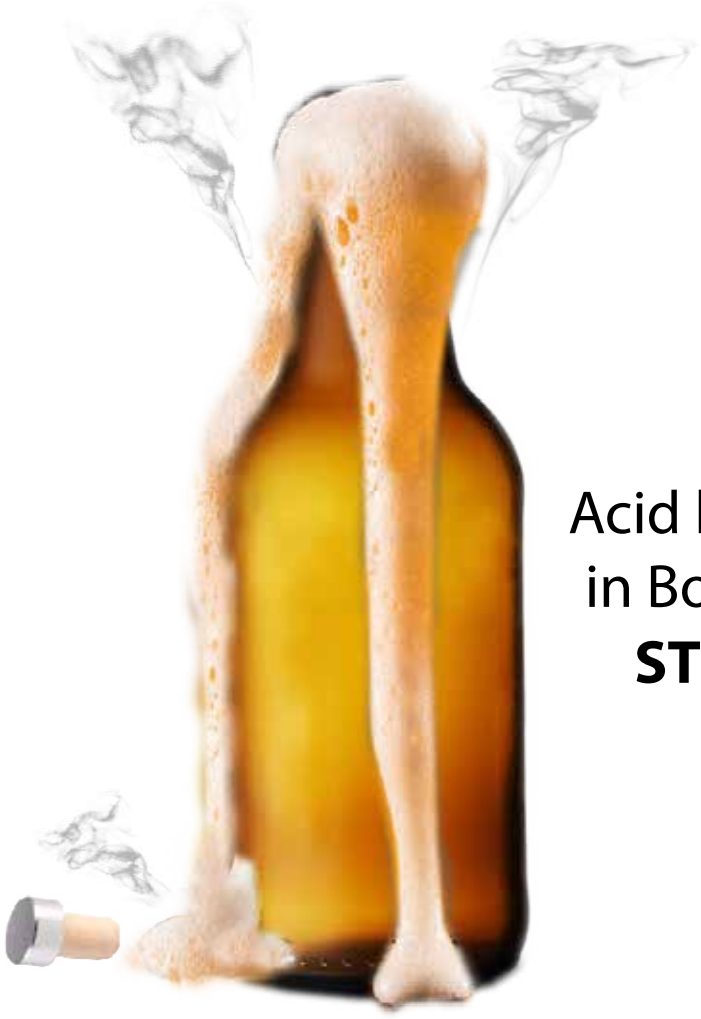
**Title: To Study the Efficacy and Safety of a Polyherbal Formulation in Nonalcoholic Fatty Liver Disease Patients**

**Authors:** Pravin Rathi, Prabha Sawant, Dipesh Waghmare

**Date of publication:** Volume 31, Number 9, February 2021 pg. 842-8

The article has been retracted from the journal and all the authors are intimated about this. The article was published after receiving a signed cover letter from the corresponding author on behalf of all the co-authors and after due diligence and completion of all required formalities.

However, due to an impending dispute between the stakeholders, a decision has been taken to retract the article from the journal.



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Indian Journal of Clinical Practice, Vol. 32, No. 4, September 2021

# Can a Registered Medical Practitioner Compel or Force his Patient to Purchase the Drug/Medicine from him Only?

No, the registered medical practitioner cannot compel or force his patient to purchase the drug/medicine from him only. Though as per Item No. 5 of the Schedule K of the Drugs and Cosmetics Rules, 1945 and Clause 6.3 of the Code of Medical Ethics, the registered medical practitioner is entitled to supply the drugs to his patients which have been prescribed by him.

However, the registered medical practitioner cannot compel or force the patients or his relatives/friends to purchase or take the medicine from the said registered medical practitioner as held by the **Hon'ble National Consumer Disputes Redressal Commission in its landmark judgment dated 22.07.2014 titled as Fortis Health Management (North) Ltd. vs Meenu Jain & Anr.**

In the case titled as **Fortis Health Management (North) Ltd. vs Meenu Jain & Anr.,** on 25.05.2009, Meenu Jain was admitted to Fortis Escort Hospital, Jaipur, Rajasthan (OP) for treatment of Guillain-Barré syndrome (GBS). The Complainant signed a general consent for admission. On 25.06.2009, the patient was on ventilator and administered life-saving drug injection Iviglob Ex, five doses daily, for 5 days. The cost of each injection- MRP was Rs. 18,990/-. Those injections were provided by hospital pharmacy and the Complainant was successfully treated and discharged on 13.06.2009. The total sum of Rs. 6,82,965/- as hospitalization charges were paid by the Complainant without any protest.

The Complainant alleges that, he was told that the cost per injection was Rs. 9,000/-. The Complainant 2 requested the hospital authorities that the injection Iviglob Ex was available at 30-40% discount in the other medical shops in the market and he may be permitted to purchase the injections from outside, but his request was not considered and he was forced to purchase the injections from the hospital itself.

The Hon'ble Commission held that:

*"8. We find that, the Complainant singed the consent and the counseling form, but it is also important to understand the state of mind of the Complainant 2 as his wife Meenu Jain was in a critical condition in OP Hospital. The OP was in a dominating position over the Complainants. Also, the Complainants agreed to pay the expenses of drugs and medicines and other consumables as per rates of the hospital, but it is also an admitted fact that the hospital authorities did not permit the Complainant to purchase the injection "Iviglob Ex" from outside, despite repeated verbal requests. Those injections were allegedly available in the market at lesser price and he was forced to buy the injections from the hospital itself. Thus, the hospital authorities indirectly imposed unjustified and unreasonable conditions on the Complainant to purchase the injections from the hospital, for the treatment of the patient. The counsel for OP argued that, to ensure quality and genuineness of the drugs, the OP did not permit the patients to buy the drugs from outside which is not at all convincing and reasonable. The OP sold the injections at the maximum retail price (MRP), and not charged any excess amount.*

*9. We have given a thoughtful consideration and feel that the patient was suffering from GBS, a serious disease, and was in a critical condition. No doubt, the OP Hospital has treated her and cured her. We know that, the corporate hospitals purchase the medicines, surgical items, consumables, in bulk. Certainly huge margin is available, while procurement. OP has not produced it's purchase bills of those injections. In the open market, certainly the distributors or Pharmacy shops offer discounts on the medicines. The injection Iviglob Ex is a very expensive drug, which will be available at discounted price in open market, hence the OP should have allowed at least marginal discount of about 10-20%. The corporate hospitals should not be a commercial/business centres for profiteering from the exploitation of such critical patients, who have to pay sky rocketing hospital bills. Regarding contention of OP about spurious drugs, the OP was at liberty to explain the pros and cons of drugs brought from outside market, and after due consent from the complainants, they could have administered the injections."*

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Indian Journal of Clinical Practice, Vol. 32, No. 4, September 2021

# HCFI Dr KK Aggarwal Research Fund

## HCFI Round Table Expert Zoom Meeting on "Solid Waste Management"

**31st July, 2021 (11 am-12 noon)**

### Key points of HCFI Expert Round Table

- Solid waste commonly includes trash and garbage consisting of everyday items. Municipal solid waste includes highly decomposable items like foods, trash, old appliances, paper, glass, etc.
- The volume of waste generation in India has been increasing rapidly over the last few years.
- The 2014 Planning Commission report by the Task Force on waste to energy estimated that urban India will generate around 2,76,342 tonnes/day of waste by 2021; 4,50,132 tonnes/day by 2031 and 11,95,000 tonnes/day by 2050.
- Waste management rules in India include the Solid Waste Management Rules, 2016; Construction and Demolition Waste Management Rules, 2016; Plastic Waste Management Rules, 2016 and amendments; Biomedical Waste Management Rules, 2016; Hazardous and Other Wastes (Management and Transboundary Movement) Rules, 2016 and e-Waste Management Rules, 2016.
- With a rapid growth in population, the annual waste generation is expected to increase by 70%, from 2.01 billion tonnes in 2016 to 3.40 billion tonnes in 2050.
- Growth of the urban population directly leads to increase in waste generation. The rapidly increasing population generates solid waste that is much more than that can be effectively handled by the urban local bodies (ULBs).
- Maharashtra generates the highest amount of solid waste at 22,080 metric tonnes (MT)/day, while Sikkim generates the lowest at 89 MT/day.
- Among the UTs, Delhi generates the highest amount of solid waste at 10,500 MT/day.
- Overall, Daman and Diu is the lowest waste generator in India.
- Improper management of solid waste is a risk to the environment and public health because of unsafe disposal, which produces dangerous gases and leachates, microbial decomposition, and climate conditions.
- ULBs are entrusted with the responsibility to keep the cities and towns clean. But they are unable to do so because of inadequate infrastructure, poor institutional capacity, financial constraints and lack of political will.
- All available landfill sites in India are already exhausted.
- Though there are several legislations and policies to regulate waste disposal, they have failed to achieve their objectives due to lack of awareness amongst the stakeholders as well as poor enforcement by the regulatory authorities.
- Solid waste can be categorized into three: Biodegradable waste or organic waste, recyclable waste and inert waste (dirt, etc.). The percentage of wet biodegradable waste is high (52%), followed by the inert and nonbiodegradable waste (31%); recyclable waste constitutes 17% of total waste.
- The Municipal Solid Wastes (Management and Handling) Rules, 2000 were modified and notified as Solid Waste Management Rules, 2016.
- These rules are applicable to: (i) Every urban local body (Mega city to Panchayat level); (ii) outgrowths in urban agglomerations; (iii) census towns as declared by the Registrar General and Census Commissioner of India; (iv) notified areas; (v) notified industrial townships; (vi) areas under the control of Indian Railways; (vii) airports/airbases; (viii) ports and harbors; (ix) defense establishments; (x) special economic zones; (xi) State and Central government organizations; (xii) places of pilgrims; (xiii) religious and historical importance as may be notified by respective State government from time to time; and (xiv) every domestic, institutional, commercial and any other nonresidential solid waste generator situated in the areas.
- Every household is a waste generator; street vendors, event organizers, resident welfare associations (RWAs) and market associations, gated communities, hotels, restaurants, malls, offices and institutions, etc., are also considered waste generators.
- Section 4 of the Rules has clearly defined the roles and duties of waste generators and authorities. To describe a few, it is the duty of waste generators

to segregate waste and hand over the segregated waste to the authorized waste collectors.

- Environment Ministry has to constitute a Central Monitoring Committee to monitor waste management every year; Ministry of Urban Development has to frame a national policy on solid waste management, provide technical guidelines, financial support, training to local bodies, etc.
- The Central Pollution Control Board (CPCB) shall coordinate with Directory of State Pollution Control Boards/Pollution Control Committees (SPCBs/PCCs) for monitoring and annual reports, formulation of standards, review new technologies, prepare guidelines for buffer zones restricting from residential, commercial and construction activities areas, and inter-state movement of waste.
- Manufacturers/brand owners shall facilitate collecting back wastes of their products and provide pouch for packaging sanitary wastes, etc.
- Industry (cement, power plant, etc.) shall use refuse-derived fuel (RDF) within 100 km.
- A key aspect of efficient solid waste management is waste segregation. Dry waste should be sent for recycling and reuse, while wet waste from the kitchen can be used for composting.
- It is mandatory for waste generators to segregate their waste in color-coded bins (blue for dry waste and green for wet waste) for proper recovery, reuse and recycling.
- The 2016 Solid Waste Management Rules also mandate door-to-door collection of segregated waste; waste generators are required to pay a "user fee" to the waste collectors.
- Around 96% of wards across India have achieved 100% door-to-door waste collection as of January 2020.
- Recycling is the process of transforming segregated solid waste or raw material for producing new product. Reusable and recyclable waste comprises ~20% of total waste.
- The recyclable material is usually collected by ragpickers and kabariwalas, which reduces the volume of solid waste and also saves costs of collection, transportation and disposal.
- Setting up facilities with adequate space for sorting of recyclable materials is the responsibility of local authorities.
- The rules prohibit waste generators from throwing, burning solid waste in open public spaces, in drains or water bodies. There is a provision for "spot fine" for littering and nonsegregation.
- The processing technologies used in India are composting, recycling, refuse-derived fuel, incineration, pyrolysis, waste-to-wealth and waste-to-energy.
- Nonrecyclable waste with calorific value of ≥1,500 kcal/kg shall not be disposed of on landfills and shall only be utilized for generating energy (waste to energy plants) either through refuse derived fuel or by giving away as feed stock for preparing refuse derived fuel. High calorific wastes shall be used for co-processing in cement or thermal power plants.
- There is a time frame for the implementation of the Solid Waste Management Rules: Landfill Identification (1 year), Procurement of waste processing facilities (2 years), Ensure segregation of waste (2 years), Cities up to 1 million population (2 years), Million plus cities (3 years), Setting up sanitary landfills (3 years) and Bioremediation/capping of old landfills (5 years).
- The waste pickers do not have legal status and protection and are not capable of enforcing systems in waste collection and segregation.
- Institutional and financial issues must be addressed on priority.
- Citizen participation needs to be promoted; community awareness and change in attitudes towards solid waste and their disposal can improve the system in India.
- On the basis of the Solid Waste Management Rules, the Delhi government has notified the Solid Waste Management By-laws in 2018, which also have provision for user fee including penalties for violation of the By-laws.
- Delhi has five local bodies: New Delhi Municipal Council (NDMC), Delhi Cantonment Board (DCB), North Delhi Municipal Corporation, South Delhi Municipal Corporation and the East Delhi Municipal Corporation.
- Delhi has a population of around 2 crores. East Delhi has a very high population density. Delhi also has heterogeneous pattern of settlements.
- Solid waste management is done at the ward level, zone and then local body.
- Major activities in solid waste management include segregation, primary collection, secondary storage, secondary transportation, processing and

finally disposal. Processing can be decentralized waste processing, centralized waste processing (composting, waste to energy), etc.

- Twin bin system has been started in Delhi. After collection, the waste is taken to the decentralized processing facility or the landfill. All garbage collection vehicles have GPS and they are monitored with daily reporting. Information, education and communication (IEC) activities towards behavior change are ongoing.
- Day sweeping is also a part of solid waste management; 80% is manual and the remaining 20% is done mechanically.
- There are 20 composting plants in Delhi for processing of wet waste. Aerobic composting takes 15 days in these plants.
- There are 10 biomethanation plants in Delhi with capacity of 5 tonnes each. Here, the wet waste is converted to biogas, which is then used for electricity generation.
- An integrated facility is being developed in East Delhi in collaboration with National Thermal Power Corporation (NTPC), which will have waste to energy plant, biomethanation plant, and inert waste processing unit. By 2023, Delhi will be able to process 100% of solid waste.
- An integrated facility already exists at Narela-Bawana plant. Ghazipur plant is based on RDF.
- Delhi has four existing landfills: Ghazipur, Okhla, Bhalswa and Narela-Bawana. Three have exhausted their capacity in 2002. Remediation of landfill was started in 2009. But not much work has been done on this. Following an order of National Green Tribunal (NGT) in 2019, remediation work has started in these three landfills. Dry waste like plastic is sent to waste to energy plants; soil type waste is used for roadside filling and filling of low lying areas.
- Challenges that are coming up are enforcement of segregation at source despite Bhagidari workshops; decentralized waste processing due to nonavailability of suitable and sufficient land, uncontrolled and unplanned development without civic infrastructure, multiple agencies, procedure of environmental clearance is cumbersome and NIMBY syndrome.
- Every individual has to fulfil his responsibility to solid waste management to make it a success.
- Concept of waste management can be added in the school curriculum to educate the children. Schools should have small units of solid waste management in their campus.
- There is a need to study small corporations/ bodies who are doing good work in solid waste management for their innovative ideas (concept of positive deviance).
- Cooperative societies should be encouraged to have these micro waste management units, totally sponsored by the government.
- Perishable waste should be managed at the source itself, but it is not happening.

**Participants:** Dr Anil Kumar, Mr Pradeep Khandelwal, Dr Ashok Gupta, Dr Arun Jamkar, Dr DR Rai, Dr SK Mittal, Dr KK Kalra, Dr Jayakrishnan Alapet, Mr Neeraj Tyagi, Dr Renu Chopra, Ms Ira Gupta, Dr S Sharma

*(Based on presentations by Dr Anil Kumar, Director-HCFI; Ex-Director-Environment Dept., Delhi Govt. & Mr Pradeep Khandelwal, Retd. Chief Engineer, East Delhi Municipal Corporation)*

## Empagliflozin Gets a New Indication

The US Food and Drug Administration (FDA) has expanded the indication for empagliflozin to treat heart failure with reduced ejection fraction (HFrEF) to reduce the risk of cardiovascular death and hospitalization for heart failure. The dose for which empagliflozin has received approval is 10 mg once daily dose. It can be started in adults with HFrEF with an estimated glomerular filtration rate (eGFR) as low as 20 mL/min/1.73 $m^2$.

This approval is based on the findings of the EMPEROR-Reduced trial published in the *New England Journal of Medicine* last year in which empagliflozin was found to reduce the risk of cardiovascular death or hospitalization for heart failure among HFrEF patients with diabetes or without diabetes.

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor and in 2014, it was approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. But it is not indicated for persons with type 1 diabetes or diabetic ketoacidosis. In 2016, following publication of the landmark EMPA-REG OUTCOME trial, empagliflozin was FDA-approved to prevent cardiovascular death in adults with type 2 diabetes and heart disease.

Empagliflozin is contraindicated in cases of hypersensitivity to empagliflozin or any of its excipients and also in patients on dialysis.

(*Source: Medpage Today August 18, 2021; European Pharmaceutical Review, August 19, 2021*)

## COVID-19 Surveillance Must also Include Asymptomatic Infections

More than one-third of patients with coronavirus disease 2019 (COVID-19) are asymptomatic, according to a systematic review and meta-analysis of studies reporting laboratory-confirmed infections. Children were more likely to have asymptomatic infections compared to the elderly, while persons with comorbid conditions had greater propensity to be symptomatic.

Researchers from the Yale School of Public Health reviewed data from more than 350 studies, which were published between January 1, 2020 and April 2, 2021. Two separate meta-analyses were conducted. For the study, *silent infections* were defined as laboratory-confirmed COVID-19 cases that did not exhibit any clinical symptoms at the time of testing. *Asymptomatic infections* were those that continued to exhibit no clinical symptoms during at least 7 days of follow-up after testing. *Presymptomatic cases* were persons who developed clinical symptoms after initial testing.

In the first meta-analysis, which included all studies with duration of follow-up sufficient to identify asymptomatic infections, 35.1% infections were found to be truly asymptomatic, i.e., they never became clinically symptomatic. The second meta-analysis, which included studies that identified asymptomatic cases at the time of testing and also conducted follow-up to distinguish the presymptomatic stage from asymptomatic infections, the percentage of asymptomatic infections was estimated to be nearly 37%.

Around 42.8% infections had no symptoms at the time of testing; this group included both the asymptomatic and presymptomatic infections. The prevalence of asymptomatic infections was lower in the elderly compared to children; 19.7% vs. 46.7%, respectively. Compared to persons with no underlying medical condition, those with comorbidities were much less likely to be asymptomatic.

It is not enough to search for and isolate the symptomatic cases. The true prevalence of infection cannot be estimated if asymptomatic cases are discounted. And, people do not come forward to test themselves, if they have no symptoms.

Evidence has shown that persons with asymptomatic COVID-19 too can transmit the infection. Effective control of the pandemic therefore requires identification of asymptomatic infections also.

India is slowly unlocking and with the imminent reopening of schools and colleges, there is a risk of them becoming super-spreaders as this study has shown high prevalence of asymptomatic infections in the younger age group. A focus on detection of symptomatic cases will miss the asymptomatic cases with the consequence that the infection will continue to silently spread in the community. Greater vigilance is required.

Until herd immunity develops and everybody eligible is vaccinated against COVID-19, it is through measures such as wearing masks, physical distancing, hand hygiene, avoiding crowded public places and targeted testing that one can protect themselves, and if infected, reduce the risk of transmission to the community.

(*Source: Medscape August 13, 2021 & PNAS August 24, 2021;118(34):*e2109229118)

## Diagnostic Features of Vaccine-induced Immune Thrombocytopenia and Thrombosis

A new UK prospective study of 220 confirmed cases of vaccine-induced immune thrombocytopenia and thrombosis (VITT) after having the first dose of the Oxford-AstraZeneca vaccine published in the *New England Journal of Medicine*, August 11, 2021, has identified five diagnostic criteria that are indicative of definite VITT:

- Time of presentation after vaccination (5-30 days and not before, or ≤42 days in patients having isolated deep-vein thrombosis or pulmonary embolism)
- Low platelet count (<1,50,000/cu mm)
- Established thrombosis
- Very elevated D-dimer
- Detection of antiplatelet factor 4 antibodies.

If all these criteria are fulfilled, VITT is confirmed. If one is not met, the diagnosis is probable, if two are not met, then the diagnosis is possible and if ≥3 are not met then it is unlikely to be VITT and there could an alternative diagnosis. While the overall mortality was 23%, in patients with very low platelet counts (<30,000/cu mm) and intracranial hemorrhage following thrombosis, the mortality increased to 73%... (*NEJM, Medscape*).

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Indian Journal of Clinical Practice, Vol. 32, No. 4, September 2021

# 72nd Annual Cardiology Conference

## VACCINATION IN HEART FAILURE

**Dr Vidyut Jain, Indore**

Heart failure (HF) is a common cardiovascular disease (CVD) and often associated with recurrent hospitalization and high mortality due to multiple comorbidities. Respiratory infections are very common in HF and more so in elderly group which forms the major group of HF patients. Common respiratory infections are pneumococcal and influenza in such patients. Preventing influenza infection with vaccines has proved to reduce HF hospitalization in multiple studies, like FLUVAC, PARADIGM-HF substudy, FLUCAD and INVEST. Frequency of vaccination of once in 5 years for pneumococcal and every year for influenza is a feasible and affordable approach for secondary prevention in HF. Guidelines from the Heart Failure Society and ESC also affirm the same but only a small number of patients receive vaccinations.

## TREATMENT OF IRON DEFICIENCY IN HF: IRONING OUT THE EVIDENCE

**Dr Anoop George, Vellore**

Iron deficiency (ID) is seen in 30% in stable and 50% in hospitalized patients (HFrEF and HFpEF). Anemia is a mediator or marker of HF severity. In healthy subjects, diagnosis of ID is made through an assessment of ferritin. As a single value transferrin saturation (TSAT) <19.8% alone performed at least as well in detecting true ID. It is linked with reduced exercise capacity, impaired quality of life, and poor prognosis independently of anemia and left ventricular ejection fraction (LVEF). Observational studies have shown that ID with and without anemia is significantly associated with mortality. The treatment options include erythropoietin stimulating agents. The other option is transfusion with a restrictive red blood cell transfusion strategy rather than a liberal threshold.

## ISCHEMIC LV DYSFUNCTION, MYOCARDIAL VIABILITY AND INDICATIONS FOR REVASCULARIZATION

**Dr Robert O Bonow, USA**

- Assessment of myocardial viability if often used to predict improvement in left ventricular (LV) function after coronary artery bypass grafting (CABG) and thus select patients for CABG. Identification of viable myocardium also predicts improved survival after CABG.
- STICH viability substudy: The presence of viable myocardium was associated with a greater likelihood of survival in patients with coronary artery disease (CAD) and LV dysfunction, but this relationship was not significant after adjustment for other baseline variables. The assessment of myocardial viability did not identify patients with a differential survival benefit from CABG, as compared with medical therapy alone.
- Viability testing does identify high risk patient subgroups and is associated with: outcome with evidence-based medical therapy; outcome with revascularization. BUT, does not independently predict survival benefit from revascularization. Viability testing should not be considered a prerequisite for decisions regarding medical vs. surgical management in patients with ischemic LV dysfunction.

## STROKE PREVENTION IN HIGH RISK PATIENTS WITH AF

**Dr Jan Steffel, Zurich**

Non-vitamin K oral anticoagulants (NOACs) are standard therapy for stroke prevention in atrial fibrillation in 2020: Based on randomized controlled trial (RCT) evidence, confirmed in large observational analyses. Individualize treatment!: No "one size fits all" NOAC; many aspects to consider. Patient engagement! Listen to patients' fears and preferences. Apixaban: Very good efficacy and safety profile across a large range of patient populations.

## IMPLICATIONS FOR DECISION-MAKING FOR THE MANAGEMENT OF PATIENTS WITH STABLE CAD

**Dr Sripal Bangalore, New York**

- Data from approximately 65,000 patient-years of follow-up from RCTs of routine revascularization vs. initial medication therapy suggest: 1 in 3 in the initial medication therapy undergo revascularization over ~4.5 years of follow-up; Similar survival; Reduced non-procedure myocardial infarction (MI); Reduced unstable angina; Greater freedom from angina; Increased procedural MI.

- Revascularization to improve survival in stable ischemic heart disease (SIHD) and high-risk subgroups: It is recommended in the left main disease and LV dysfunction. It is not recommended in 3-vessel disease, proximal left anterior descending (LAD) disease, and extensive ischemia. Patient preference matters!

## ANTIHYPERTENSIVE DRUG CHOICES AND SEQUENCING: GUIDELINE UPDATE AND PERSPECTIVES

**Prof Neil R Poulter, UK**

- 2018 ESC/ESH guideline: Initial therapy – Dual combination: angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) + calcium channel blocker (CCB) or diuretic; Step 2 – Triple combination: ACE inhibitor or ARB + CCB + diuretic; Step 3 – Triple combination + spironolactone or other drug.
- ISH 2020: Drug choice and sequencing – Step 1: Dual low-dose combination (ACE inhibitor or ARB + CCB); Step 2: Dual full-dose combination (ACE inhibitor or ARB + CCB); Step 3: Triple combination (ACE inhibitor or ARB + CCB + Thiazide-like diuretic); Step 4: Triple combination + spironolactone or other drug.
- Amlodipine is the choice of CCB as it is most effective, has longest duration of action and has robust RCT evidence.
- Single pill combinations – More effective and rapid BP control than monotherapy and two 'free' drugs; reduced side effects; enhanced adherence; improved cardiovascular (CV) protection; more cost-effective.

## ACUTE ISCHEMIA WITH NORMAL CORONARY ARTERIES – HOW, WHY AND WHAT NEXT?

**Dr Rajiv C, Kochi**

The optimal evaluation for patients with a diagnosis of MINOCA (Myocardial Infarction with Non-Obstructed Coronary Arteries), after excluding other causes for troponin elevation, should be aimed at determining the specific cause for each patient so that targeted therapies can be used. In general, patients who have survived ST-segment elevation MI (STEMI) without evidence of significant CAD have a better long-term outlook than those with atherosclerotic-mediated STEMI; in-hospital mortality is approximately 60% lower, and 1-year mortality, 40% lower. However, the subsequent risk for patients presenting with MINOCA is largely based on the underlying etiology and comorbidities.

## STATINS: DURING COVID TIMES

**Dr Sandeep Chopra, Ludhiana**

Patients with COVID-19 infection have an increased risk of CV complications and thrombotic events. Statins are known for their pleiotropic anti-inflammatory, antithrombotic and immunomodulatory effects. Studies in patients with CVD have shown decreased C-reactive protein, thus providing evidence of the anti-inflammatory benefits of statins along with their cholesterol-lowering effects. The same anti-inflammatory activity might improve outcomes in COVID-19 patients with increasingly severe illness, worsening respiratory failure, and increasing D-dimer and IL-6 levels, all of which are associated with increased mortality. Earlier studies have pointed to the possible effectiveness of statins in decreasing influenza-related hospitalizations and deaths. During the 2009 H1N1 pandemic, statin therapy was found to be linked with reduced disease severity among hospitalized patients. Features such as relatively good lung compliance despite poor oxygenation, lack of pulmonary vasoconstriction with resultant significant shunting, as well as thrombotic microangiopathy indicate that vascular endothelial dysfunction has a key role in the pathogenesis of COVID-19. Statins might improve endothelial and vascular function in these patients. A combination of statin/ARB was used in an unconventional and poorly documented experience to target the host response and prevent endothelial barrier damage in Ebola patients during the outbreak in West Africa.

The JUPITER trial assessed relatively healthy patients with high CRP levels and noted a significantly decreased rate of deep vein thrombosis in those administered rosuvastatin compared to placebo. Another study noted that statin therapy was associated with a 50% decline in recurrent pulmonary embolism. It is believed that statins might mitigate the effects of COVID-19 infection in selected patients based on the understanding of its associated coagulopathy, endothelial dysfunction and dysregulated inflammation.

**Suggested Reading:** [1]Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: The Pravastatin Inflammation/CRP Evaluation (PRINCE): A randomized trial and cohort study. JAMA. 2001;286(1):64-70. [2]Arslan F, Pasterkamp G, de Kleijn DP. Unraveling pleiotropic effects of statins: bit by bit, a slow case with perspective. Circ Res. 2008;103(4):334-6.

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# News and Views

## Physical Activity and Good Sleep Quality are Both Important for Good Health

A new research has suggested that the adverse effects of poor sleep quality can be countered by increasing the weekly physical activity.

The study measured the baseline weekly physical activity levels and sleep quality of nearly 4,00,000 middle-aged adults. Their physical activity levels were categorized into low (0 to <600 MET-min/wk), medium (600 to <1,200 MET-min/wk) or high (≥1,200 MET-min/wk), including a "no moderate-to-vigorous physical activity" category. Sleep was also categorized into healthy, intermediate and poor, based on a sleep score derived from five characteristics - chronotype, sleep duration, insomnia, snoring and daytime sleepiness. Score ≥4 was taken as healthy sleep and ≤1 poor sleep. All participants were followed for a mean of 11.1 years.

Participants with poor and intermediate sleep were found to be at risk of higher mortality. Those with low physical activity levels were also at higher risk for all-cause mortality.

Analysis of data showed that over an 11-year period, those with poor sleep and low physical activity levels had 57% higher risk for all-cause mortality, a 67% higher risk for death from cardiovascular disease, a 45% higher risk for death from any type of cancer and a 91% higher risk for death from lung cancer.

Participants who were younger, women, thinner, faced less socioeconomic deprivation, consumed more vegetable and fruits, were physically active, had no mental health issues, non-smokers, were employed in non-shift work, drank less alcohol, had healthier sleep scores.

Poor sleep and low physical activity are independently associated with adverse health outcomes. What this study has shown is their synergistic detrimental effects. Those who had the poorest sleep quality and least physical activity were at the greatest risk for adverse outcomes, compared to individuals with healthy sleep and high physical activity levels. Though these findings show only an association and not causality, it is important that physicians should educate their patients about the importance of physical activity as well as good sleep.

The study was published online June 29, 2021 in the *British Journal of Sports Medicine*.

(*Source: Medscape & Br J Sports Med. Published online June 29, 2021*)

## Aerobic Exercise Helps Decrease BP in Resistant Hypertension

Aerobic exercise may help decrease blood pressure (BP) in patients with resistant hypertension, suggests a new study published online in *JAMA Cardiology*.

Researchers conducted a randomized controlled clinical trial which revealed that patients with resistant hypertension who underwent a moderate-intensity aerobic exercise training program were found to have lower BP compared to patients who were given usual care. Fifty-three patients, 40 to 75 years of age, with resistant hypertension were enrolled. It was noted that 24-hour ambulatory systolic BP decreased by 7.1 mmHg among patients in the exercise group compared to the control group. Additionally, in the exercise group, the following reductions were also noted:

- –5.1 mmHg of 24-hour ambulatory diastolic BP
- –8.4 mmHg of daytime systolic BP
- –5.7 mmHg of daytime diastolic BP
- –10 mmHg of office systolic BP.

(*Source: Medscape*)

## COVID-19 Vaccination Effective in Immunosuppressed People

In a real-world situation, full vaccination against coronavirus disease 2019 (COVID-19) has been found to be over 80% effective at reducing infection in individuals with inflammatory bowel disease (IBD) who were on immunosuppressive therapy.

The study looked into post-vaccine infection rates in a Veterans Affairs cohort, and confirmed the benefit of COVID-19 vaccines, especially in a subgroup of individuals who have the greatest risk for having a compromised immune system. The retrospective cohort study included 14,697 patients from the Veterans Health Administration database who had IBD diagnosed prior to the initiation date of the administration's vaccination program. In the cohort, 7,321 patients had been administered at least one dose of either the Pfizer or

Moderna COVID-19 vaccines. In all, 3,561 patients who received the Moderna vaccine and 3,017 who received the Pfizer vaccine had been given both doses. Unvaccinated patients had a higher rate of COVID-19 infection compared to the fully vaccinated patients (1.34% vs. 0.11%, respectively) in follow-up data. Over a 20 days median follow-up, 14 infections (0.28%) were noted in partially vaccinated individuals. A total of 7 infections (0.11%) were noted in fully vaccinated individuals over a median follow-up of 38 days. The findings were published in *Gastroenterology*.

(*Source: Medscape*)

## A Potential Biomarker to Evaluate Risk of Future Cognitive Impairment

New research published August 4, 2021 in the journal *Neurology* has shown an association of midlife plasma amyloid beta (Aβ) levels with cognitive impairment in late-life.

A subsample of 2,284 participants in the Atherosclerosis Risk in Communities (ARIC) cohort study, who had normal cognition in midlife, was analyzed to look at the relationship of plasma Aβ42, Aβ40 and Aβ42:Aβ40 ratio measured in midlife, late-life and the change from midlife to late-life, to risk of mild cognitive impairment (MCI), dementia and combined MCI/dementia outcomes in late-life. The study participants were followed-up for more than 25 years.

Analysis of data over 25 years showed that 22% (n = 502) of the study participants had developed dementia, 36% (n = 832) had MCI, while 38% (n = 859) had normal cognition. The midlife plasma Aβ levels in cognitively normal people were found to be linked to the risk of dementia or MCI in old age. Higher levels of plasma Aβ40 (67 pg/mL) at midlife were associated with increased risk of late-life MCI or dementia by 15%, whereas increase in plasma midlife plasma Aβ42 (10 pg/mL) levels was associated with 13% lower risk of later MCI or dementia. A 37% reduced risk of MCI or dementia in late-life was seen with each doubling of the Aβ42/Aβ40 ratio at midlife.

Based on their findings, the researchers suggested that the midlife plasma Aβ levels can be considered as a potential biomarker to evaluate the risk of future cognitive impairment. Screening of younger individuals can help prevent the onset of dementia.

Alzheimer's disease, the most common cause of dementia, is considered a disease of old age. An article published in *Alzheimer's & Dementia*, the journal of the Alzheimer's Association has hypothesized that "*it is not a disease of the elderly but rather a clinically silent pathology of midlife (approximately 40-65 years or even younger), whose terminal phase is characterized by dementia. If this were so, then on the broadest social level AD would no longer be considered a disease of end-of-life but rather a disease of the young. The clinical consequences of such a change would also be significant, reorientating disease management away from palliative care to active prevention strategies in younger, healthier individuals.*" (*Alzheimers Dement (N Y).* 2015;1(2):122-30.) This study is a step in this direction.

(*Source: Medpage Today & Neurology. 2021 Aug 4; doi: 10.1212/WNL.0000000000012482*)

## Full-dose Blood Thinners Reduce the Need for Cardiac and Respiratory Support in Moderately Ill COVID-19 Patients

The moderately ill hospitalized COVID-19 patients who received full-dose heparin did not require much of cardiovascular or respiratory support and were also more likely to be discharged from hospital, according to findings of a large clinical trial published in *The New England Journal of Medicine*.[1] But, similar outcomes were not seen in the critically ill patients in intensive care.

Last year in April, hospitalized patients with COVID-19 were administered either a low or full dose of heparin for up to 14 days following enrollment. Interim results, by the year end, showed that therapeutic anticoagulation did not reduce the need for organ support in the critically ill COVID-19 patients who needed intensive care. But, a month later, in January 2021, it was found that full-dose blood thinners improved outcomes and reduced the need for ventilation or other organ supportive interventions in the moderately ill hospitalized COVID-19 patients.

Moderately ill patients hospitalized with COVID-19 were defined as those who did not receive "organ support", including high-dose oxygen therapy, mechanical ventilation, life support, medicines that increase BP or those that change the force of the heart's contraction.

For quicker analysis of data, three trials collaborated and aligned their design into one integrated, multiplatform, randomized clinical trial to study the impact of initial strategy of full (therapeutic) dose of heparin vs. low (prophylactic) dose of heparin on in-hospital survival in moderately and critically ill patients with confirmed COVID-19. The outcomes in terms of the duration of intensive care unit (ICU)-level cardiovascular or respiratory organ support in critically ill patients with COVID-19 were also evaluated. The trials are:

- Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)[2]

- Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 (ACTIV-4a): ACTIV-4a Antithrombotics Inpatient A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19[3]
- Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC).[4]

The final analysis included 1,098 critically ill and 2,219 moderately ill patients. For both the groups, researchers evaluated for how long they were free of organ support up to 21 days after enrollment.

Analysis of data showed that in moderately ill patients, there was 99% chance that the full-dose heparin reduced the need for organ support and also improved survival compared to those who received low-dose heparin.

While therapeutic anticoagulation reduced major thrombotic events in severely ill patients, it did not increase the probability of survival to hospital discharge or the number of days free of cardiovascular or respiratory organ support. It had a 95% probability of being inferior to usual-care pharmacologic thromboprophylaxis. There was also an 89% probability that therapeutic anticoagulation resulted in a lower probability of survival to hospital discharge compared to usual-care thromboprophylaxis. According to the authors, though the incidence of major bleeding was numerically higher with therapeutic-dose anticoagulation than with usual-care thromboprophylaxis, it was still low (3.8%).

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(*Source: NIH Press Release, August 4, 2021*)

## MRI Predicts the Risk of Disease Relapse in Children with Juvenile Idiopathic Arthritis

A subclinical synovitis seen on magnetic resonance imaging (MRI) examination in children with clinically inactive juvenile idiopathic arthritis (JIA) is predictive of disease flare, suggests a new study published in the journal *Arthritis Care & Research*.

The study included 90 children with JIA who underwent contrast-enhanced MRI from 2012 to 2016. Each joint was evaluated for synovitis, tenosynovitis and bone marrow edema. Their disease outcomes were retrospectively analyzed. At the time of study entry, about 17% of patients were not on any medication on account of their disease being in remission, while the rest 83.3% were on medications, mainly biologics. Inactive disease was defined as no arthritis, fever, serositis, rash, splenomegaly, lymphadenopathy or uveitis; a normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level; physician global assessment indicating no active disease with duration of morning stiffness ≤15 minutes.

MRI showed subclinical synovitis in 65.5% children and bone marrow edema in 46.7%. A disease flare was reported in 63.3% of patients during follow-up.

About 44% of those who were in clinical remission on medication at baseline stopped their treatment, while 36% reduced dose and frequency of use. Seventy-two percent of children who discontinued their treatment experienced a disease flare; a disease flare was also reported in 53% of children who had reduced their original dose or continued their medication in the previously prescribed doses. Progression of joint damage was seen in 31.5% evident on X-ray.

Nearly 75% of patients with subclinical synovitis reported a disease flare compared with around 42% of those with no residual synovitis on MRI. A high MRI score for bone marrow edema and age >17 years strongly predicted progression of joint damage.

Treatment of JIA aims to prevent disease progression and induce clinical remission. This study shows evidence of subclinical inflammation that persists in a large majority of JIA patients even though their disease is clinically in remission. MRI during follow-up can help predict the risk of disease flare and joint deterioration with timely management in order to prevent physical disability.

(*Source: Medpage Today & Arthritis Care Res (Hoboken). 2021 Jul 19. doi: 10.1002/acr.24757*)

## Increased Risk of Infection-related Hospitalizations in Persons with Diabetes

Persons with diabetes are prone to develop infections; the healing process is also delayed in them. Reiterating

this, a new prospective study has shown that people with diabetes are at a higher risk for hospitalization for any infection.

Researchers at the Johns Hopkins Bloomberg School of Public Health evaluated more than 12,000 adults, aged 45-64 years from the ARIC study. They were recruited between 1987 and 1989, and were followed-up until 2019 for almost three decades. A total of 10,894 participants were free of diabetes, while 1,485 had diabetes. Results of the study are published in the journal *Diabetologia*.

The study found a 67% higher risk for infection-related hospitalization compared with adults without diabetes over the course of nearly 30 years (hazard ratio [HR] 1.67). A major share of this was contributed to by a sixfold increased risk for foot infections (HR 5.99). Besides foot infections, the diabetic population was also vulnerable to risk of other infections, such as respiratory infections (HR 1.49), urinary tract infection (HR 1.58), sepsis (HR 1.92) and postoperative infections (HR 1.95) that required hospitalizations. Diabetes was more strongly associated with hospitalization for infection in younger participants.

During follow-up, hospital discharge records showed 4,229 episodes of hospitalizations due to injection. Individuals with baseline diabetes had an infection rate of 25.4 per 1,000 person-years compared with 15.2 per 1,000 person-years for those without diabetes.

This study has shown a significant association with infection-related hospitalization in persons with diabetes. This underscores the need to assess them on follow-up visits to prevent infections and also their timely treatment to reduce infection-related morbidity and mortality. This study assumes importance given the ongoing COVID-19 pandemic as people with diabetes have been shown to have severe disease and serious COVID-19-related complications.

(*Source: Medpage Today & Diabetologia*)

## Survey in Israel Finds 3rd Vaccine Dose has Similar Side Effects to 2nd

A survey conducted in Israel has noted that most people who were administered a third dose of the Pfizer COVID-19 vaccine had similar or fewer side effects than that after the administration of the second dose.

Close to 4,500 people, who had received the booster dose between July 30 and August 1, participated in the survey. Around 88% of the participants stated that they felt similar or better, in the days following the third shot, to how they had felt after the second vaccine dose. About 31% reported experiencing some side effect, with the most common being soreness at the site of injection. Only about 0.4% had difficulty breathing, and 1% had to seek medical treatment owing to a side effect.

(*Source: Reuters*)

## Mix of Covishield, Covaxin Provides Better Immunogenicity: Study

A study that included 98 individuals, of which 18 had been accidently given Covishield as first dose and Covaxin as the second dose in Uttar Pradesh, revealed that combining the two vaccines evoked better immunogenicity compared to two doses of the same vaccine.

The study, conducted by the Indian Council of Medical Research (ICMR), noted that inoculation with a combination of Covishield and Covaxin was safe and the adverse effects appeared to be similar to the same dose regimen. Apart from the 18 individuals who had been administered one dose of Covishield and second dose of Covaxin, 40 individuals who had received two doses of Covishield and 40 who had been given two doses of Covaxin, were included in the study. The duration of the study was from May to June this year. The immunogenicity profile against Alpha, Beta and Delta variants in the heterologous group appeared to be superior and IgG antibody and neutralizing antibody response was significantly higher in the heterologous group, compared to the homologous groups.

(*Source: ET Healthworld – PTI*)

## Vaccination may Reduce Risk of COVID Reinfection to Half: CDC

The US Centers for Disease Control and Prevention (CDC) recommends that every individual should get a COVID-19 vaccine, even if they've had the infection previously.

A study published in *Morbidity and Mortality Weekly Report* has shown that people who have recovered from COVID-19 but haven't yet received a vaccine have over twofold increased risk of testing positive for the virus again, compared to an individual who was vaccinated after a previous infection. Investigators assessed 738 residents of Kentucky who had COVID-19 infection in 2020. About 250 of them again tested positive for COVID-19 from May through July 2021, when the Delta variant was dominant. People who were unvaccinated had more than double the risk of contracting the infection again during the Delta wave. Partial vaccination had no significant effect on the risk of reinfection.

(*Source: Medscape*)

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# The Science Behind Observing Shradhs

According to the Vedas, every individual has three debts to be paid off - firstly, of the Devtas (Dev Rin), secondly of Guru and teachers (Rishi Rin) and, thirdly, of Ancestors (Pitra Rin). From the scientific point of view, Devtas represent people with Daivik qualities; teachers the ones who have taught us and Pitra, three generations of our ancestors. Rin from scientific point of view would mean unfinished desires or tasks.

The rituals scientifically would mean detaching oneself from the guilt of unfinished tasks of our ancestors by detoxifying our mind.

Debt means desires of our ancestors that had not been fulfilled during their lifetime. The responsibility to fulfil them automatically falls onto the eldest son in the family and they need to be carried out. If not, it is a sign of guilt disorder in the family and may present with loss of wealth, loss of direction and courage and health. The resultant problems faced were called Pitra Dosh in mythology.

In the rituals, Tarpan of Jal (water) is offered to ancestors. Jal in mythology means flow of thoughts and offering Jal in mythology equates to confession and getting connected. Tarpan is always done with an aim to purify the mind and wash off the guilt.

Tarpan is always done after the desires of our ancestors have been fulfilled by the person performing the Shradh. Tarpan and Arpan on the day of Shradh mean getting connected to our consciousness and informing that all the unfinished tasks are over, so that we can get rid of the long persisting guilt from our mind. Offering and making food which was liked by our ancestors on that day is just to remember and pay respect to them.

Confession is only possible in a Satwik state of mind, which requires eating of Satwik food for a few days. The ritual of offering Satwik food to Brahmins during the Shradh means making only Satwik food on that day, so that everyone in the family is forced to eat Satwik food during Shradhs.

Pind Daan denotes medicinal ways of detaching oneself from the guilt. All the four offerings (black sesame, Kusha grass, Jwar and boiled or roasted rice) in Ayurveda have been described to detoxify the mind and making it Satwik by removing Rajas and Tamas.

If the guilt does not go by repeated Shradhs, then one is required to go for a spiritual vacation during Shradh period, so that he is away from the worldly desires for a few days before the Shradh and this is what going to Gaya means. This spiritual retreat works like an incubation period to the disturbed mind and gets rid of the disturbed mind and allows the undisturbed state of mind to confess and purify.

It is said that once a Shradh is successfully performed or Gaya Shradh is performed, there is no need to perform Shradh rituals thereafter. Once the guilt is over, there is no need for further detoxification of the mind. After that the only ritual that needs to be performed is remembrance, which is usually performed on the death anniversary of the deceased ancestor, usually by doing some charity on their names.

One is not supposed to do auspicious things during Shradh as during this period, the mind is in a process of detoxification.

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## Key Factors Tied to Higher Infection Risk in Alcoholic Hepatitis

Among patients hospitalized with alcohol-associated hepatitis (AAH), certain factors could signal high infection risk, suggests a retrospective cohort study. Investigators evaluated the outcomes of around 300 patients hospitalized for AAH over the past 2 decades. It was noted that ascites at the time of admission (hazard ratio [HR] 2.06, 95% confidence interval [CI] 1.26-3.36) and corticosteroid use (HR 1.70, 95% CI 1.05-2.75) were significant risk factors for a bacterial infection. Additionally, higher Model for End-Stage Liver Disease (MELD) scores (HR 1.05 per point, 95% CI 1.02-1.09) and white blood cell count (WBC) at the time of admission (HR 1.02 per unit, 95% CI 1.00-1.05) also predicted infection risk to a significant level. The findings are published in *Hepatology Communications*.

(*Source: Medpage Today*)

# A Simple Gesture

A little boy selling magazines for school walked up to a house that people rarely visited. The house was very old and run down and the owner hardly ever came out. When he did come out, he would not say hello to neighbors or passers-by but simply just glare at them.

The boy knocked on the door and waited, sweating from fear of the old man. The boy's parents told him to stay away from the house, a lot of the other neighborhood children were told the same from their parents.

As he was ready to walk away, the door slowly opened. "What do you want?" the old man said. The little boy was very afraid but he had a quota to meet for school with selling the magazines.

"Uh, sir, I uh am selling these magazines and uh I was wondering if you would like to buy one." The old man just stared at the boy. The boy could see inside the old man's house and saw that he had dog figurines on the fireplace mantle. "Do you collect dogs?" the little boy asked. "Yes, I have many collectibles in my house, they are my family here, they are all I have." The boy then felt sorry for the man, as it seemed that he was a very lonely soul. "Well, I do have a magazine here for collectors, it is perfect for you, I also have one about dogs since you like dogs so much." The old man was ready to close the door on the boy and said, "No boy, I don't need any magazines of any kind, now goodbye."

The little boy was sad that he was not going to make his quota with the sale. He was also sad for the old man being so alone in the big house that he owned. The boy went home and then had an idea. He had a little dog figure that he got some years ago from an aunt. The figurine did not mean nearly as much to him since he had a real live dog and a large family. The boy headed back down to the old man's house with the figurine. He knocked on the door again and this time the old man came right to the door. "Boy, I thought I told you no magazines."

"No, sir I know that, I wanted to bring you a gift." The boy handed him the figurine and the old man's face lit up. "It is a Golden Retriever, I have one at home, this one is for you." The old man was simply stunned; no one had ever given him such a gift and shown him so much kindness. "Boy, you have a big heart, why are you doing this?" The boy smiled at the man and said, "Because you like dogs."

From that day on the old man started coming out of the house and acknowledging people. He and the boy became friends; the boy even brought his dog to see the man weekly.

This simple gesture changed both of their lives forever.

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## First Drug for Idiopathic Hypersomnia

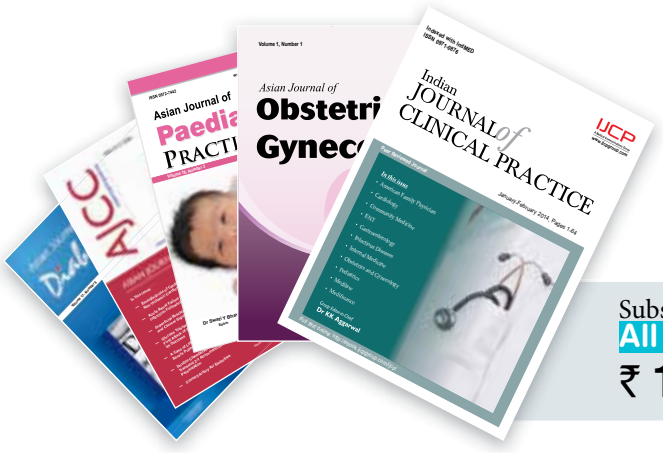
Physicians now have an option to treat their patients with idiopathic hypersomnia. Recently, the US FDA approved the first drug to treat adults with idiopathic hypersomnia, adding a new indication to a calcium, magnesium, potassium and sodium oxybate oral solution. This oral solution is already approved for the treatment of cataplexy or excessive daytime sleepiness in patients aged ≥7 with narcolepsy.

**Adverse effects:** Nausea, headache, dizziness, anxiety, vomiting.

**Drug interactions:** Co-administration with central nervous system (CNS) depressants including opioids, benzodiazepines, sedating antidepressants, antipsychotics, sedating antiepileptic medicines, general anesthetics, muscle relaxants, alcohol or street drugs may cause respiratory depression, hypotension, drowsiness, syncope and death.

The active ingredient in the drug is oxybate, also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Hence, the drug carries a boxed warning as a CNS depressant and for its abuse and misuse potential, which can lead to seizures, respiratory depression, drowsiness, coma and death.

(*Source: US FDA & Medpage Today*)



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Indian Journal of Clinical Practice, Vol. 32, No. 4, September 2021

# Lighter Side of Medicine

HUMOR

**Can I help you:** A young businessman had just started his own firm. He had just rented a beautiful office and had it furnished with antiques. He saw a man come into the outer office. Wishing to appear the hot shot, the businessman picked up the phone and started to pretend he had a big deal working. He threw huge figures around and made giant commitments.

Finally, he hung up and asked the visitor, "Can I help you?"

"Yeah, I've come to activate your phone lines."

Did you hear about the guy who lost his whole left side? He's is all right now!

Why did the doctor tell the nurse to walk past the pill cupboard quietly? So, she wouldn't wake the sleeping pills.

Woman: My husband swallowed an Aspirin by mistake, what shall I do? Doctor: Give him a headache now, what else!

**Funny meanings:**

**Coma:** A punctuation mark

**Genes:** Blue denim slacks

**Nitrates:** Cheaper than day rates

**Tumor:** More than one, an extra pair

**Artery:** The study of fine paintings

**Bacteria:** Back door to cafeteria

**Terminal illness:** Getting sick at the airport.

**Coffee dilemma:** A man and his wife were having an argument about who should brew the coffee each morning.

The wife said, "You should do it, because you get up first, and then we don't have to wait as long to get our coffee."

The husband said, "You are in charge of the cooking around here and you should do it, because that is your job, and I can just wait for my coffee."

Wife replies, "No you should do it, and besides it is in the Bible that the man should do the coffee."

Husband replies, "I can't believe that, show me." So she fetched the Bible, and opened the New Testament and shows him at the top of several pages, that it indeed says: "HEBREWS".

**Getting dressed:** Hospital regulations required a wheelchair for patients being discharged. However, while working as a student nurse, I found one elderly gentleman – already dressed and sitting on the bed with a suitcase at his feet – who insisted he didn't need my help to leave the hospital.

After a chat about rules being rules, he reluctantly let me wheel him to the elevator. On the way down I asked him if his wife was meeting him.

"I don't know," he said. "She's still upstairs in the bathroom changing out of her hospital gown."

## Dr. Good and Dr. Bad

**SITUATION:** A 62-year-old female with type 2 diabetes (BMI: 32.4 kg/m$^2$) was advised investigations to determine combined serum free light chain level and its relation with B-score and high-sensitivity C-reactive protein.


**LESSON:** The findings of a study demonstrated an association between levels of combined serum free light chain and carotid atherosclerosis in individuals with type 2 diabetes mellitus.

*Diab Vasc Dis Res. 2018;15(2):162-4.*



*IJCP SUTRA: "With an increase in number of heart patients, a corresponding increase in prostate cancer patients is also seen in the society."*

# Talking Point Communications

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- The introduction should state why the study was carried out and what were its specific aims/objectives.

## Methods

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

### Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

### Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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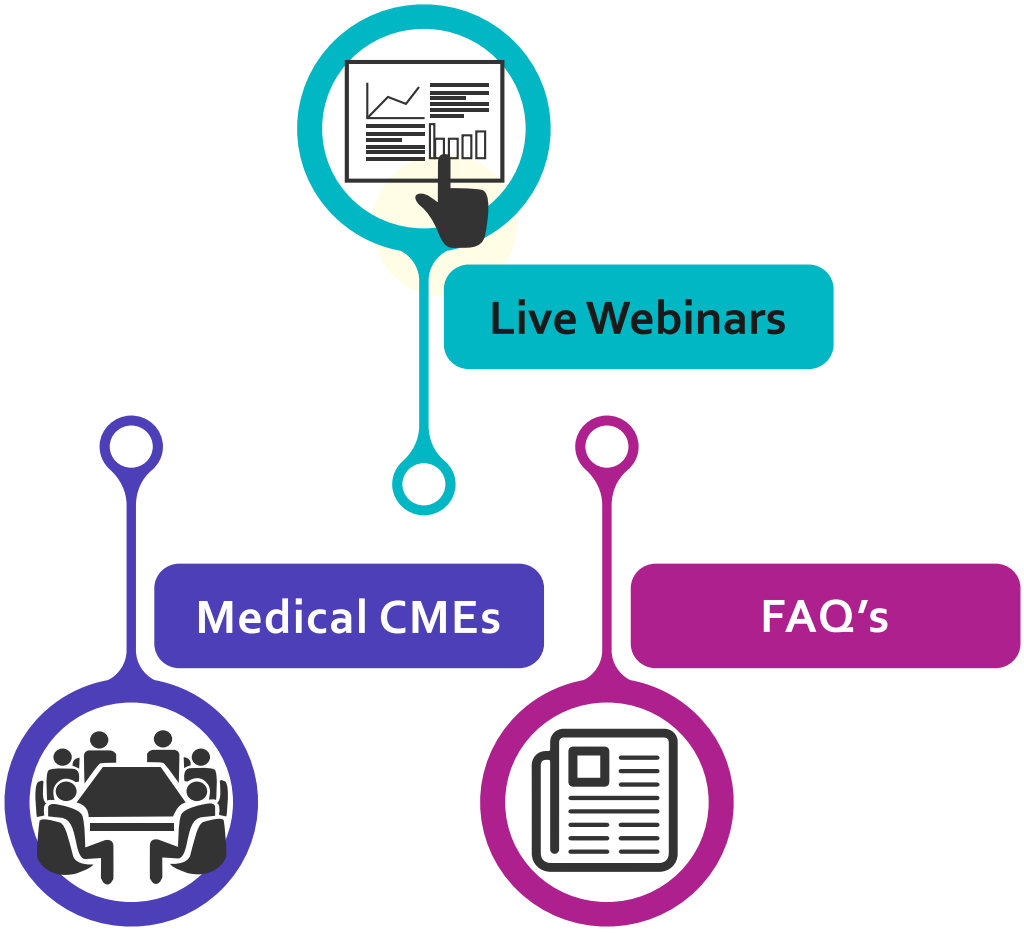


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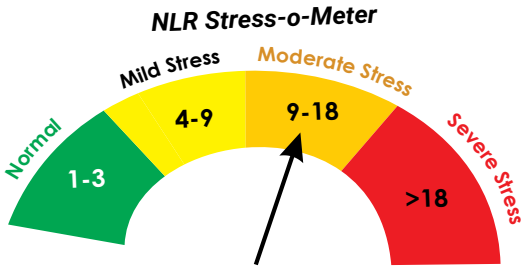


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