Journal of The Association of Physicians of India

VOL NO. 73 | ISSUE NO. 8 | AUGUST 2025 | ISSN: 0004 - 5772

SUPPLEMENT TO JAPI

Supplement Copy

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JAPI

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Published on 1st of every month

JAPI JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA
Editor-in-Chief: **Prof. Dr. Mangesh H Tiwaskar**

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Subscription Information
Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹12,000 (India) and US $500 (other countries). The Journal is dispatched within India by surface mail and to other countries by sea mail.

Business Correspondence
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Published and Edited by
Prof. Dr. Mangesh Tiwaskar, on behalf of **The Association of Physicians of India**, Journal of The Association of Physicians of India, Turf Estate, Unit No. 006 & 007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Railway Station (West), Mumbai-400 011.
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Supplement Copy on

Real World Data on Dehydration

Contents

Preface

Mangesh Tiwaskar*

This special issue of the "Journal of the Association of Physicians of India" focuses on an underappreciated aspect of patient care: dehydration in nondiarrheal illnesses, particularly in diabetic nondiabetic, adult, and elderly populations as well as highlight ways to enhance oral rehydration therapy utilization in India.[1] Dehydration in acute nondiarrheal diseases, often resulting from reduced intake or increased fluid losses, can lead to critical deficits in fluid, electrolytes, and energy (FEE).[2,3] Oral FEE supplementation, when used as an adjuvant to standard care, has shown clinical benefits in improving hydration and energy levels in earlier small studies, particularly in patients with fever, general weakness, and metabolic conditions such as diabetes.[2–6] The reported studies in this issue delve into the clinical consequences of dehydration, its underrecognition in certain populations, and the therapeutic role of oral FEE solutions like ORSL® in supporting patient recovery, especially in diabetic and elderly individuals.

Data have shown that dehydration is not adequately recognized or managed in patients with nondiarrheal illnesses, particularly among nondiabetic adults and older adults. Even without the typical symptoms of gastrointestinal fluid loss, patients may suffer from significant electrolyte imbalances, which can exacerbate underlying health conditions. Furthermore, in diabetic populations, hyperglycemia can lead to osmotic diuresis, significantly increasing the risk of dehydration.[6] The role of oral rehydration products, such as ORSL®, is discussed extensively as a potential intervention in managing these imbalances. Despite limited use of such products in nondiarrheal settings, the findings suggest that ready-to-drink electrolyte solutions could help shorten the duration of symptoms like fever and improve outcomes in respiratory tract infections (RTIs) and other acute conditions. Moreover, the research underscores the necessity of maintaining adequate hydration in diabetic patients to prevent complications related to electrolyte disturbances.

For elderly patients, dehydration poses unique risks due to age-related factors like diminished thirst sensation and impaired kidney function. The studies emphasize the critical need for better hydration management in older adults, who may not exhibit the classic signs of dehydration but are nonetheless vulnerable to fluid and electrolyte imbalances. Oral electrolytes, such as ORSL® and its variants, are shown to offer potential benefits in managing both dehydration and related symptoms in these populations.

An *in vitro* study showed the immunomodulation benefits of oral FEE formulation optimized with addition of zinc and selenium with triple actions—phagocytic activity, antioxidant properties, and mitigating oxidative stress.

The clinical implications of these findings are significant. They call for heightened awareness among healthcare providers regarding the risks of dehydration in nondiarrheal illnesses, particularly in vulnerable groups like diabetics and the elderly. Furthermore, they highlight the value of incorporating oral FEE solutions into standard treatment protocols to mitigate fluid imbalances, impact immunity, and enhance recovery. The data presented in the present issue advocate a tailored and evidence-based approach to dehydration management, ultimately aiming to improve patient outcomes across various clinical scenarios and their immunity.

Oral rehydration therapy (ORT) remains the cornerstone of diarrheal disease management especially as first-line treatment for acute diarrhea. Despite significant advances in ORT, persistent issues such as inaccuracy of preparation (or reconstitution), lack of caregivers' and HCPs' knowledge and awareness, alongside access to clean and potable water, continue to limit the effectiveness of ORS in India. A narrative review herein examines the challenges and barriers impeding diarrheal disease management in India and address the identified gaps in healthcare delivery and improve treatment outcomes.

By bringing attention to these overlooked aspects of patient care, especially in diabetics and the elderly, this issue contributes meaningfully to the practice of internal medicine, offering both new insights and practical recommendations for the management of dehydration in nondiarrheal conditions.

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How to cite this article: Tiwaskar M. Preface. J Assoc Physicians India 2025;73(8):6–6.

ORIGINAL ARTICLE

Dehydration with Nondiarrheal Illnesses in Adults and Older Adults: Insights from Retrospective, Real-world, Electronic Medical Record-based Data

Harshad Malve[1*], Sumit Bhatia[2], Manoj Chawla[3], Priti Thakor[4], Amol Patil[5]

Abstract

Introduction: Nondiarrheal dehydration, though a physiologically common condition, remains underreported. There are no specific guidelines for its treatment, and physicians usually rely on the guidelines for diarrheal dehydration. Until now, no study has reported the epidemiology of dehydration in nondiarrheal conditions.

Materials and methods: This was an electronic medical record (EMR)-based retrospective observational study. Anonymized and aggregated data of patients meeting the eligibility criteria from January 2017 to March 2023 were retrieved from the EMR database. Analysis was done to evaluate the prevalence of dehydration and associated conditions in adults and older adults.

Results: The EMR platform had 2,24,90,146 patients, including 1,57,13,317 (69.87%) adults and 44,43,851 (19.76%) older adults (≥60 years). A total of 1,84,89,088 patients had nondiarrheal illnesses, of which 1,43,56,271 (77.65%) were adults and 41,32,817 (22.35%) were older adults. Dehydration was reported only for 4,917 (0.026%), of which 3,451 (70.19%) were adults without diabetes, and 666 (13.54%) were older adults without diabetes. The diabetic adults and older adults with dehydration accounted for 547 (0.0035%) and 253 (0.0057%), respectively.

Conclusion: The recorded prevalence of dehydration in patients with nondiarrheal illnesses is very low, highlighting the need for proactive screening for dehydration. There is a need to effectively diagnose nondiarrheal dehydration and highlight the significance of proactively documenting it in the prescriptions.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1087

Introduction

Nondiarrheal conditions like fever, nausea, vomiting, and various respiratory and urinary tract infections (UTIs) may also lead to dehydration. This nondiarrheal dehydration is an under-recognized and poorly managed condition that causes excessive loss of fluid from the body. It is mostly unintended and sometimes is an associated factor for mortality and morbidity.[1] Excessive water loss due to diarrhea, vomiting, perspiration, high blood sugar level, hypoaldosteronism, etc., primarily contribute to dehydration. Diarrhea, a frequent cause of dehydration in adults and geriatric populations, has well-defined guidelines for effective management.[2] However, nondiarrheal conditions like fever, nausea, vomiting, and illnesses like viral flu, dengue, malaria, chikungunya, typhoid, and respiratory tract infections (RTIs) can lead to fluid–electrolyte deficits and imbalance, potentially causing or exacerbating the dehydration and contributing to weakness in affected patients.[3] The older adults are more susceptible to dehydration due to reduced thirst sensation, decreased fluid reserve due to reduced muscle mass, reduced sensitivity to antidiuretic hormone, poor water and food intake.[4,5] Dehydration complications in older adults can be severe, leading to conditions such as muscle weakness, seizures (resulting from low potassium and sodium levels), shock, and coma. Dehydration in adults can also lead to Urinary tract infections (UTIs), kidney stones, and kidney failure in some cases.[6]

Chronic metabolic conditions like diabetes may lead to dehydration due to persistent hyperglycemia leading to osmotic diuresis.[7] Poor hydration has impact on blood pressure and glycemic status.[7,8] Moreover, hyperlipidemia, which is one of the most common comorbid conditions observed in patients with uncontrolled diabetes mellitus (DM), also lessens the serum water fraction up to 80%.[9] Water intake is insufficient to replenish the mineral loss caused due to dehydration.[10]

Oral rehydration therapy (ORT) balances the blend of glucose and electrolytes that promotes fluid absorption to treat dehydration. Components of a typical ORT include sodium, potassium, and a small amount of glucose. Such solutions are generally unpalatable due to strong salty taste.[11] ORT effectively utilizes the sodium–glucose cotransporter 1 (SGLT1) to stimulate the absorption of sodium (Na+) ions and fluids in the small intestine through a cyclic adenosine monophosphate (cAMP)-independent mechanism.[12] However, in the case of conditions like fever and infections, increased metabolic response creates a requirement for additional energy.[13,14] Patients also might feel anorexia in such conditions, and recommendation of solid food in such conditions is expected to result in low compliance. Role of oral fluids, electrolytes, and energy is defined to address the dehydration in nondiarrheal conditions and known to have impact on its recovery.[13,14] Ready-to-drink (RTD) formulations with added energy component (glucose) serve to improve palatability and patient compliance. These prepacked formulations are very convenient for use.[10,13,14]

To date, there is no study done to present the epidemiology of nondiarrheal dehydration in adults and older adults. Hence, this study was conducted to understand the prevalence of dehydration due to nondiarrheal conditions in diabetic and nondiabetic adults and older adults

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How to cite this article: Malve H, Bhatia S, Chawla M, *et al.* Dehydration with Nondiarrheal Illnesses in Adults and Older Adults: Insights from Retrospective, Real-world, Electronic Medical Record-based Data. J Assoc Physicians India 2025;73(8):7–10.

using anonymized and aggregated data from electronic medical records (EMRs).

Materials and Methods

This was a retrospective, real-world, observational, EMR-based study. Anonymized and aggregated data of the patients meeting eligibility criteria were retrieved from the EMR database. Adults (≥18 years to <60 years) and older adults (≥60 years) diagnosed with nondiarrheal conditions were considered for this study. Patients with a mention of diarrhea, loose motions, loose stools, gastroenteritis, and related terms were excluded from this study. Patients with cardiac failure, renal failure, or liver ailments like liver cirrhosis, acute pancreatitis, and ascites were also excluded.

This study was approved by the Royal Pune Independent Ethics Committee on October 26, 2023 (RPIEC341023). Registration on the Clinical Trials Registry—India was not mandatory for this retrospective analysis of data.

Results

Patient Flow and Prevalence Data

There were records of 1,57,13,317 adults and 44,43,851 older adults on the platform. Most of the patients in both the groups were nondiabetic. Of the patients with nondiarrheal conditions, dehydration was reported for a very sparse number of patients. The proportion of prevalence of dehydration was higher in older adults. Table 1 presents patient disposition and the prevalence of dehydration.

Dehydration and Its Associated Conditions in Adult and Older Adult T2DM Patients

Hypertension was the most common condition in the adult (27.24%) and older adult (44.27%) diabetic population. Gastritis, fungal infection, and thyroid disorders were the other conditions reported for both adult and older adult age-groups (Fig. 1).

Dehydration and Its Associated Conditions in Nondiabetic Adult and Older Adult Patients

In the case of nondiabetic adults, gastritis was the most reported condition, followed by fever, dengue, RTI, and hypertension.

In the dehydrated older adults, hypertension was the most associated condition. Other common conditions were gastritis, fever, dengue, and RTI.

Associated conditions for nondiabetic adults and older adults with dehydration are presented in Figure 2.

Table 1: Patient disposition and prevalence of dehydration

	n (%)	*n (%)*
	*Adults**	*Older adults#*
Total patients on EMR platform	1,57,13,317 (100)	44,43,851 (100)
Patients with T2DM	23,59,652 (15.02)	13,77,787 (31.00)
Patients without T2DM	1,33,53,665 (84.98)	30,66,064 (69.00)
Patients with nondiarrheal illnesses	1,43,56,271 (91.36)	41,32,817 (93.00)
Diabetic patients with nondiarrheal illnesses	21,46,938 (13.66)	12,79,459 (28.79)
Nondiabetic patients with nondiarrheal illnesses	1,22,09,333 (77.70)	28,53,358 (64.21)
Diabetic patients with dehydration	547 (0.0035)	253 (0.0057)
Nondiabetic patients with dehydration	3,451 (0.0022)	666 (0.0150)

T2DM, type 2 diabetes mellitus; *Percentages have been calculated based on the number of adult patients; #Percentages have been calculated based on the number of older adult patients

Discussion

Dehydration is a common condition affecting patients of all ages, complicating other medical problems and may cause significant morbidity and mortality. The issue of dehydration is an important public health concern, yet it often goes undiagnosed, leading to a low reported prevalence.[13–15] There are multiple studies reporting dehydration due to diarrhea; however, none of the studies reported dehydration due to other nondiarrheal causes. In our study, the prevalence of dehydration due to nondiarrheal conditions was observed to be very low. This might be attributed to the numerous definitions of dehydration and absence of its accurate assessment.[16,17] Documentation of dehydration is not a part of physicians' routine practice, particularly at primary care settings in India where healthcare professionals (HCPs) barely examine patients for few minutes. This also might be one of the reasons for underreporting. Bennett et al. reported

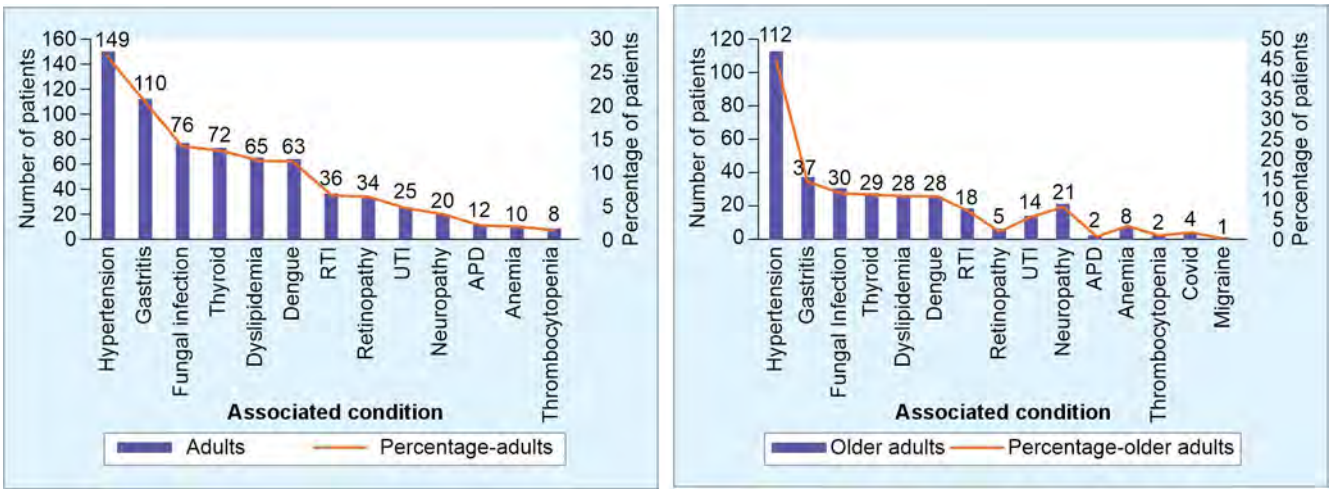

Fig. 1: Associated conditions for adult and older adult diabetic patients with dehydration; APD, acid peptic disease; RTI, respiratory tract infections; UTI, urinary tract infections

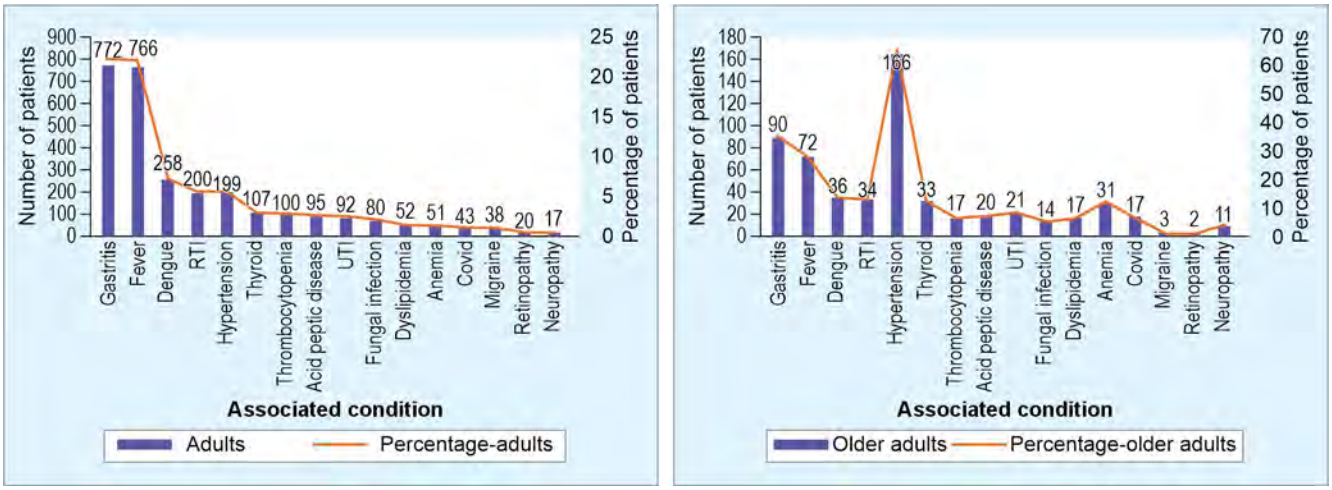

Fig. 2: Associated conditions for nondiabetic adult and older adult patients with dehydration; APD, acid peptic disease; RTI, respiratory tract infections; UTI, urinary tract infections

in their study that 48% of 185 older adults had chronic dehydration, whereas it was documented for merely 26% of the patients.[18] This is in alignment with our study, where we have observed a low prevalence. Further, older adults were observed to be more dehydrated in comparison to the adults. Literature reports that age-related physiological factors make older people more prone to dehydration.[19] This is mostly due to reduced physiological reserves and increased comorbidity.[20] In addition to diabetes, hypertension was observed to be the most reported associated condition for dehydrated adults and older adults. Mohammedin et al. conducted a study to understand the correlation between blood pressure and hydration levels. It was concluded that hypertensive patients had lower total body water in comparison to the normotensive patients. Plausible reasons for these results are elevated levels of serum sodium triggering inflammatory mediators, resulting in endothelial layer dysfunction and impairment of peripheral artery vasodilatory capacity. Also, elevated levels of angiotensin II in a dehydrated state can elicit vasoconstrictive effects.[21] It was also observed that dehydration is common in nondiabetic adults and older adults with fever, upper respiratory tract infection (URTI), and dengue. The physiological reasons for dehydration with fever are well known, which include insensible losses of fluids and electrolytes. Dehydration is known to be well associated with dengue. Anorexia, increased water loss due to fever, and vomiting during the febrile phase of dengue result in a hypohydration state.[22]

The EMR platform is available in specific settings, particularly urban ones, and hence the reach to HCPs is limited. Additionally, the number of HCPs every year depends on their enrollment to the platform, which may have impact on this data. The EMR platform has distinct free-text fields for diagnosis and complaints. At times, doctors may not add every symptom, leading to missing data. These issues limit the findings of this study; however, it is consistent with clinical practice scenarios.

Conclusion

This is the first study reporting the prevalence of nondiarrheal dehydration in adults and older adults. The current numbers for dehydration appear to be on a lower side. Of the data studied, prevalence proportion was higher for older adults. There is a need to highlight the significance of documentation of dehydration associated with nondiarrheal illnesses among HCPs. Adequate reporting and management are expected to avoid many serious consequences of dehydration in adults and older adults.

Disclosure

This study was sponsored by JNTL Consumer Health (India) Pvt. Ltd.

Acknowledgments

The authors are grateful to HealthPlix (a third-party research agency), which provided support for conducting the literature search, electronic medical records data aggregation and analysis, medical writing support, which was funded by JNTL Consumer Health (India) Private Limited.

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ORIGINAL ARTICLE

Prevalence of Dehydration and Use of Oral Electrolytes in Adults and Older adults with Nondiarrheal Conditions: A Retrospective, Real-world, Database Study

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Abstract

Introduction: Dehydration due to nondiarrheal conditions often goes underrecognized. Physicians rely on the guidelines for the treatment of diarrheal dehydration to treat nondiarrheal dehydration. However, treatment of nondiarrheal dehydration requires fluid, electrolyte, and energy (FEE) drinks with additional energy, which help overcome the FEE deficits created due to hypermetabolic response to such conditions.

Methodology: Anonymized and aggregated data retrieved from the HealthPlix electronic medical record (EMR) database was used to understand the usage of oral electrolytes in nondiarrheal conditions in nondiabetic patients and their effect on the resolution of fever and respiratory tract infection (RTI).

Results: There was a significant gap between the number of patients with documented dehydration and those prescribed oral electrolytes. ORSL® emerged as the top prescription choice for multiple conditions and symptoms among the products studied. Recovery from fever was relatively faster in the case of the patients prescribed oral electrolytes. The proportion of patients resolved from RTI was higher for the oral electrolyte arm. This suggests the crucial role of oral electrolytes to support recovery from nondiarrheal conditions.

Conclusion: Dehydration in nondiarrheal conditions should be appropriately examined and documented in the prescriptions. There exists a need to highlight the importance of prescribing oral electrolytes with standard medical care to benefit the patients.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1088

Introduction

Dehydration is known to negatively impact the older population more than younger adults and can go undetected.[1–3] This becomes even more severe in the case of those with multiple chronic conditions.[3,4] There are formal guidelines by the World Health Organization (WHO) for the treatment of diarrheal dehydration. The treatment relies on the use of WHO oral rehydration solution (ORS) that comprises fluids and electrolytes (sodium and potassium) with a small amount of glucose. These ingredients aid the absorption of sodium and water in the small intestine and help replace the lost ions.[4,6]

Acute nondiarrheal conditions like dengue, malaria, typhoid, respiratory tract infections (RTI), and others can also lead to subclinical dehydration, creating imbalances in fluid, electrolyte, and energy (FEE).[4,6,7] Patients generally feel anorexia during phases of such illnesses and might require an extra component of energy to overcome the hypermetabolic response. Recommendations to have solid food during illness might result in low patient compliance, as the patients would find it difficult to consume solids, whereas consumption of fluids would be easier and more convenient for them. Additionally, patients might find the WHO ORS unpalatable due to its strong salty taste. Aseptically packed, ready-to-drink (RTD) FEE drinks with added glucose have improved palatability and are convenient for consumption.[4,6]

This is the first study to highlight the usage of oral electrolytes in the real world. The data was also analyzed to evaluate and compare the resolution of fever and RTI in patients who were prescribed oral electrolytes with the ones who were not.

Methodology

Anonymized and aggregated data for this study (January 2017 to March 2023) was retrieved from the electronic medical record (EMR) database of HealthPlix Technologies Private Limited (https://healthplix.com/). The study was approved by the Royal Pune Independent Ethics Committee (EC approval number: RPIEC341023) on 26th October 2023.

The study included adults (≥18 to <60 years) and older adults (≥60 years) of either gender diagnosed with nondiarrheal diseases who were prescribed oral electrolytes. Patients diagnosed with diarrheal diseases (had a mention of diarrhea, loose motions, gastroenteritis, and related terms), administered systemic electrolyte therapy, used homemade oral rehydration fluids, and suffered from chronic illness such as cardiac failure, renal failure, and liver ailments (e.g., ascites, liver cirrhosis, and acute pancreatitis) were excluded. For symptom resolution, data of patients who had a follow-up visit within 10 days of diagnosis of nondiarrheal diseases and prescription of oral electrolytes was retrieved and analyzed. Persons with diabetes (type 1 or 2) were also excluded.

Statistical Analysis

The proportion of patients prescribed oral electrolytes for different conditions and symptoms was presented as frequency and percentage. For assessment of symptom resolution, patients were divided into two arms—an oral electrolyte arm and another in which patients were not prescribed oral electrolytes for similar conditions. The two arms were made comparable using propensity score matching (PSM), a quasi-experimental method. Factors like age, gender, diabetic status (nondiabetic), and indications such as fever and RTIs were considered in this matching process. Missing data was not imputed. Subsequently, these matched groups were analyzed to assess how effectively symptoms were resolved in patients in both

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How to cite this article: Bhatia S, Chawla M, Thakor P, *et al.* Prevalence of Dehydration and Use of Oral Electrolytes in Adults and Older adults with Nondiarrheal Conditions: A Retrospective, Real-world, Database Study. J Assoc Physicians India 2025;73(8):11–15.

arms. *p*-values and confidence intervals (CI) were computed for both the arms.

Results

Prevalence of Dehydration and Prescription of Oral Rehydration Products

There was a significant difference between the number of patients who were diagnosed with dehydration and the number of patients who were recommended oral electrolytes. Of the RTD electrolytes studied, ORSL® was the most prescribed among adults and older adults (Table 1).

Recommendation of Oral Electrolytes for Nondiarrheal Conditions as Adjuvants to Restore Fluid Electrolytes Energy

Oral electrolytes were commonly prescribed for conditions like dengue, typhoid, dehydration, and malaria. Among RTD electrolytes, ORSL® was the top prescription choice for all these conditions. The prescription preferences were the same for the adult patients, where gastritis, RTIs, dengue, typhoid, dehydration, and malaria were the common conditions for the prescription of oral electrolytes, and ORSL® was the most prescribed. In the case of older adults, the maximum prescriptions of ORSL® were for dengue, typhoid, and dehydration (Table 1 of Supplementary Material).

Recommendation of Oral Electrolytes as Adjuvants to Restore Fluid Electrolytes Energy for Nondiarrheal Symptoms—Adults and Older Adults

In nondiabetic patients, maximum prescriptions of oral electrolytes were observed for patients with complaints of dry cough, body ache, dehydration, chills, and vomiting. ORSL® was observed to be the top RTD prescription choice for all the symptoms for which oral electrolytes were the most prescribed. ORSL® was the most prescribed for adults too, for the complaints of dry cough, body ache, dehydration, and vomiting. In the case of older adults, ORSL® was the most recommended for the symptoms of dry cough, body ache, chills, and vomiting. ORSL Plus® was the most prescribed in the case of dehydrated older adults (Table 2 of Supplementary Material).

Daily Recommendation of Oral Electrolyte Formulations

There are no specific dosage recommendations for ORSL®, ORSL Plus®, and ORSL Rehydrate®. From the analysis of the EMR data, it was observed that the maximum proportion of adult patients were prescribed ORSL® and ORSL Plus® on a thrice-a-day (TID) regimen. However, a twice-a-day (BID) schedule was the most recommended.

In the case of older adults, ORSL® was prescribed with a TID schedule to the maximum number of patients. ORSL Plus® and ORSL Rehydrate® were mostly prescribed with a BID regimen (Fig. 1).

Duration of Recommendation of Oral Electrolytes—Adults and Older Adults

From the data evaluated, it was observed that in the case of adult patients, the maximum prescriptions of ORSL®, ORSL Plus®, and ORSL

Table 1: Prevalence of dehydration and prescription of oral electrolyte products

		Adults n (%)	*Older adults n (%)*
Prevalence of dehydration	Dehydration reported	3451 (0.026)	666 (0.022)
Rehydration products	Oral electrolytes*	154306 (1.16)	20342 (0.66)
	RTD electrolytes	43991 (28.51)	5266 (25.89)
	ORSL®	10173 (23.13)	960 (18.23)
	ORSL Plus®	3465 (7.88)	417 (7.92)
	ORSL Rehydrate®	2178 (4.95)	299 (5.68)
	All other RTD electrolyte brands (except ORSL® formulations)	28175 (64.04)	3590 (68.17)

*Nondiabetic patients with nondiarrheal illnesses prescribed oral electrolytes; Percentages for RTD electrolytes were calculated based on the number of patients prescribed oral electrolytes; Percentages for ORSL®, ORSL Plus®, and ORSL Rehydrate® were calculated by taking the number of patients prescribed with RTD electrolytes; RTD, ready-to-drink

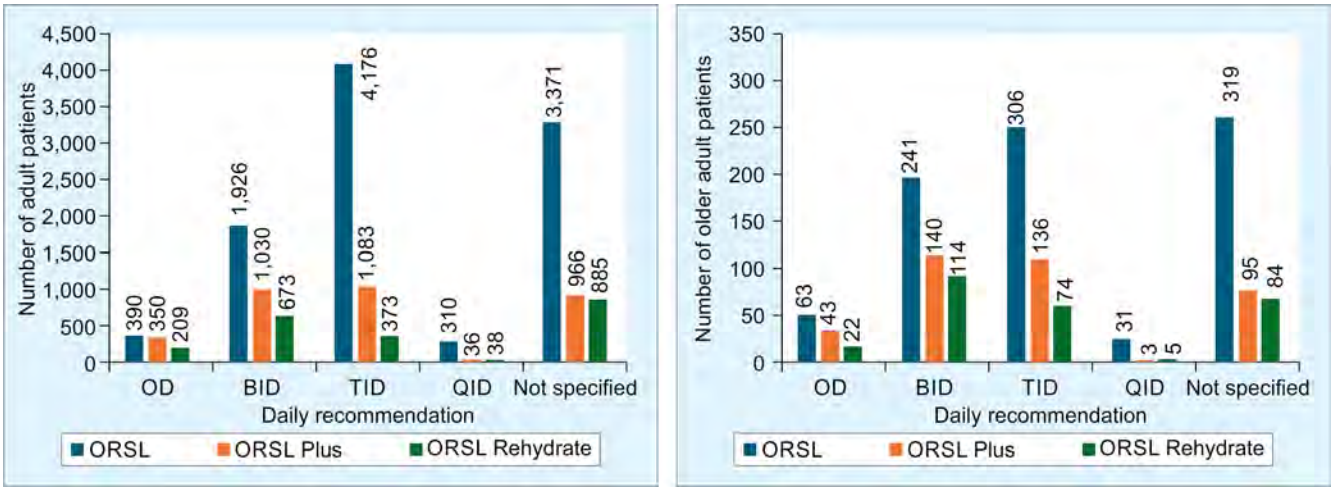

Fig. 1: Daily recommendation of oral electrolyte formulations

Rehydrate® were for 1–3 days. The pattern was the same for older adults (Fig. 2).

Symptom Resolution in Patients Prescribed with Oral Electrolytes and Patients Not Prescribed with Oral Electrolytes, Fever, and Respiratory Tract Infections—Adults and Older Adults

Patients who had a follow-up visit within 10 days of diagnosis of nondiarrheal conditions were included in this analysis. A higher proportion of adults and older adults who did not receive oral electrolytes showed resolution of fever compared to those who received electrolytes. The reverse was true in the case of RTI, where a higher proportion of patients who were prescribed oral electrolytes showed resolution of RTI (Fig. 3). These outcomes could be due to multiple factors, including the primary treatments.

Duration of Resolution of Fever

The proportion of patients given ORSL® variants tend to recover faster from fever compared to those who were not given any oral electrolytes (Table 2).

Discussion

Dehydration due to nondiarrheal conditions is generally overlooked. From our study, it was observed that there was a huge difference between the number of patients with a mention of dehydration (n = 4,117) and the number of patients who were prescribed oral electrolytes (n = 174,648). This gap indicates underreporting of the condition in the prescriptions. This might be because mentioning dehydration as a complaint/diagnosis is not a routine practice. A study was done by Shetty et al. to evaluate prescriptions from tertiary care hospitals across India. On analysis of the prescriptions, it was reported that 1,870 of 4,838 prescriptions were incomplete.[8] Incomplete prescriptions might also be one of the reasons for the underreporting observed from our data.

In the case of nondiarrheal conditions, there is a requirement for an additional energy component due to the hypermetabolic response, and patients might be anorectic during the phase of such illnesses. In such conditions, physicians generally extrapolate the guidelines for diarrheal conditions and may prescribe the WHO ORS, which may or may not support the patient. However, besides fluid and electrolyte deficits, such conditions are often accompanied by energy deficits too. Therefore, prepacked drinks with added energy (glucose) and better palatability could help overcome the FEE deficits in such conditions.[4,6]

From the RTD formulations evaluated in our study, ORSL® was observed to be the top prescription choice for several conditions and symptoms. In a prospective, interventional, real-world study conducted by Reddy et al., statistically significant improvements were observed in the energy levels 6 hours post-first consumption of a FEE RTD formulation (ORSL®). RTD FEE formulations like ORSL® drinks are aseptically packed fruit-based juice drinks containing electrolytes, vitamin C, and carbohydrates.[9] This aspect of RTD electrolytes may influence prescribing patterns. Evidence suggests that healthcare providers preferentially recommend RTD electrolyte formulations over traditional ORS, especially in scenarios where rapid hydration and electrolyte replenishment are needed without additional preparation.[10]

In our analysis, ORSL® products were mostly prescribed for 1–3 days with a BID or TID regimen. In a previously reported study, it was noted that three packs of ORSL® a day for the first 3 days of illness were effective in hydration and providing energy to patients with fever and/or general weakness.[9]

Further, it was observed that recovery from fever tend to be faster in the case of patients prescribed oral electrolytes like ORSL® variants. This aligns with the role of electrolytes in supporting hydration and potentially aiding in faster recovery from conditions causing fever.[9] The data on symptom resolution for RTIs highlighted the higher resolution rates among the patients prescribed oral electrolytes compared to those who were not. This suggests that oral electrolytes may contribute to support recovery in RTIs.[11]

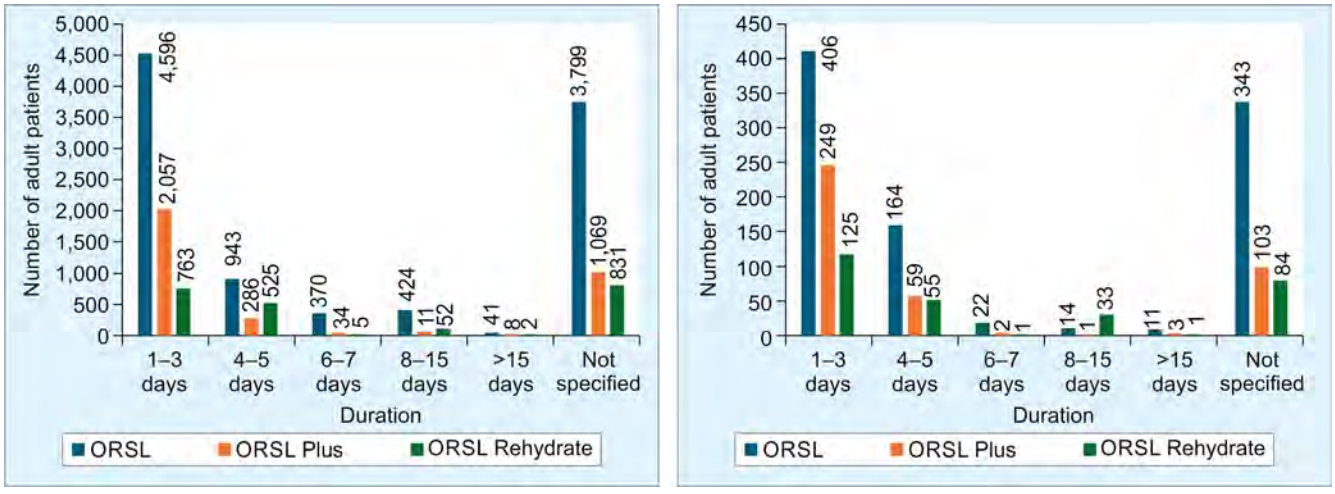

Fig. 2: Duration of prescription of oral electrolytes

Table 2: Duration of resolution of fever (in days)—adults and older adults

	Adult patients		*Older adult patients*	
Statistics	*ORSL® variants*	*No oral electrolyte*	*ORSL® variants*	*No oral electrolyte*
n	1590	2029	231	295
Mean	4.44	5.08	4.65	5.71
SD	2.41	2.44	2.55	2.42

n, number of patients; SD, standard deviation

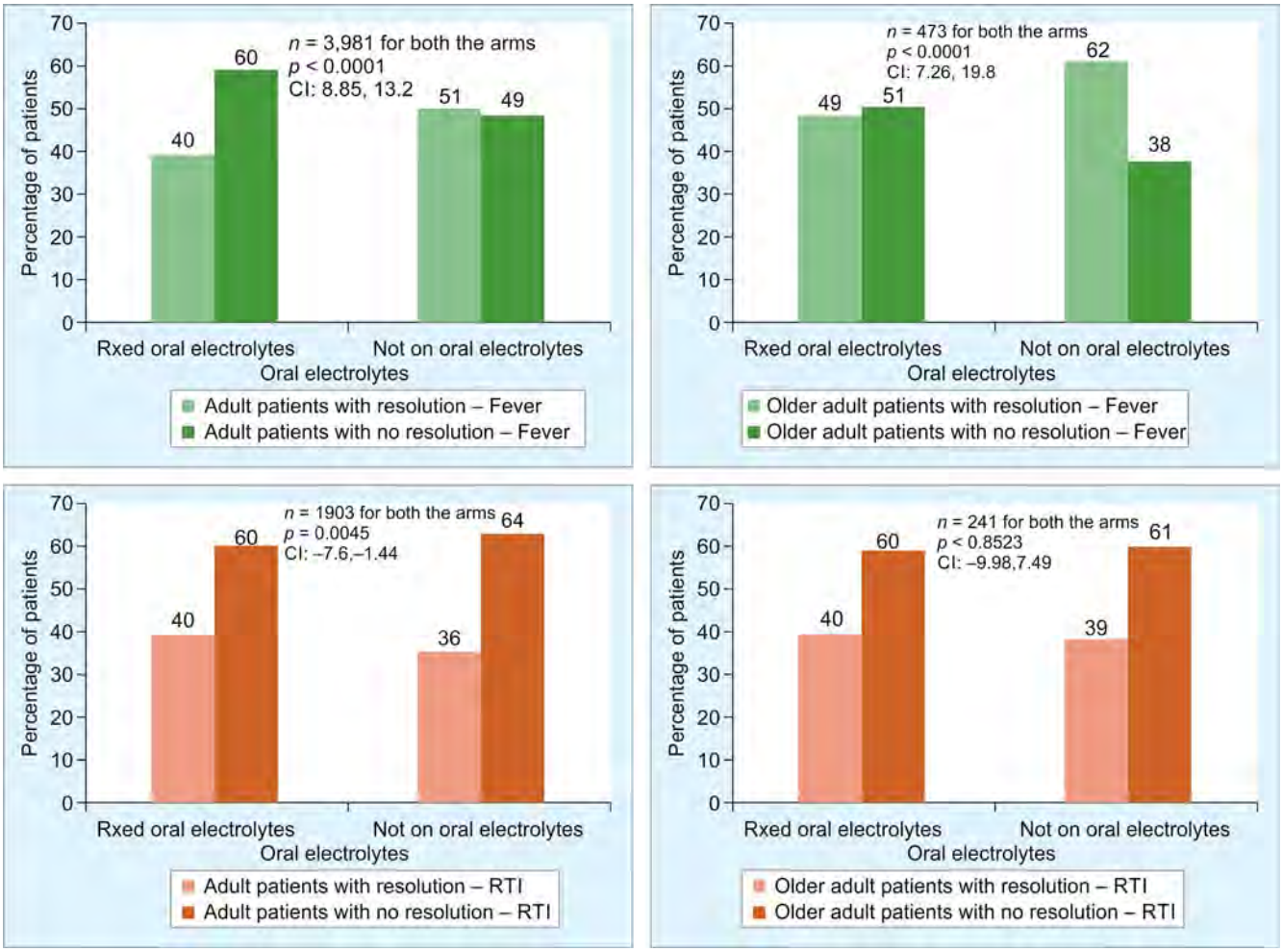

Fig. 3: Symptom resolution in adults and older adults

The study has inherent limitations considering its retrospective nature. Since this study involves the EMR, there might be limitations in the data capture or missing data points. Not all the fields in the EMR might be filled by the doctors. Concurrent treatments for fever, RTI, and other nondiarrheal conditions may have impacted the recovery from these nondiarrheal conditions. However, the importance of adjunct treatment in the form of fluid, electrolytes, and energy cannot be undermined.

Conclusion

This study highlights the underreporting of dehydration due to nondiarrheal conditions. Among RTDs, ORSL® emerged as the preferred variant across different conditions and symptoms. The resolution of RTI symptoms was better for the oral electrolyte arm; however, the results were opposite in the case of resolution of fever, though it was observed that recovery from fever tended to be faster when oral electrolytes like ORSL® variants were used compared to no oral electrolytes. Considering the preference of RTDs in various conditions and their positive effect recovery, the study encompasses the crucial role of oral electrolytes in nondiarrheal conditions.

Supplementary Material

Supplementary files are available with the author. Please connect with the author for the supplementary content.

Disclosure

This study was sponsored by JNTL Consumer Health (India) Pvt. Ltd.

Acknowledgments

The authors are grateful to HealthPlix (a third-party research agency), which provided support for conducting the literature search, electronic medical records data aggregation and analysis, medical writing support, which was funded by JNTL Consumer Health (India) Private Limited.

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ORIGINAL ARTICLE

Prevalence of Dehydration and Use of Oral Electrolytes in Diabetic Adults and Older Adults with Nondiarrheal Conditions: A Retrospective, Real-world, Database Study

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Abstract

Introduction: Pediatric and geriatric populations are at a greater risk of dehydration than the adult population. Diabetes plays a synergistic role and makes persons with diabetes more susceptible to dehydration. Nondiarrheal conditions like fever, infections, nausea, vomiting, heat-related illnesses, tropical illnesses like dengue, malaria, etc., increase the insensible fluid and electrolyte losses and make patients susceptible to dehydration. However, there is hardly any evidence on the incidence or prevalence of the same. There is no data available on nondiarrheal dehydration and the use of oral electrolytes in persons with diabetes.

Methodology: This retrospective observational study was conducted using anonymized and aggregated data from the HealthPlix electronic medical records (EMR) database.

Results: There was a large difference between the number of patients with dehydration documented in their prescriptions and those prescribed oral electrolytes, suggesting the underreporting of dehydration. ORSL Rehydrate®, a low-sugar variant of ORSL®, suitable for diabetic patients, was observed to be the preferred prescription choice for patients with symptoms like chills, vomiting, and others. However, for some of the conditions, other variants were the most prescribed. These variants were mostly prescribed for 1–3 days with twice daily (BID) or thrice daily (TID) regimen. Recovery from fever tends to be faster in the case of patients prescribed ORSL® variants.

Conclusion: There is a need to emphasize the documentation of dehydration in prescriptions and prescribe the most suited variant of oral electrolytes for diabetic patients. Prescription of oral fluid, electrolyte, and energy (FEE) drinks along with the standard of care treatment supports patients of nondiarrheal conditions for faster recovery.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1089

Introduction

India has the world's second-largest population with diabetes. A study reported that India had 74.9 million diabetics within the age-group of 20–79 years in the year 2021 and is projected to increase to 124.9 million by 2045.[1] Persons with diabetes are at increased risk of dehydration due to the pathophysiology of diabetes, which leads to hyperglycemia and osmotic diuresis.[2] Certain treatments for the management of type 2 diabetes further increase the risk of dehydration, for example, SGLT-2 inhibitors. Elderly are known to be more prone to dehydration due to age-related physiological changes, reduced sensitivity to vasopressin, and alterations in water and sodium balance. Also, with age and numerous medications for various impairments, disabilities, or comorbidities, the risk of dehydration increases.[2–6]

Dehydration due to diarrhea is a well-studied topic with formal management guidelines. However, dehydration due to nondiarrheal conditions like diabetes, fever, tropical fevers, nausea, vomiting, and respiratory tract infections often remains unrecognized and unreported.[6] Currently, there is hardly any epidemiological data reported for nondiarrheal dehydration in diabetic patients.

Hydration and electrolyte balance are important aspects of managing such nondiarrheal conditions.[7] Oral rehydration solution (ORS) is an oral powder containing a mixture of salts to manage diarrheal dehydration.[8] Management of dehydration in the case of nondiarrheal conditions requires fluids and electrolytes with an additional energy component that can help overcome the fluid, electrolyte, and energy (FEE) deficits created in such conditions. These FEE deficits are generated due to the hypermetabolic response to such nondiarrheal conditions. Patients might also feel anorectic during such phases, and recommendations to have solids for energy might result in lower patient compliance. Patients generally find the typical World Health Organization (WHO) ORS unpalatable due to the strong salty taste. However, the addition of glucose as a source of energy to fluid-electrolyte drinks can help address the energy deficits, improve palatability, and increase patient compliance. Aseptically packed ready-to-drink (RTD) formulations are convenient for consumption.[9,10] Consensus recommendations by Reddy et al. mentioned that oral FEE drinks should be prescribed along with the core treatment from day one of acute nondiarrheal conditions.[6] To date, data on the use of oral electrolytes for nondiarrheal conditions in the diabetic population are unavailable. Hence, this study was planned to understand the usage of oral electrolytes in real-world settings. The data were also analyzed to understand the effectiveness of these oral electrolytes in nondiarrheal illnesses like fever and respiratory tract infections (RTIs).

Methodology

Anonymized and aggregated data of patients who met the eligibility criteria (January 2017 to March 2023) were retrieved from the electronic medical records (EMR) database of HealthPlix (https://healthplix.com/). The study was approved by the Royal Pune Independent Ethics Committee (EC approval number: RPIEC341023) on 26th October 2023.

The study included diabetic adults (≥18 to <60 years) and older adults (≥60 years) of either gender diagnosed with diabetes and nondiarrheal diseases who were prescribed oral electrolytes. Patients diagnosed with diarrheal diseases, prescribed systemic

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How to cite this article: Chawla M, Bhatia S, Thakor P, *et al.* Prevalence of Dehydration and Use of Oral Electrolytes in Diabetic Adults and Older Adults with Nondiarrheal Conditions: A Retrospective, Real-world, Database Study. J Assoc Physicians India 2025;73(8):16–20.

electrolyte therapy, advised homemade oral rehydration fluids, and those with chronic illnesses such as cardiac failure, renal failure, and liver conditions like ascites, liver cirrhosis, and acute pancreatitis were excluded from the study. For evaluation of symptom resolution, patients who had a follow-up visit within 10 days of diagnosis of nondiarrheal conditions were considered. Patients were divided into two arms—one where patients were prescribed oral electrolytes and another in which patients were diagnosed with nondiarrheal illnesses but were not prescribed oral electrolytes.

Statistical Analysis

Prescription of oral electrolytes for different conditions and symptoms has been presented as frequency and percentage. Propensity score matching (PSM), a quasi-experimental technique, was used to make the number of patients in the two arms comparable. Factors such as age, gender, diabetic status, and indications like fever and RTIs were considered for matching. Missing data were not imputed. Confidence interval (CI) and *p*-values were calculated for both arms.

Results

Prevalence of Dehydration and Prescription of Oral Rehydration Products

Dehydration was reported for a very small proportion of patients. A large disparity was observed between these and the number of patients prescribed oral electrolytes. This indicates that dehydration is a highly underreported condition. Of the RTDs evaluated, ORSL® was the most prescribed brand for both adults and older adults (Table 1).

Indications for Prescription of Oral Electrolytes as Adjuvants to Restore Fluid Electrolytes Energy

Though hypertension and hyperthyroidism appeared as indications where oral electrolytes were commonly prescribed, it could be due to the frequent co-occurrence of diabetes with hypertension as part of metabolic syndrome, which is common in India. Oral electrolytes were frequently prescribed for COVID-19, RTIs, dengue, typhoid, dehydration, thrombocytopenia, and malaria. Within the RTD formulations evaluated, ORSL Rehydrate® was the preferred choice in persons with diabetes and nondiarrheal conditions.

In adult patients, oral electrolytes were mostly prescribed for COVID-19, RTIs, UTIs, fever, dengue, dehydration, typhoid, and malaria. Of dengue patients prescribed RTD electrolytes, ORSL Rehydrate® was the most prescribed. For dehydration, ORSL Plus® was prescribed to the maximum proportion of patients. Among patients diagnosed with typhoid, 22.22% were advised RTD electrolytes. In the case of patients suffering from UTI, ORSL® was the most recommended.

Among older adults, typhoid, dehydration, dengue, malaria, thrombocytopenia, and fever were the most common conditions for which oral electrolytes were recommended. These indications are presented in Table 1 of the Supplementary Material.

Prescription of Oral Electrolytes as Adjuvants to Restore Fluid Electrolytes Energy for Nondiarrheal Symptoms

In patients with type 2 diabetes mellitus (T2DM), the highest prescriptions of oral electrolytes were for those with symptoms of dry cough, body ache, dehydration, chills, and vomiting. Among the RTDs evaluated, ORSL Rehydrate® was prescribed to the highest proportion of patients with dry cough. For patients experiencing body ache too, ORSL Rehydrate® was the most prescribed. Of the patients with symptoms of dehydration, RTD electrolytes were recommended for 27.27% of patients, and of this subset, ORSL® was the most recommended. ORSL Rehydrate® was most prescribed for chills, and ORSL® was most prescribed for vomiting.

Among adult patients, the maximum prescription for oral electrolytes was observed for patients with symptoms of dry cough, body ache, dehydration, chills, and vomiting. ORSL Rehydrate® was most prescribed for dry cough. In the case of patients with body ache, the prescription of ORSL® was slightly higher than ORSL Rehydrate®. Among dehydrated patients prescribed RTDs, ORSL Rehydrate® was the most advised. ORSL®, followed by ORSL Rehydrate®, were the preferred variants for vomiting.

The prescribing patterns for oral electrolytes in the older adult population closely mirrored those of adults. The common symptoms for which oral electrolytes were recommended were dry cough, body ache, dehydration, chills, and vomiting. In the case of older adults too, ORSL Rehydrate® was most prescribed for dry cough. This was the most recommended variant for chills as well. The trend for resolution of vomiting was also similar to the adult population, where ORSL®, followed by ORSL Rehydrate®, was most advised.

Daily Recommendation of Oral Electrolyte Products—Adults and Older Adults

No guidelines specify a recommended dosage for ORSL®, ORSL Plus®, and ORSL Rehydrate®. ORSL® was most frequently prescribed twice daily (BID), followed by thrice daily (TID). ORSL Plus® was predominantly recommended to adult patients with a BID regimen, whereas ORSL Rehydrate® was prescribed TID.

In the case of older adults, most of the patients were advised a TID schedule for ORSL® and ORSL Rehydrate®, and BID for ORSL Plus® (Fig. 1).

Duration of Recommendation of Oral Electrolytes—Adults and Older Adults

ORSL® was mostly recommended to adult patients for a duration of 1–3 days, followed by 4–5 days. ORSL Plus® was recommended for 1–3 days to the highest number of patients.

Table 1: Prevalence of dehydration and prescription of oral electrolytes

		Adults n (%)	*Older adults n (%)*
Prevalence of dehydration	Diabetic patients	23,59,652	13,77,787
	Dehydration reported	547 (0.023)	253 (0.018)
Rehydration products	Oral electrolytes*	6886 (0.29)	4898 (0.36)
	RTD electrolytes	2442 (35.46)	1690 (34.50)
	ORSL®	388 (15.89)	304 (17.99)
	ORSL Plus®	156 (6.39)	124 (7.34)
	ORSL Rehydrate®	218 (8.93)	164 (9.70)

*Diabetic patients with nondiarrheal illnesses prescribed oral electrolytes; Percentages for RTD electrolytes were calculated based on the number of patients prescribed oral electrolytes; Percentages for ORSL®, ORSL Plus®, and ORSL Rehydrate® were calculated by taking the number of patients prescribed with RTD electrolytes; RTD, ready-to-drink

Maximum prescriptions for ORSL Rehydrate® were for 4–5 days. The prescription trend for older adults was similar to that of adult patients. ORSL® was maximally prescribed for a window of 1–3 days, whereas ORSL Plus® and ORSL Rehydrate® were advised for 4–5 days (Fig. 2).

Resolution of Fever and Respiratory Tract Infection Symptoms

Resolution of fever and RTI in both adult and older adults with diabetes was observed to be better in the case of patients who were not prescribed oral electrolytes (ORSL® formulations). However, there was no statistically significant difference in symptom resolution for both conditions across both groups (Fig. 3). Such comparison needs to be done with a higher sample size to obtain any statistically significant difference. Also, many confounding factors, like concurrent treatments and limited data capture in records, may have impacted the outcomes.

Duration of Resolution of Fever

The mean duration of resolution of fever was shorter for the group of patients who were prescribed ORSL® formulations. The observation was similar for both adults and older adults, indicating a trend toward faster recovery for the patients who received ORSL® formulations (Table 2), though the difference was not statistically significant.

Discussion

Increased blood sugar levels exert an osmotic pressure that leads to a shift of body water from the intracellular to the extracellular space, preserving blood osmolality and volume at the cost of cellular dehydration. Diabetes can also raise the risk of dehydration through increased urinary output.[11] Additionally, various nondiarrheal conditions like fever, infections, nausea, and vomiting increase the risk of dehydration through insensible fluid and electrolytes loss. To date, there is no data on nondiarrheal dehydration in diabetic patients and the use of oral electrolytes.

A disparity was observed between the number of patients diagnosed with dehydration and the number of patients prescribed oral electrolytes. This highlights the gap in reporting this condition and handling incomplete prescriptions. This aligns with the study by Joshi et al., which reported that 38.65% of the prescriptions ($n = 4,838$) were incomplete.[12] The data suggest that in the case of adults diagnosed with dengue, ORSL Rehydrate® was the most prescribed, whereas ORSL® was the preferred choice in the case of UTIs. ORSL Rehydrate® was prescribed to the maximum number of diabetic adults and older adults for symptoms of dry cough, vomiting, and chills. ORSL Rehydrate® can be observed as a preferred option because it is a low-sugar variant and more suitable for the diabetic population.

ORSL® drink is a food product categorized as an electrolyte drink by the Food Safety and Standards Authority of India (FSSAI). It is a fruit-based drink constituting electrolytes (sodium, potassium, and chloride), vitamin C, and carbohydrates.[13] A prospective, real-world study was conducted by Reddy et al. to

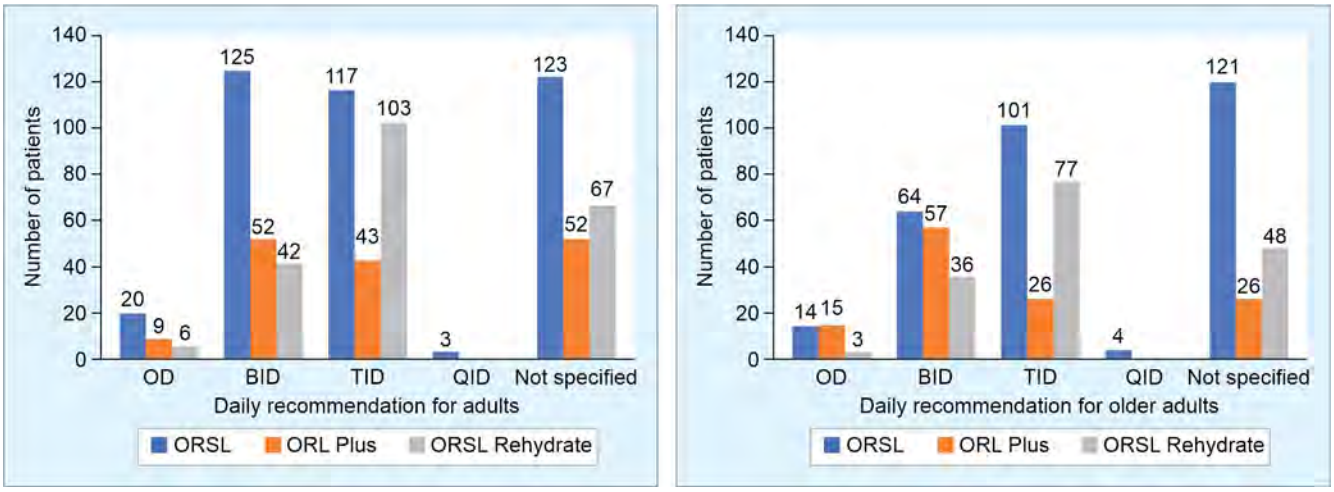

Fig. 1: Daily recommendation of oral electrolyte products—adults and older adults

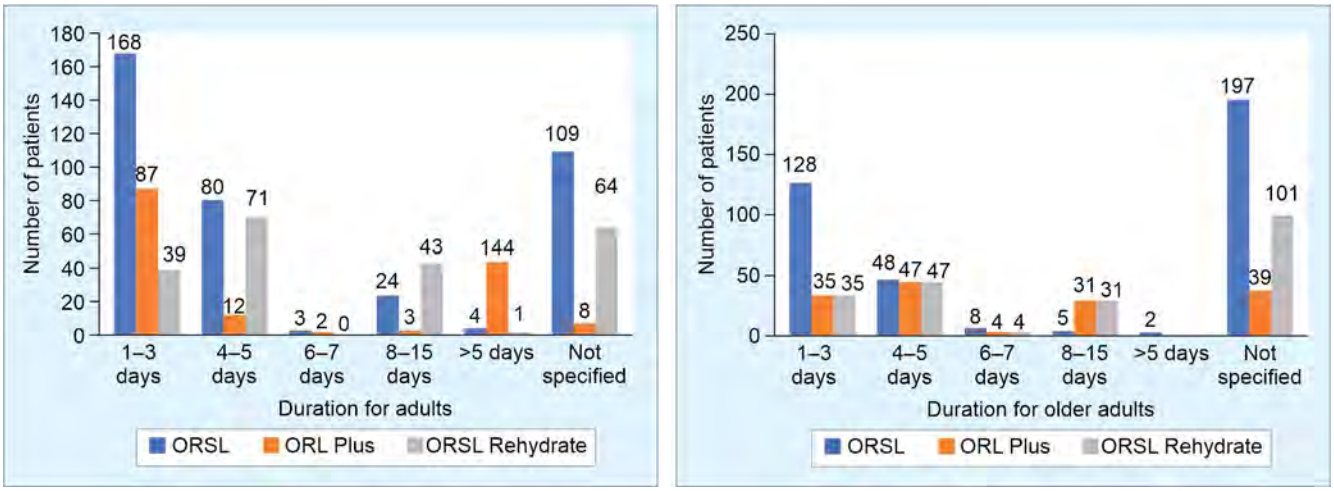

Fig. 2: Duration of recommendation of oral electrolytes—adults and older adults

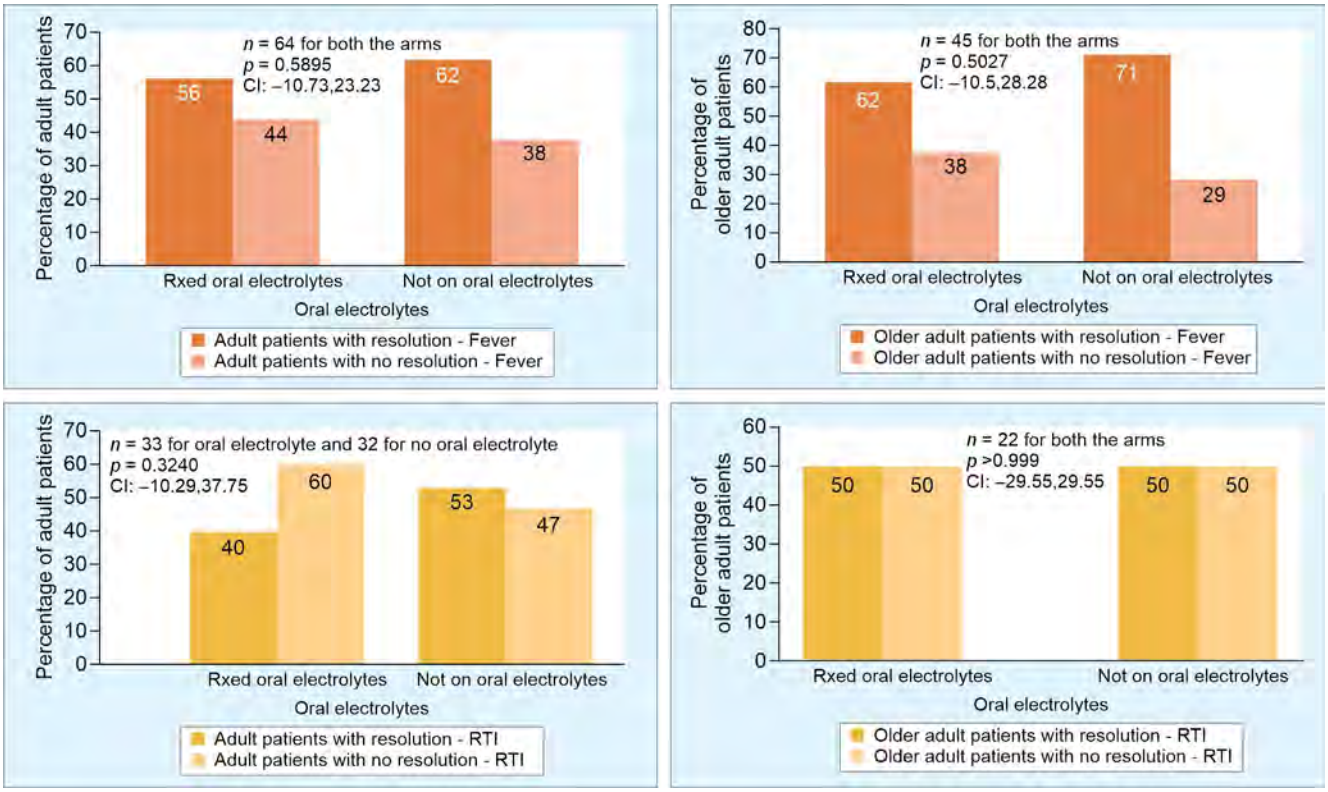

Fig. 3: Resolution of fever and RTIs—adults and older adults

Table 2: Duration of resolution of fever

Parameter	*Adult patients*		*Older adult patients*	
	ORSL® formulations	*No oral electrolyte*	*ORSL® formulations*	*No oral electrolyte*
n	36	40	28	32
Average days	5.53	5.80	5.18	6.28
SD	2.96	2.64	2.33	2.13

n, number of patients; SD, standard deviation

evaluate the effectiveness of ORSL® variants as an adjuvant with the standard of care in patients with nondiarrheal illnesses with fever and/or general weakness. ORSL® variants were found to be clinically effective in both conditions for providing hydration and energy.[13] In our study, ORSL® variants were either prescribed TID or BID and were mostly prescribed for 1–3 days. In the study by Reddy et al., it was observed that an average of three ORSL® packs a day for the initial three days was effective in hydrating and energizing patients with fever and/or general weakness.[13] From our study, it was observed that the duration of fever was shorter for the group of patients who were prescribed oral electrolytes, which is in line with the reported literature.[13]

Conclusion

Timely recognition and management of dehydration in diabetic patients, particularly those with nondiarrheal illnesses, is imperative to save them from complications. This investigation reveals that dehydration risk extends beyond diarrhea, and physicians are prescribing oral electrolytes for curbing such symptoms. The prescription patterns indicated a preference for RTD electrolyte solutions, emphasizing their acceptance and perceived effectiveness in managing FEE deficits. There is a need to create awareness among physicians to prescribe the right variant of ORSL®, particularly for people with diabetes, where the low-sugar variant ORSL Rehydrate® needs to be preferred. Despite limitations in sample size, the findings suggest that oral electrolytes play a beneficial role in recovery from fever among diabetic patients. Overall, this research underlines the importance of hydration management in diabetic care to mitigate complications associated with nondiarrheal conditions.

Supplementary Material

Supplementary files are available with the author. Please connect with the author for the supplementary content.

Disclosure

This study was sponsored by JNTL Consumer Health (India) Pvt. Ltd.

Acknowledgments

The authors are grateful to HealthPlix (a third-party research agency), which provided support for conducting the literature search, electronic medical records data aggregation and analysis, medical writing support, which was funded by JNTL Consumer Health (India) Private Limited.

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ORIGINAL ARTICLE

Evaluation of the Anti-inflammatory, Phagocytic, and Antioxidant Potential of ORSL® Immunity+ in Lipopolysaccharide-stimulated Human Peripheral Blood Mononuclear Cells

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Abstract

Background: Maintaining optimal hydration and electrolyte balance is essential for immune function, as it supports cellular homeostasis and immune defense mechanisms. Electrolyte-based micronutrient drinks helps replenish essential nutrients, including zinc, selenium, and vitamin E, which play key roles in modulating immune responses, mitigating oxidative stress, and regulating inflammation. Lipopolysaccharide (LPS)-induced inflammation and oxidative stress are major contributors to immune dysfunction, necessitating interventions that enhance immune resilience.

Objective: To evaluate the immunomodulatory potential of ORSL® Immunity+ in mitigating inflammation, enhancing phagocytic activity, and providing antioxidant protection in LPS-stimulated peripheral blood mononuclear cells (PBMCs)

Materials and methods: PBMCs were isolated from human blood and stimulated with LPS to induce an inflammatory response. The effects of ORSL® Immunity+ on the immune function of treated cells were assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay for cytotoxicity, enzyme-linked immunosorbent assay (ELISA) for inflammatory markers [tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin 6 (IL-6), interferon gamma (IFN-γ), nitric oxide (NO)], oxygen radical absorbance capacity (ORAC) assay for antioxidant capacity, and phagocytosis assay.

Results: ORSL® Immunity+ demonstrated no cytotoxic effects on PBMCs. The treatment significantly reduced the levels of inflammatory markers, indicating an anti-inflammatory effect. Additionally, ORSL® Immunity+ enhanced phagocytic activity in a dose-dependent manner against *Escherichia coli,* suggesting improved immune response. Antioxidant capacity was also significantly increased, as evidenced by the ORAC assay, highlighting its potential in mitigating oxidative stress.

Conclusion: ORSL® Immunity+ exhibits promising immunomodulatory properties by reducing inflammation, enhancing phagocytosis, and improving antioxidant potential in LPS-stimulated PBMCs. These findings support a potential role in immune health alongside improving hydration status, warranting further clinical evaluation.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1090

Introduction

Dehydration negatively impacts immune function by disrupting fluid–electrolyte balance and cellular homeostasis, leading to impaired immune defenses and increased susceptibility to infections. Even mild dehydration can weaken immunity by reducing lymphocyte proliferation and cytokine production.[1] Furthermore, micronutrient deficiencies, particularly in vitamin C, B_6, B_{12}, E, folic acid, sodium, potassium, calcium, zinc, iron, magnesium, copper, and selenium levels, can disrupt immune regulation and exacerbate immune dysfunction by impairing antimicrobial protein synthesis.[2] Conversely, proper hydration and electrolyte replenishment play a vital role in supporting immune function, such as phagocytosis, cell migration, and antigen uptake. This reinforces the need for micronutrient-based formulations, including relevant electrolytes, to maintain immune resilience and overall well-being.[1]

Dehydration-associated inflammation and oxidative stress are key contributors to immune dysfunction, as they impair immunological signaling and defense mechanisms. Inflammation can lead to excessive production of reactive oxygen species (ROS), damaging lipids, proteins, and deoxyribonucleic acid (DNA), and further weakening immune responses.[3] Elevated nitric oxide (NO) levels worsen oxidative stress by inducing proinflammatory pathways and mitochondrial dysfunction, ultimately compromising immunological resilience. The resulting imbalance is associated with recurrent infections, inflammatory disorders, and delayed recovery, highlighting the necessity of antioxidant support to restore immune homeostasis.[4]

A fundamental cause of inflammation is lipopolysaccharide (LPS), a key component of gram-negative bacterial cell walls, which strongly induces immune activation in peripheral blood mononuclear cells (PBMCs). LPS binds to lipopolysaccharide-binding protein (LBP) and transfers to cluster of differentiation 14 (CD14), initiating downstream signaling pathways such as activator protein 1 (AP-1), phosphoinositide 3-kinase (PI3K), and nuclear factor kappa

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How to cite this article: Kalra S, Gilada T, Dabhi A, *et al.* Evaluation of the Anti-inflammatory, Phagocytic, and Antioxidant Potential of ORSL® Immunity+ in Lipopolysaccharide-stimulated Human Peripheral Blood Mononuclear Cells. J Assoc Physicians India 2025;73(8):21–27.

B (NF-κB) through toll-like receptor 4 (TLR4) activation.[5] This cascade leads to the release of proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interferon gamma (IFN-γ), which can exacerbate symptoms of infections.[6] Additionally, various stimuli—including cytokines such as TNF-α and interleukin-1 beta (IL-1β), damaged cell components, pathogen-associated molecular patterns (PAMPs), viral ribonucleic acid (RNA), toxins, allergens, and environmental irritants—can trigger inflammatory responses in PBMCs, further compounding immune dysregulation.

During infections and inflammatory conditions, excessive immune activation triggered by factors such as LPS can lead to heightened oxidative stress and fluid–electrolyte imbalance, especially in the context of dehydration. This imbalance impairs normal cellular function and weakens both innate and adaptive immunity, making targeted nutritional support essential for restoring immune balance.[5,6] Micronutrient supplementation plays a crucial role in counteracting these effects by supporting antioxidant defenses, modulating inflammatory pathways, and maintaining membrane integrity and immune cell function. The combination of zinc, selenium, and vitamin E is unique because their complementary and synergistic actions target multiple aspects of immune modulation, inflammation control, and antioxidant defense simultaneously.[7] Zinc enhances membrane integrity, regulates cytokines *via* the NF-κB pathway, supports regulatory T-cell function, and exhibits antiviral properties.[8] Selenium contributes to selenoprotein function, mitigates oxidative stress, and enhances natural killer (NK) cell activity.[9] Meanwhile, vitamin E strengthens NK and T-cell responses, protects cellular membranes, and may reduce respiratory infections.[10] Together, these micronutrients aid in maintaining immune balance, controlling inflammation, and reinforcing host defense mechanisms.

Hydration has well-established immunomodulatory effects and is particularly critical during acute conditions such as fever and infections, as it helps maintain fluid–electrolyte balance, supports temperature regulation through sweating, and preserves overall homeostasis.[1] Despite these benefits, along with those of antioxidants and micronutrients, the impact of micronutrient-based electrolyte drinks on immune function remains to be fully elucidated. Limited studies have explored their role in inflammation regulation, antioxidant defense, and immune cell activity. ORSL® Immunity+ is a scientifically formulated electrolyte drink containing optimal levels of electrolytes like Na, K, and Cl along with addition of purposeful micronutrients like zinc, selenium, and vitamin E, which are known to play key roles in immune modulation and providing hydration. By assessing the key mechanisms, this study aims to generate scientific evidence supporting the immune-modulating potential of ORSL® Immunity+ and its role in supporting immune balance, ultimately contributing to a better understanding of its impact on immune health.

Materials and Methods

Study Design

PBMCs were isolated from healthy donors and stimulated with LPS at a concentration of 1 µg/mL to induce an inflammatory response. The study included three test groups to assess the effects of ORSL® Immunity+. The experimental setup consisted of a negative control group (PBMCs without LPS stimulation), a positive control group (PBMCs stimulated with LPS but untreated), and treatment groups where PBMCs were stimulated with LPS and treated with ORSL® Immunity+.

ORSL® Immunity+ Composition and Dosages

The composition and dosages of ORSL® Immunity+ were determined based on the physiological plasma concentrations of key micronutrients to ensure optimal immune support.[6–10] The formulation includes essential vitamin and minerals known for their immunomodulatory properties, designed to address hydration and provide immune support in non-diarrheal conditions. This formulation was standardized to ensure consistency in bioavailability, enabling effective absorption and utilization of nutrients. Test solutions for active ingredients and excipients were identified from pharmacokinetic studies on zinc, selenium, and vitamin E as single-agent supplementation in healthy subjects.[11–13] Medium-dose ORSL® Immunity+ reflects the key ingredient levels closest to micronutrient plasma concentrations following supplementation. Low and high doses were included to generate a dose range for evaluating dose-response trends *in vitro*. Stock solutions of the active ingredients were prepared at appropriate concentrations and then diluted to obtain the working solutions for each test group, ensuring that the final concentration of elemental actives made up 100 µL per well. The experimental setup included defined test groups, with PBMCs treated under controlled conditions to evaluate the immunological impact of ORSL® Immunity+ at different concentrations (Table 1).

Peripheral Blood Mononuclear Cell Isolation and Lipopolysaccharide Stimulation

Peripheral blood mononuclear cells were isolated from freshly collected human blood using BD Vacutainer K2 EDTA tubes.[5,14–17] The collected blood was diluted with phosphate-buffered saline (PBS; pH 7.2) at a 1:2 ratio and carefully layered over 10 mL of Ficoll-Paque

Table 1: Test groups and preparation of working solutions for actives

Groups	*Test products*	*Doses*	*Actives (per 100 µL/well)*		
			Zn	*Se*	*Vit E*
Group I	Control	–	–	–	–
Group II	LPS	1 µg/mL	–	–	–
Group III	FML + LPS (1 µg/mL)	LD	3.4	0.23	16
Group IV	FML + LPS (1 µg/mL)	MD	6.8	2.3	28
Group V	FML + LPS (1 µg/mL)	HD	13.6	23	40

FML, finished formulation; LPS, lipopolysaccharide; RPMI, Roswell Park Memorial Institute; Se, selenium; Vit E, vitamin E; Zn, zinc

PLUS (ρ = 1.077 g/mL) for density gradient separation. After sequential centrifugation and PBS washes, the isolated PBMC pellet was then resuspended in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS) and adjusted to the desired cell concentration for further assays. To induce an inflammatory response, PBMCs in the positive control and treatment group were stimulated with LPS. The treatment group was additionally exposed to varying dosages of ORSL® Immunity+.

Experimental Assays and Analysis

Assessment of Cytotoxicity using MTT Assay

Cell cytotoxicity was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay in PBMCs.[16–19] Cells were seeded at a density of 1×10^3 cells/well in a 96-well plate and incubated with test products in triplicates at 37°C with 5% CO_2 for 24 hours. Following incubation, plates were centrifuged at 2500 rpm for 5 minutes, and the supernatant was discarded. The MTT solution (50 µL in PBS) was added to each well, gently shaken, and incubated for 3 hours. After removing the supernatant, 50 µL of dimethyl sulfoxide (DMSO) was added to dissolve the formazan crystals. Absorbance was measured at 540 nm using a microplate reader for cytotoxicity assessment.

Evaluation of Anti-inflammatory Activity

The anti-inflammatory activity of ORSL® Immunity+ was assessed by measuring the levels of proinflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ) and NO in LPS-stimulated PBMCs.[15,16,19] Cells (1×10^5 cells/well) were seeded in the well plates with RPMI 1640 medium and 10% FBS, treated with test products alongside 1 µg/mL LPS, and incubated at 37°C with 5% CO_2 for 24 hours. Following incubation, the cell supernatant was collected, centrifuged, and stored at −20°C. Cytokines and NO levels were quantified using standard enzyme-linked immunosorbent assay (ELISA) and colorimetric assay kits, following the manufacturer's protocol.

Phagocytosis Assay (Flow Cytometry with Fluorescein Isothiocyanate-labeled Escherichia coli)

Phagocytic activity of immune cells was assessed in LPS-stimulated PBMCs treated with ORSL® Immunity+ using flow cytometry.[15,17,18] PBMCs were isolated from human whole blood *via* the Lymphoprep method and seeded at a density of 1×10^5 cells/well in RPMI 1640 medium supplemented with 10% FBS. After treatment with the test formulations for 24 hours, cells were harvested, washed, and incubated with fluorescein isothiocyanate (FITC)-labeled *Escherichia coli* at a 1:2 ratio for 1–2 hours at 37°C in the dark. To differentiate between internalized and extracellular bacteria, trypan blue quenching solution was added, followed by washing with assay buffer. The phagocytic activity was quantified using flow cytometry (FL-1 channel) with excitation/emission wavelengths of 485/535 nm.

Assessment of Antioxidant Potential (Oxygen Radical Absorbance Capacity Assay)

The antioxidant potential of ORSL® Immunity+ was evaluated using the oxygen radical absorbance capacity (ORAC) assay.[14] Test products were diluted in saline at different concentrations, and 25 µL of each sample and antioxidant standard was added to a 96-well microtiter plate. Fluorescein solution (150 µL) was added to each well, mixed thoroughly, and incubated at 37°C for 30 minutes. A free radical initiator solution (25 µL) was then introduced, and the reaction mixture was homogenized by pipetting. Fluorescence intensity was measured at 480 nm excitation and 520 nm emission every 5 minutes for 60 minutes using a microplate reader.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism software (version 18.02263). Data were expressed as mean ± standard deviation (SD). One-way ANOVA followed by Dunnett's test was used to determine significant differences between ORSL® Immunity+ treatment groups and the LPS-treated control group. Additionally, the Kruskal–Wallis test was applied to assess statistical variations within the treatment groups. Significance thresholds were set at $p < 0.05$, $p < 0.01$, $p < 0.001$, and $p < 0.0001$.

Results

ORSL® Immunity+ Demonstrates No Significant Cytotoxicity

The *in vitro* cytotoxicity of ORSL® Immunity+, assessed using the MTT assay, demonstrated no significant cytotoxic effects on PBMCs. The percentage (mean ± SD) of cytotoxicity observed was 6.67 ± 1.25, 9.33 ± 0.54, and 12.89 ± 0.83 for groups III, IV, and V, respectively. According to ISO 10993-5 guidelines, which outline test methods for assessing the *in vitro* cytotoxicity, a reduction in cell viability by more than 30% compared to the untreated control is considered cytotoxic.[20] Since all tested concentrations of ORSL® Immunity+ exhibited cytotoxicity well below this threshold, the formulation was deemed nontoxic to PBMCs.

ORSL® Immunity+ Significantly Reduces Pro-inflammatory Cytokines and Nitric Oxide Levels

The anti-inflammatory potential of ORSL® Immunity+ was assessed by evaluating its impact on the levels of proinflammatory cytokines (TNF-α, IL-1β, IL-6, and IFN-γ) and NO in LPS-stimulated PBMCs. Group I exhibited baseline cytokine and NO levels,

Table 2: Concentration of proinflammatory cytokines and NO in PBMCs

Biomarker	*Group II*	*Group III*	*Group IV*	*Group V*
	LPS	*LD*	*MD*	*HD*
TNF-α (ng/mL)	0.1927 ± 0.0017	0.1619 ± 0.0019***	0.1517 ± 0.002****	0.1371 ± 0.0044****
IL-1β (ng/mL)	2.7175 ± 0.0351	2.2046 ± 0.0789****	2.1455 ± 0.0919****	2.0822 ± 0.0527****
IL-6 (ng/mL)	0.1700 ± 0.0013	0.1500 ± 0.0142	0.1390 ± 0.0044**	0.1166 ± 0.0139****
IFN-γ (ng/mL)	116.05 ± 0.65	114.25 ± 1.30	112.60 ± 1.53	110.91 ± 0.74***
NO (ng/mL)	34.636 ± 2.71	29.700 ± 2.71	27.232 ± 1.03	25.861 ± 2.42*

HD, high dose; IFN-γ, interferon gamma; IL-1β, interleukin-1 beta; IL-6, interleukin 6; LD, low dose; LPS, lipopolysaccharide; MD, medium dose; NO, nitric oxide; TNF-α, tumor necrosis factor alpha; Data represented by mean ± SD. Statistical significances are compared between the LPS-alone group vs various doses of ORSL® Immunity+; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, ****$p < 0.0001$

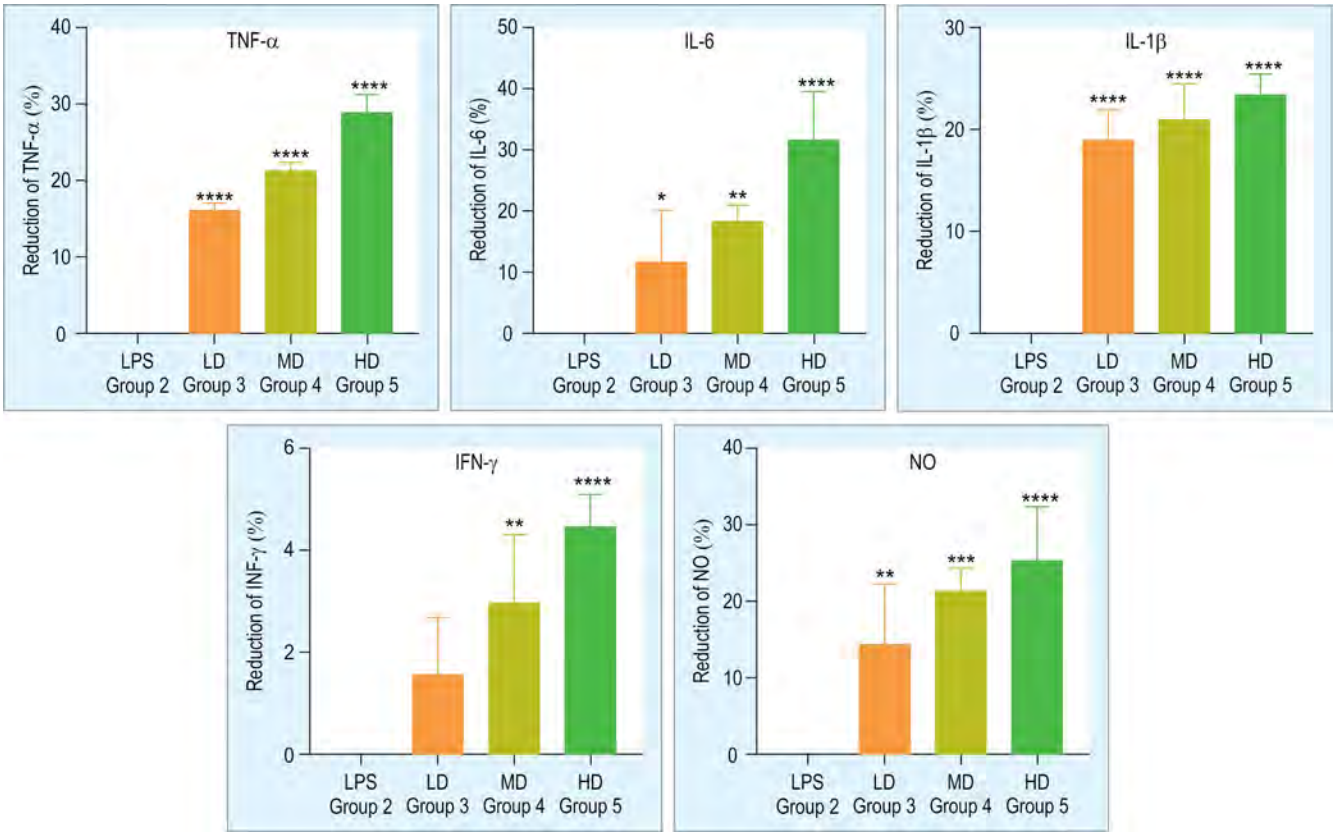

Fig. 1: Immunomodulatory evaluation for all biomarkers and NO in LPS-induced PBMCs: LPS alone (group II) and LPS with low (LD) (group III), medium (MD) (group IV), and high dosage (HD) (group V) of ORSL® Immunity+, respectively. LPS-alone treatment was used as positive control (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, ****$p < 0.0001$)

with mean ± SD values of TNF-α at 0.0573 ± 0.0100 ng/mL, IL-1β at 1.4577 ± 0.1265 ng/mL, IL-6 at 0.0988 ± 0.0057 ng/mL, IFN-γ at 106.30 ± 1.45 ng/mL, and NO at 19.218 ± 2.50 ng/mL. In contrast, group II showed significantly elevated levels of these inflammatory markers (Table 2), confirming successful immune activation. Groups III to V exhibited a significant, dose-dependent inhibition of LPS-induced TNF-α, IL-1β, IL-6, and NO levels, demonstrating its strong anti-inflammatory activity (Table 2).

Cytokine analysis demonstrated that TNF-α, IL-1β, IL-6, and IFN-γ levels were significantly reduced in dose-dependent manner in the ORSL® Immunity+ groups (Group 3–5) compared to the LPS group (Group 2) (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$), with the changes being statistically significant for Group 5. Although no significant differences were observed in IFN-γ and NO levels between groups III and IV when compared to group II, the percentage reduction in all cytokine levels was statistically significant relative to the absence of reduction in group II (0.00%) due to the lack of interventional treatment (Fig. 1). Additionally, while the absolute NO concentrations in groups III and IV did not significantly differ from group II, the percentage reduction in NO levels was highly significant when compared to LPS alone (0.00%) (Fig. 1).

ORSL® Immunity+ Enhances Phagocytic Activity in Lipopolysaccharide-induced Peripheral Blood Mononuclear Cells

Phagocytic activity was significantly enhanced in groups III to V in a dose-dependent manner compared to group II. Group I exhibited a high percentage (mean ± SD) of phagocytic cells (93.40 ± 0.02) ($p < 0.0001$), indicating optimal phagocytic capacity in the absence of LPS-induced inflammation. In contrast, group II showed a substantial reduction in phagocytic activity, with only 6.08 ± 1.08% of cells exhibiting phagocytosis. Groups III to V showed markedly improved phagocytic efficiency, with the percentage of phagocytic cells increasing to a value (mean ± SD) of 33.92 ± 2.35, 43.74 ± 1.54, and 57.43 ± 5.15 for groups III to V, respectively ($p < 0.0001$) (Fig. 2).

ORSL® Immunity+ Demonstrates Strong Antioxidant Activity

ORSL® Immunity+ exhibited significant antioxidant activity, as evidenced by its high ORAC values across different doses. The ORAC assay results showed that in group III,

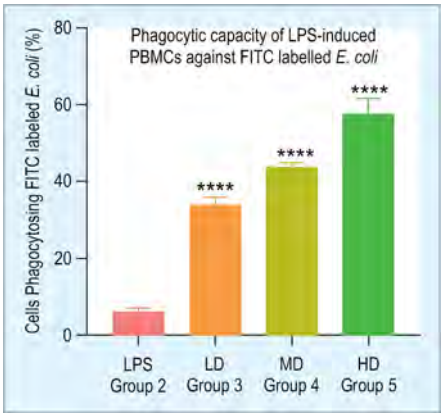

Fig. 2: Percentage of cells phagocytosing the FITC-labeled *E. coli* in LPS-induced PBMCs: LPS alone (group II) and LPS with LD (group III), MD (group IV), and HD (group V) of ORSL® Immunity+ (group III), respectively. LPS alone treatment was used as positive control (****$p < 0.0001$)

Fig. 3: Trolox equivalent (µmol TE/200 mL) in LPS with LD (group III), MD (group IV), and HD (group V) of ORSL® Immunity+ (group III), respectively

the ORAC value was 1530.35 µmol Trolox equivalent units/200 mL, while in group IV, it was 2856.28 µmol Trolox equivalent units/200 mL. The group V formulation demonstrated the highest antioxidant potential, with an ORAC value of 2894.58 µmol Trolox equivalent units/200 mL (Fig. 3).

Discussion

The results demonstrate that in this *in vitro* study ORSL® Immunity+ effectively supports immune function through a multi-faceted approach, by enhancing key immunomodulatory processes. Specifically, ORSL® Immunity+ showed strong anti-inflammatory effects, significantly reducing proinflammatory cytokines in LPS-induced PBMCs. Additionally, it enhanced phagocytosis, as evidenced by the increased uptake of FITC-labeled *E. coli*, indicating improved innate immune function. Furthermore, the formulation provided potent antioxidant protection, with a dose-dependent increase in ORAC values, highlighting its role in counteracting oxidative stress.

ORSL® Immunity+ effectively suppressed LPS-induced inflammatory responses in PBMCs, with significant reductions in proinflammatory cytokines and NO production. These findings highlight its potential as an anti-inflammatory agent, warranting further exploration in immunomodulatory applications.

Cytokines are small, secreted proteins involved in immune regulation, and their controlled release is essential for maintaining immune balance.[21] Although proinflammatory cytokines initiate immune responses, their excessive release can cause a cytokine storm, exacerbating inflammation. A balanced release of pro- and anti-inflammatory cytokines is essential for immune regulation.[15,21] Cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ play pivotal roles in immune regulation, inflammation, and disease pathogenesis. TNF-α, primarily produced by macrophages and T cells, is a key mediator of inflammation, autoimmunity, and bone metabolism, with TNF inhibitors proving effective in conditions like rheumatoid arthritis and Crohn's disease.[21] IL-1β, regulated by the inflammasome, drives immune responses and is implicated in infections, autoinflammatory diseases, and inflammatory conditions such as atherosclerosis.[21] IL-6, a pleiotropic cytokine, exerts both pro- and anti-inflammatory effects and serves as a critical biomarker in autoimmune diseases, infections, and cancer.[21] IFN-γ, predominantly produced by helper T cells, cytotoxic T cells, and NK cells, enhances macrophage activation and antigen presentation, playing a vital role in defense against intracellular pathogens.[15] Additionally, NO, a signaling molecule involved in vasodilation and immune responses, exerts anti-inflammatory effects under physiological conditions but contributes to inflammation and tissue damage when overproduced. Given their central roles in immune regulation, imbalances in these cytokines and NO can exacerbate inflammation, oxidative stress, and immune dysfunction—factors particularly relevant for patients with weakened immunity, active infections, or dehydration who may be more vulnerable to cytokine-driven complications.[22] Understanding these pathways helps highlight the importance of supporting balanced cytokine responses through appropriate hydration and nutritional strategies, such as micronutrient-enriched oral electrolyte solutions. This provides a clinically relevant perspective on how such interventions could help maintain immune homeostasis in vulnerable patient populations, although further clinical validation is required.[23]

The present *in vitro* study assessed the immunomodulatory effects of ORSL® Immunity+ on human PBMCs exposed to LPS-induced inflammation. The findings of this study demonstrated that ORSL® Immunity+ exerted a significant anti-inflammatory effect by reducing proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IFN-γ, and NO in a dose-dependent manner. The suppression of these cytokines aligns with the product's potential role in modulating immune responses and limiting excessive inflammation, which is critical in infection management and immune homeostasis.

Phagocytosis is essential for tissue homeostasis and plays a pivotal role in modulating inflammation and immune responses. Key phagocytes, including monocytes, macrophages, neutrophils, dendritic cells, osteoclasts, and eosinophils, are responsible for pathogen elimination and antigen presentation to the adaptive immune system.[24] Although significant progress has been made in understanding the mechanisms of phagocytosis, predicting how immune cells decode and respond to specific pathogens remains an ongoing challenge.[25] The present study highlighted a significant enhancement in phagocytic activity, as demonstrated by the increased uptake of FITC-labeled *E. coli* in PBMCs treated with ORSL® Immunity+. This suggests an improvement in innate immune function, essential for early pathogen clearance and overall immune defense. The dose-dependent enhancement in phagocytic activity indicates that ORSL® Immunity+ restores immune function in LPS-induced PBMCs, facilitating FITC-labeled *E. coli* clearance and highlighting its immunomodulatory potential.

Given the limited trials on antioxidant-based adjunct therapies, evidence suggests their role in mitigating cytokine storms and improving clinical outcomes.[26] Additionally, maintaining a balance between exogenous and endogenous antioxidants is crucial for redox homeostasis, as excessive antioxidant supplementation may interfere with the body's natural response to oxidative stress.[4] In addition to its anti-inflammatory and immune-enhancing effects, ORSL® Immunity+ exhibited strong antioxidant properties, as evidenced by its high ORAC values. The antioxidant capacity was found to increase in a dose-dependent manner, with the high-dose group showing an ORAC value of 2894.58 µmol Trolox equivalent units/200 mL. The strong antioxidant profile of ORSL® Immunity+ supports its role in neutralizing ROS, enhancing immune function, and cellular defense. Its triple-action mechanisms—supporting phagocytosis, limiting inflammation, and reducing oxidative stress—indicate its potential to help modulate immune responses in individuals with weakened immunity. The observed dose-dependent enhancement in antioxidant capacity suggests that it may contribute to neutralizing free radicals and mitigating oxidative stress, which can otherwise compromise immune function. However, these findings are based on preliminary *in vitro* data and require further verification

through additional studies and clinical evidence.[1,27]

The immune-supportive effects observed in this study are consistent with previous findings on the immunomodulatory role of key micronutrients, such as zinc, selenium, and vitamin E.[6–10] These micronutrients are well documented for their ability to regulate cytokine production, enhance phagocytosis, and reduce oxidative stress, aligning with the mechanisms demonstrated by ORSL® Immunity+. Studies have shown that zinc plays a crucial role in modulating innate and adaptive immune responses, selenium contributes to antioxidant defense, and vitamin E helps in reducing lipid peroxidation and inflammation.[6–10] Furthermore, other micronutrient-based formulations have also exhibited dose-dependent immunomodulatory activity by inhibiting TNF-α and IL-1β in LPS-treated dendritic cells.[28] These findings reinforce the potential of micronutrient-based formulations in modulating immune responses, further supporting the relevance of ORSL® Immunity+ as an effective immunomodulatory intervention.

The ORAC assay, a widely recognized method, which was developed by Prior et al., measures the inhibition of peroxy radical-induced oxidation and quantifies antioxidant capacity in Trolox equivalents.[29] It assesses both hydrophilic (H-ORAC) and lipophilic (L-ORAC) components, providing a comprehensive evaluation of a substance's antioxidant potential. ORSL® Immunity+ demonstrated an ORAC value ranging from 1530.35 to 2894.58 µmol Trolox equivalent units/200 mL, aligning with United States Department of Agriculture (USDA)-recommended dietary antioxidant intake levels. Notably, consuming two packs of ORSL® Immunity+ provides an ORAC antioxidant value of 5789, effectively meeting the USDA daily recommended requirement for antioxidants.[30]

By limiting inflammation, activating immune defenses, and protecting against oxidative damage, ORSL® Immunity+ may contribute to the following events:

- Infection prevention and control, by enhancing phagocytic activity.
- Reducing the severity and recurrence of infections, through its anti-inflammatory action.
- Promoting overall immune resilience, by mitigating oxidative stress.

These attributes reinforce its scientifically backed triple-action mechanism, referring to its three key nutrient-function actions in strengthening immunity.

Despite its promising results, the study's *in vitro* nature presents a limitation, as cellular responses in a controlled laboratory environment may differ from *in vivo* physiological conditions. Although the study successfully demonstrated immunomodulatory potential at the cellular level, further scientific validation could assess the potential of ORSL® Immunity+ in modulating immune responses, particularly in the context of LPS-stimulated PBMCs and to validate these findings in human populations. Additionally, the scope of tested formulations was limited; future research should explore variations in ingredient composition and their synergistic effects to better establish the role of ORSL® Immunity+ in infection management and immune resilience.

Conclusion

These findings demonstrate that ORSL® Immunity+ may play an important role in mitigating inflammation and oxidative stress, two key factors influencing immune health and recovery from infection. By combining immune support with hydration benefits, ORSL® Immunity+ offers a holistic approach to maintaining overall immune resilience, particularly in individuals with weakened immunity.

Future research could explore its long-term impact on immune health, infection prevention, and recovery outcomes in diverse populations. With its triple-action benefits, activating phagocytosis, limiting inflammation, and protecting against oxidative stress, ORSL® Immunity+ presents itself as a potential nutritional intervention for enhancing immune defenses.

Disclosure

This study was sponsored by JNTL Consumer Health (India) Pvt. Ltd., and SK, TG & AD received honoraria from JNTL Consumer Health (India) Pvt. Ltd. for providing their expert inputs, suggestions, feedback for the evaluation of study outcome. For this study, sponsor collaborated with AG from Radiant Research Services Private Limited as contract research organization to conduct the research.

Funding

JNTL Consumer Health (India) Pvt. Ltd.

Acknowledgment

The authors want to thank Bioquest Solutions Pvt. Ltd. for providing writing and editorial support.

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REVIEW ARTICLE

From Barriers to Best Practices: Enhancing Oral Rehydration Therapy Utilization for Diarrhea Management in India

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Abstract

Diarrheal diseases are the third leading cause of childhood mortality in India. Oral rehydration therapy (ORT) remains the cornerstone of diarrheal disease management, especially as first-line treatment for acute diarrhea. However, ORT faces significant barriers that compromise its effectiveness in India. Children with diarrheal dehydration frequently fail to receive recommended treatment, primarily due to knowledge gaps among caregivers and preparation inaccuracies. These are further compounded by water safety concerns, poor palatability of home-based preparations, and the practical challenges of handling 1 L volumes. A critical factor determining ORT effectiveness is osmolarity optimization, with current World Health Organization (WHO) [also known as the reduced-osmolarity oral rehydration solution (ORS)]-recommended low-osmolarity ORS demonstrating superior efficacy than the earlier standard-osmolarity formulations that increased risks of hypernatremia and stool output. However, many caregivers deviate from the recommended osmolality in ORS solutions. Creating awareness among caregivers and healthcare providers and training them on proper reconstitution of ORT is essential for optimizing ORT outcomes and reducing preventable dehydration-related morbidity and mortality, especially in resource-constrained settings. Ready-to-drink ORS (RTD-ORS) can be considered as a viable alternative, especially in specific scenarios where convenience and adherence are prioritized. This review aims to examine the challenges and barriers impeding diarrheal disease management in India and address the identified gaps in healthcare delivery and improve treatment outcomes.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1091

Introduction

Diarrheal diseases are the third leading cause of childhood mortality in India, accounting for 13% of deaths in children under five every year.[1] The burden of diarrheal disease varies significantly across India, with 71 districts in central and eastern India identified as hotspots.[2] The state-level incidence of diarrheal diseases ranges from 1.8% in Sikkim to 1.5% in Uttarakhand.[2] The national prevalence of diarrheal diseases among children was 7.3% in 2019–21, with rates higher in rural areas (7.7%) than urban areas (6.2%). Bihar reported the highest incidence (13.5%) while Lakshadweep had the lowest (2.3%) incidence of diarrheal diseases in children.[3] This disparity may reflect inadequate healthcare program effectiveness in enhancing provider performance along with low usage of zinc supplementation in effective diarrheal management.[3] Regional variations in diarrheal incidence reflect epidemiological factors including poor sanitation, inadequate clean water access, low maternal literacy, and socioeconomic disparities that disproportionately affect rural populations.[1,4]

In diarrhea, there is disruption of intestinal absorption and secretion, causing rapid fluid and electrolyte loss that leads to hyponatremia, hypokalemia, and metabolic acidosis.[5,6] The World Health Organization (WHO) categorizes dehydration by severity: mild (3–5% fluid loss), moderate (6–10% fluid loss), and severe (>10% fluid loss).[5,7,8] However, dehydration episodes can rapidly progress from mild dehydration to life-threatening severe dehydration. Despite being largely preventable, untreated dehydration due to diarrheal diseases remains a major health burden, especially in rural areas with limited healthcare access.[5,7]

In India, mortality rates due to diarrheal diseases are lower in children under five (47/100,000) than adults aged 70+ years (682/100,000) and those aged 50–69 years (62/100,000).[9] This may be partly due to WHO and UNICEF advocating oral rehydration therapy (ORT) using oral rehydration solution (ORS) programs since 1978. The current WHO, UNICEF as well as Indian Academy of Pediatrics (IAP) guidelines recommend that children should be given low-osmolarity ORS plus zinc supplementation (20 mg daily for children >6 months, 10 mg for infants <6 months), as first-line treatment for acute diarrhea. These treatment protocols emphasize preventing dehydration through early administration of home-based fluids, correcting mild-to-moderate dehydration with ORS, and managing severe dehydration with intravenous fluids.[10–12] Additionally, several government-driven initiatives, such as the National ORT Program, National Health Mission, and the recent National STOP Diarrhea Campaign, aim to promote the use of ORT in childhood illnesses like diarrhea and dehydration. These programs focus on early intervention and community education[13–15] and are further supported by the Global Task Force on Cholera Control (GTFCC) and Gavi, the Vaccine Alliance, which strongly emphasize the promotion of ORT to prevent and/or treat diarrheal diseases.[16,17]

The cornerstone of all these national and international efforts remains rehydration therapy using low-osmolarity ORS (245 mOsm/L; containing sodium chloride, 2.6 gm; glucose anhydrous, 13.5 gm; potassium chloride, 1.5 gm; trisodium citrate dehydrate, 2.9 gm; total, 20.5 gm per packet), necessitating optimal reconstitution in 1 L of clean water.[10] Yet the actual utilization of ORS remains suboptimal in many parts of the country, partly due to caregiver perceptions, lack of awareness, adherence, and accessibility issues. Ready-to-drink ORS (RTD-ORS) addresses these challenges by providing convenient, accurately dosed rehydration therapy, particularly in regions where water quality and limited caregiver knowledge compromise treatment effectiveness. This review aims to examine the challenges and barriers impeding diarrheal disease management in India and address the identified gaps in healthcare delivery and improve treatment outcomes.

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How to cite this article: Shankar J, Nagpal R, Patil A, *et al.* From Barriers to Best Practices: Enhancing Oral Rehydration Therapy Utilization for Diarrhea Management in India. J Assoc Physicians India 2025;73(8):28–33.

Barriers to Optimal Oral Rehydration Therapy

Practical Knowledge Gaps about Oral Rehydration Therapy among Caregivers in India

Mothers and caregivers are the frontline players in the effective management of dehydration caused by diarrhea through early intervention. However, their inadequate training in home-based ORS preparation, including accurate ingredient measurement, proper mixing with clean water, optimal storage, and correct administration, limits effective ORT use for treating dehydration.[18] In India, basis a study published in 2010 <40% of children with diarrheal dehydration receive the recommended treatment.[19] In a cross-sectional survey study conducted at a tertiary care center in South Rajasthan, among 235 mothers, only 72.7% knew how to prepare and administer ORS. Lack of education among mothers was one of the key factors contributing to this, as mothers who were less educated (up to 8th grade) were less likely to know about ORS than those who were better educated (70 vs 30%).[20] Consistent with this, a study from urban Aligarh, Uttar Pradesh, found that less than half (46.5%) of mothers were aware of ORS. Among those who knew about ORS, only 29.8% understood how to prepare it correctly. Additionally, only 38.7% of mothers were familiar with appropriate homemade fluid alternatives, with salt-sugar solution being the most commonly known option.[21] Data analyzed from the fourth round of the District Level Household and Facility Survey-4 (DLHS-4), 2012–2013 under the purview of the Ministry of Health and Family Welfare, Government of India, involving 14,532 primary sampling units further corroborates these findings. The survey revealed that only 76.36% of mothers had knowledge about diarrhea management in India and 54.76% of mothers gave ORS to their children, whereas 43.43% of mothers used salt and sugar solution for the treatment of childhood diarrhea at their homes.[22] A prior study has documented the correlation between parental knowledge and diarrheal incidence through implementation of practices like personal and environmental hygiene ($r = 0.455$, $p = 0.0001$), reinforcing the importance of educating the parents towards better prevention and management of diarrhea among children.[23] Another study reported that a structured educational program significantly improved the mother's knowledge, attitude, and practice ($p < 0.05$) for prevention and management of diarrhea.[24] These studies highlight that educating mothers and caretakers on early home-based case management of childhood diarrhea is crucial to substantially decrease morbidity and mortality due to diarrhea. Oral therapy education programs, conducted through theoretical messages and practical demonstrations, can help to increase the use of ORS and improve knowledge retention among mothers, resulting in effective implementation of ORT.[25]

Knowledge and Educational Gaps among Healthcare Providers

Increasing evidence indicates that children receiving diarrheal treatment from private healthcare practitioners (HCPs) are less likely to receive ORS therapy compared to those treated by public HCPs.[26–28] This is also evident in India, where both public and private HCPs identified ORS as essential for treating childhood diarrhea. However, only 35% of private sector providers dispense medications on-site compared to 85% of public providers. This difference creates an additional obstacle for private sector patients, who need to make a separate pharmacy visit, potentially explaining the disparity in ORS usage between sectors despite similar treatment preferences.[29] Multiple private HCPs interviewed observed that while they prescribe ORS to patients, there was lack of any mechanism to verify whether patients ever obtained or used the treatment.[29] Furthermore, HCPs themselves often demonstrate inconsistent understanding of ORS indications, contraindications, and administration protocols, leading to missed opportunities for early intervention.[18] Lastly, most formal training programs for HCPs focus on the theoretical knowledge of ORS preparation, patient counselling, and follow-up, but offer limited practical, hands-on, or culturally tailored training, thereby failing to address the diverse educational and cultural backgrounds of caregivers.[30,31] These gaps advocate comprehensive educational interventions and improved formulations to enhance ORS acceptance and appropriate use in varied community settings.[30,31]

Palatability Concerns in Home-based Oral Rehydration Solution Preparations

Cereal-based ORT powders, while potentially more effective due to improved sodium absorption and reduced osmotic load, are not always available in resource-limited settings and require strict adherence to preparation guidelines to avoid complications.[32,33] Additionally, both home-based and cereal-based solutions may suffer from poor palatability, which can reduce compliance among children, and caregiver misconceptions about their effectiveness further hinder proper use.[32,34] Importantly, children often refuse to drink these solutions due to their strong salty taste and unappealing organoleptic properties.[33] This low acceptability is a major barrier to successful rehydration, as it can lead to inadequate intake and treatment failure. Moreover, even minor alterations to home-based ORS, such as the addition of fruit juice, can disrupt the electrolyte balance and reduce rehydration efficacy. An earlier study demonstrated that any additions to home-made ORS (such as apple juice, orange juice, or orangeade) did not improve the palatability of these solutions. Instead, these additions decreased the sodium (−30 to −53 mmol/L) and chloride (−27 to −47 mmol/L) concentrations and increased the osmolality to >311 mOsm/kg and thus demonstrated inconsistencies in preparation which may impact efficacy. These modified home-made solutions thus did not fulfil European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGAN) criteria for ORS, and rehydration was less effective.[35]

Challenges in Osmolarity Optimization in Oral Rehydration Solution

The use of traditional home-based ORS and powdered formulations presents several challenges primarily due to the risk of incorrect preparation, which can result in solutions with dangerously high or low concentrations of salt and sugar, potentially causing hypernatremia or hyponatremia in children.[36,37] Studies have shown that caregivers frequently prepare home-based ORS solutions inaccurately, often using incorrect quantities of salt and sugar, which can lead to dangerous electrolyte imbalances.[7,36] This risk is compounded by the lack of standardized measuring tools and clear instructions at the household level, making consistent preparation difficult.[36]

The osmolarity of ORS is one of the pivotal factors in determining the therapeutic effectiveness of ORT. Clinical refinement over decades led to the current low-osmolarity ORS (245 mOsm/L), developed by WHO after evidence that high-osmolarity formulations (311 mOsm/L) increased risks of hypernatremia and stool output, especially in children (Fig. 1).[38] Despite this, effective ORT remains challenged by wide variations in osmolarity due to inconsistent home-based preparation and powder reconstitution, often resulting in hyperosmolar or hypo-osmolar

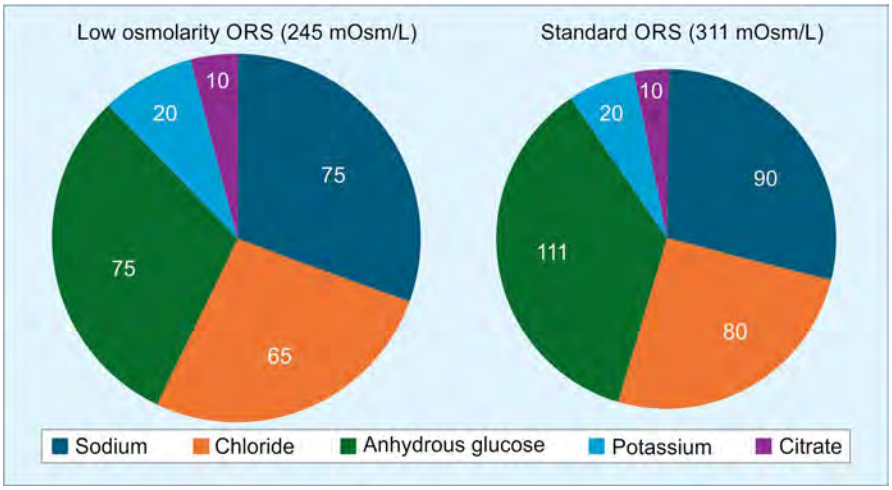

Fig. 1: Composition of the low osmolarity and standard ORS; Note: Each of the components of the ORS are expressed in mOsm/L. ORS, oral rehydration solution

solutions with inaccurate electrolyte or glucose concentrations.[36,37] In a consumer behavior study conducted in 120 caregivers from Bengaluru to Pune, 43% of caregivers prepared ORS solutions with osmolality >310 mOsm/kg, while 29.16% of caregivers had their ORS in the range of 200–310 mOsm/kg, and only 14.16% of caregivers prepared their ORS in the reduced osmolality range of 210–268 mOsm/kg. The volume of water and quantity of ORS powder used ranged between 100–1000 mL and 1.38–23 gm, respectively. Caregivers reconstituted the powdered ORS according to their own preferences rather than following package instructions, resulting in solution osmolality that deviated from the recommended value of 245 mOsm/kg.[37]

Water Safety and Contamination Risks during Oral Rehydration Solution Preparation

Contaminated water represents a major safety concern for ORS preparation, particularly in rural areas where access to safe drinking water is compromised. Studies have demonstrated that improper water sources or insufficient water treatment can introduce microbial pathogens, including coliform bacteria and *Escherichia coli*, into prepared ORS, increasing the risk of further diarrheal illness and compromising the therapeutic efficacy of ORT.[12,39] Recent research highlights additional concerns regarding chemical contaminants, as organic pollutants such as plasticizers, organophosphorus flame retardants, and plastic-derived oligomers have been detected in both tap and purified water, even from household filtration systems, and inadequate water treatment infrastructure or environmental contamination add to the risk of inappropriate ORT.[40,41] ORS preparation should ideally utilize boiled and cooled water; however, compliance remains inadequate, particularly in emergencies or in the absence of adequate facilities. Consequently, safe clean, unboiled water can suffice for immediate consumption. Moreover, improper storage containers, unhygienic handling practices, or extended ambient storage can lead to bacterial growth, compromising ORS efficacy and introducing health risks. Therefore, it is crucial to consume the ORS within 24 hours postpreparation, necessitating disposal of any remaining fluid and reconstitution of a fresh solution thereafter.[36]

Practical Challenges in Oral Rehydration Solution Preparation and Administration: Handling the 1 L Volume after Reconstitution

The rational use of ORS necessitates reconstitution of the powdered formulation (ORS sachet) in standard 1 L of potable water to ensure proper concentrations for optimal dehydration management. However, errors in the domestic preparation, inappropriate fluid intake volumes, and infrequent administration are major concerns affecting ORT efficacy.[42] Caregivers often struggle to handle the 1 L volume, with a prior study documenting that only 69% of users fully dissolve ORS sachets and a mean consumption of just 354 mL within 24 hours.[43] In recent times, the availability of 200 mL ORS sachets has been advantageous, with majority of the caregivers from India favoring this smaller ORS pack size rather than the 1 L packs.[42] Furthermore, the lack of appropriately sized containers for accurate measurement and mixing leads to incorrect dilution and dosing errors, while improper storage or use beyond the recommended 24-hour period, especially in rural populations, further compromises safety and effectiveness.[36] Additionally, the handling of the large volume can be intimidating or confusing for caregivers, who are unfamiliar with the ORT regimen, often resulting in underuse or wastage, particularly when treating pediatric patients who require small, frequent doses, necessitating disposal of unused solution within 24 hours to prevent contamination.[33,36,42] Potability issues as well as lack of secure storage facilities during travels, and large-volume ORS preparation in water-scarce environments present additional challenges. These volumetric and practical constraints highlight the need to advocate the use of smaller, single-use ORS sachets as well as commercially available RTD-ORS, while improvising the guidance on safe storage and volume management at the household level.

Optimization of Oral Rehydration Solution for Effective Dehydration Management

The easy accessibility and cost of ORS in powder formats make them a preferred therapeutic intervention to address dehydration and mortality concerns in diarrheal diseases.[44] Despite these advantages, several barriers including insufficient healthcare awareness and knowledge, and improper preparation techniques impede their optimal clinical utilization.[18] These challenges necessitate strategic approaches focused on knowledge dissemination for effective ORS preparation and implementation to improve health outcomes. The pivotal considerations for proper reconstitution of powdered ORS include accurate powder-to-water ratios in 1 L of water using clean and safe drinking water to ensure recommended ORS osmolarity and prevent contamination-related risk.[10–12] Moreover, the caregiver education programs should emphasize practical skills such as recognizing early dehydration signs, understanding when to initiate ORS therapy, and implementing proper feeding techniques depending on age group and stage of dehydration.[18,30,31] Training for HCPs should be aimed at highlighting common errors in ORS preparation, associated risk, and the appropriate administration techniques.[18,26,37] Ongoing health education initiatives, including regular skill development programs for HCPs and hands-on training for caregivers, can substantially enhance the effectiveness

and therapeutic outcomes of ORS use. Such efforts are particularly crucial in resource-limited settings, positioning powdered ORS as a practical and essential intervention for dehydration management in India.[18,30,31,37]

There have been industry and public sector partnerships to support education and awareness about diarrhea. The "Diarrhoea Se Darr Nahi" (Not Afraid of Diarrhea) is an important and recent public healthcare initiative launched by a well-known company in collaboration with Population Services International India (PSI India) in 2025. This joint initiative aims to reach approximately 5 million children under the age of five across 10 districts in Uttar Pradesh and Bihar over the next 2 years, with the goal of reducing diarrhea-related mortality and improving healthcare outcomes.[45,46] The initiative aligns with the Government of India's "Stop Diarrhoea Campaign," which aims to achieve zero child deaths due to diarrhea.[15,45,46]

Addressing Implementation Barriers and Clinical Advantages with Ready-to-drink-oral Rehydration Solution

Limitations of traditional ORS in low-resource environments and knowledge gaps among caregivers and HCPs have led to the development of premixed ORS, referred to as RTD-ORS. These premixed solutions are easy to administer to patients suffering from acute dehydration and eliminate the probability of errors during preparation or reconstitution, thereby ensuring ORS with optimal osmolarity[47] (Fig. 2). In subsequence, they also ensure accurate dosing, facilitating optimal absorption of sodium and glucose, leading to fluid retention, thus minimizing the risk of dehydration and diarrhea. Notably, the osmolarity of most of these RTD-ORS is standardized as per WHO/UNICEF guidelines.[47] With shelf lives of 18–24 months at ambient temperatures, these solutions offer stability and reliability for emergency preparedness, particularly in resource-constrained settings with limited water access. Extensive packaging and quality control ensure contamination-free products with maintained electrolyte concentrations, pH stability, and microbiological safety.[8,47] Enhanced palatability through various flavours and sweeteners improves patient acceptance, especially in children, without compromising osmolarity.[47]

However, RTD-ORS must not be confused with commercial carbonated beverages, energy drinks, sports drinks, or fruit juices, which contain excessive sugars, artificial additives, and inappropriate electrolyte compositions that can worsen dehydration. Unlike consumer drinks, pharmaceutical-grade ORS contains precise sodium-glucose co-transport ratios scientifically formulated for optimal intestinal absorption and successful treatment of dehydration and electrolyte imbalances.[8] It goes beyond doubt that WHO formula ORS is the recommended rehydration solution for diarrheal dehydration. While RTD formats of oral fluid electrolyte energy (electrolyte drinks) may be preferred in non-diarrheal conditions due to their palatable taste that helps increase compliance, as well as their known quality, convenience, and a ccuracy.[48,49]

The Canadian Pediatric Society (CPS) guidelines supports the use of premixed oral rehydration solution in children with mild to moderate diarrheal dehydration.[50] The guidelines suggest starting rehydration with ORS (50 mL/kg in mild dehydration and 100 mL/kg in moderate dehydration) over 4 hours at an approximate rate of 1 mL/kg every 5 minutes (fluid deficit volume), followed by ORS from 4 to 24 hours to ensure replacement of maintenance requirements and any losses. The guidelines also suggest initiating extra ORS after each emesis (for example, 2 mL/kg) or diarrheal stool (for example, 5–10 mL/kg) in these children.[50] This is in line with the other guidelines, like the WHO-UNICEF and IAP, as presented in Table 1.

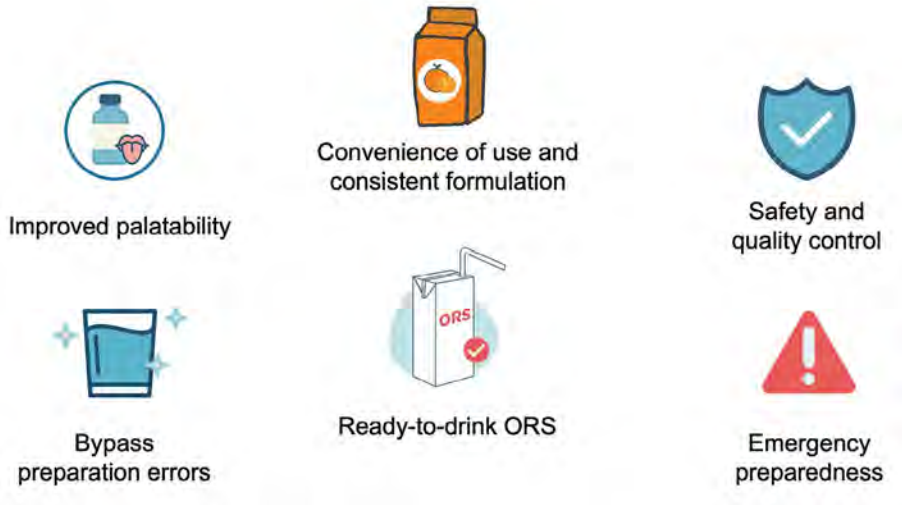

Fig. 2: Advantages of using RTD-ORS; RTD-ORS, ready-to-drink oral rehydration solution

Cost-effectiveness and Practical Considerations: Ready-to-drink-oral Rehydration Solution vs Powder Oral Rehydration Solution Formulations

Powder formulations of ORS remain highly cost-effective, with the cost of 1 L of commercially prepared ORS ranging from $3 to 6.54.[44] These formulations are of excellent value in resource-limited settings where price is a critical barrier to ORS use. On the other hand, RTD-ORS typically incurs higher production and retail prices due to packaging and convenience features. However, in contexts where caregiver compliance, ease of use, and rapid access are priorities, such as in travel or emergencies, RTD-ORS can improve timely rehydration and potentially reduce indirect costs associated with delayed care or hospitalization.[44] Thus, while powder ORS remains the most cost-effective option for mass distribution and routine management, RTD-ORS may be justified in specific scenarios where its convenience and palatability translate into better adherence and outcomes.

Conclusion

Despite significant advances in ORT, persistent issues such as inaccuracy of preparation (or reconstitution), lack of caregivers' and HCPs' knowledge and awareness, alongside access to clean and potable water, continue to limit the effectiveness of ORS in India. Optimizing the use of powdered ORS, through proper education and training, to ensure accurate preparation and administration, remains a reasonable and effective option, particularly in resource-limited settings, when supported by access to safe water. In addition, RTD-ORS offers a practical, standardized, and potentially cost-effective solution that can support better clinical outcomes. They ensure accurate osmolarity, simplify administration, and improve patient compliance. Bridging the gaps in implementation through caregiver education, HCP training, and policy-driven accessibility of RTD-ORS can significantly

Table 1: Comparison of the international guidelines on diarrheal management (IAP, WHO-UNICEF, CPS)

Guidelines	*WHO-UNICEF*	*IAP*	*CPS*
ORS formulation	Low osmolarity ORS (245 mOsm/L; containing 75 mEq/L sodium)	Low osmolarity ORS (245 mOsm/L; containing 75 mEq/L sodium)	Low osmolarity ORS (optional: rice-based ORS)
Zinc supplementation	10 mg/day (for <6 months); 20 mg/day (for 6 months to 5 years) over 14 days	10 mg/ day (for <6 months); 20 mg/day (for 6 months to 5 years) over 14 days	10 mg/ day (for <6 months); 20 mg/day (for 6 months to 5 years) over 14 days; Zinc-fortified ORS is not used routinely due to cost constraints
ORS administration tips	1 L ORS packets (reconstituted in clean water) for home use; knowledge on recognition of the signs of dehydration	Small sips of ORS with a spoon; avoid premade drinks	Frequent small doses; flavored ORS or popsicles to be administered to reluctant children
Home fluids	Support home fluids with ORS when required	Advises local safe fluids if ORS is not available	Discourages sugary drinks; warns against plain water due to the risk of hyponatremia
Feeding advice	Continue or increase breastfeeding and regular feeding during/after illness	Continue breastfeeding; recommend local fluids (rice water, lassi, etc.)	Encourages early refeeding; continue age-appropriate diet postrehydration

CPS, Canadian Pediatric Society; IAP, Indian Academy of Pediatrics; ORS, oral rehydration solution; WHO-UNICEF, World Health Organization–United Nations Children's Fund

strengthen diarrheal disease management, particularly in resource-constrained settings, thereby improving treatment outcomes and reducing dehydration-related morbidity and mortality.

Author Contributions

AP, HM, VC: conceptualization, writing, review, and editing. JS, RN: review and editing.

Funding

The funding support for manuscript writing was provided by Kenvue.

Acknowledgment

The manuscript writing was funded by Kenvue. We thank Dr Anuradha Chatterjee and Dr Dipanwita Mukherjee of Turacoz Healthcare Solutions (https://www.turacoz.com) for providing medical writing support.

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