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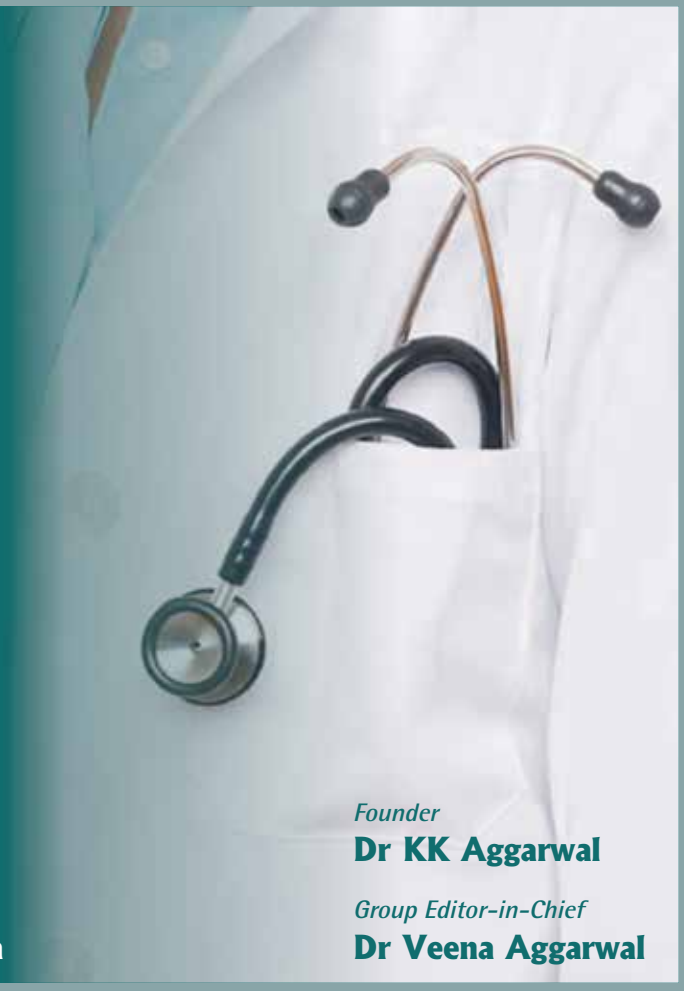

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Interpregnancy Interval and Risk of Gestational Diabetes

A new study published in the journal *BMC Pregnancy and Childbirth* has found that interpregnancy intervals of 24 months or longer were associated with a higher risk for gestational diabetes in subsequent pregnancies[1]. This risk was evident independent of the age of the mother.

A retrospective cohort study was carried out from 2013 to 2021 with data from 2,392 women who had consecutive deliveries at the Peking University Shenzhen Hospital. After being divided into seven groups (<12 months, 12 to <18 months, 18 to <24 months, 24 to <36 months, 36 to <48 months, 48 to <60 months, and ≥60 months), the interpregnancy interval was added to a multivariate logistic regression model along with additional confounding variables. Additionally, the data was categorized according to the age of the first pregnancy, body mass index, and history of gestational diabetes. The purpose of this study was to examine how the interpregnancy interval affected the risk of developing gestational diabetes.

Analysis revealed that the interpregnancy interval in women with gestational diabetes was considerably longer than in those without gestational diabetes in a subsequent pregnancy. This difference was statistically significant ($p < 0.05$). Participants with an interpregnancy interval of 24 to 36 months were 1.5 times more likely to develop gestational diabetes in the next pregnancy with adjusted odds ratio (aOR) of 1.58. A similar enhanced risk was observed with longer pregnancy intervals ranging from 36 to 48 months, 48 to 60 months, and ≥60 months with aORs of 2.38, 2.48, and 2.56, respectively. Interpregnancy intervals of 36 months or longer were found to have a substantially higher risk of gestational diabetes in the subsequent pregnancy ($p < 0.05$) for women <30 years, ≥30 years, with or without a history of gestational diabetes. However, no such association was noted for interpregnancy intervals shorter than 18 months ($p > 0.05$).

Interpregnancy intervals of 12 to 18 months, 24 to 36 months, 36 to 48 months, and ≥60 months showed a significant correlation with the risk of gestational diabetes mellitus in participants with a history of the disease (aOR 2.61, 3.74, 4.35, and 5.37, respectively). The slope value of linear regression (0.5161) was significantly higher compared to participants without a history of gestational diabetes mellitus (0.1891) ($F = 284.168$, $p < 0.001$), noted the authors. Based on these findings the study concluded that the risk of gestational diabetes mellitus in a subsequent pregnancy is elevated by long interpregnancy interval, and this risk is unaffected by the mother's age. Interpregnancy interval has a greater impact on women having a history of gestational diabetes when it comes to their likelihood of developing gestational diabetes during a second pregnancy. "These findings can be utilized by women to make informed decisions about the appropriate length of time between pregnancies in order to minimize the risk of gestational diabetes mellitus in subsequent pregnancies," concluded the authors.

REFERENCE

1. Deng Y, Xu C, Yang A, Wang Y, Peng Y, Zhou Y, et al. Effect of interpregnancy interval on the risk of gestational diabetes mellitus during a second pregnancy. BMC Pregnancy Childbirth. 2024;24(1):406.

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Glycemic Warming: A Glycemic Warning

Global warming impacts our environment, and our health, in multiple ways[1]. While global warming garners global attention, another challenge continues to grow as a disaster in slow motion. This is the pandemic of diabetes. Similar to global warming, 'glucose warming' or the diabetes epidemic, has affected every country on earth[2].

Statistics for global warming and glucose warming exhibit striking similarities. The difference is just that climatic change and weather-related disasters are headlined in media, while diabetes-related disease and death are usually not considered newsworthy enough. This is in spite of the fact that diabetes kills, and maims more people than natural disasters do.

Just as global-warming is associated with multiple climatic and weather changes, glucose warming or the diabetes epidemic represents a multifaceted challenge. Managing diabetes means not just keeping glucose levels under control, but ensuring optimal control of blood pressure, cholesterol, and body weight[3].

Put together, these four targets are known as the metabolic quadriga. Apart from these, diabetes is linked with various complications such as cardiovascular disease, kidney impairment, fatty liver, and obstructive sleep apnea (OSA). The complex presentation of diabetes can be explained by its equally complex pathophysiology, or development. Many factors, including deficient production as well as function of the hormone insulin, and inadequate performance of the incretin system, lead to diabetes[4].

Advances in diagnosis and treatment now allow affected persons to live a healthy life with diabetes. Timely screening, diagnosis, and monitoring of diabetes are essential if optimal health is to be achieved, and maintained.

Newer drugs, which work on all these causative factors, allow multifaceted management of diabetes. By controlling glucose as well as body weight, improving lipids and blood pressure, and reducing the risk of heart and kidney disease, they improve the overall health of the person living with diabetes. Modern medications such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors have also been reported to improve liver health and reduces the symptoms of OSA. They have also been found to reduce the risk of cardiovascular disease and improve survival[5,6].

Thus, such medications can be viewed as a defense against glycemic warming and its long-term effects. Timely use of these drugs will help reduce the impact of uncontrolled diabetes and its various complications. This benefit will be felt not only at an individual level, but will accrue to the society and nation as well.

We need to view global and glycemic warming, as a global glycemic warning, and act against it; we need to manage diabetes in a timely, and appropriate, manner.

REFERENCES

1. Lenton TM, Xu C, Abrams JF, Ghadiali A, Loriani S, Sakschewski B, et al. Quantifying the human cost of global warming. Nat Sustainabil. 2023;6(10):1237-47.
2. Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al; GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203-34.
3. Kalra S, Kapoor N, Jacob JJ. Management of obesity: finding the metabolic magic wand. Indian J Endocrinol Metab. 2022;26(6):499-500.
4. Ojo OA, Ibrahim HS, Rotimi DE, Ogunlakin AD, Ojo AB. Diabetes mellitus: From molecular mechanism to pathophysiology and pharmacology. Med Novel Technol Dev. 2023;19:100247.
5. Chong K, Chang JK, Chuang LM. Recent advances in the treatment of type 2 diabetes mellitus using new drug therapies. Kaohsiung J Med Sci. 2024;40(3):212-20.
6. Kalra S, Das AK, Priya G, Ghosh S, Mehrotra RN, Das S, et al. Fixed-dose combination in management of type 2 diabetes mellitus: expert opinion from an international panel. J Family Med Prim Care. 2020;9(11):5450-7.

REVIEW ARTICLE

Iron Deficiency in Heart Failure: Unveiling the Hidden Culprit

KAMAL KISHOR*, ASHWANI KUMAR†, DEVENDRA SINGH BISHT‡, SHEKHA VOHRA#

ABSTRACT

Iron deficiency (ID) is a frequent comorbidity in patients with heart failure (HF). Coexistent HF and ID make the issues more challenging to diagnose and treat. Iron deficiency exacerbates clinical symptoms, impairs quality of life and increases the risk of recurrent hospitalization for HF. Conversely, a proinflammatory state and altered gut kinetic in HF may result in absolute or functional ID, which conventional laboratory makers may not diagnose and differentiate accurately. Novel diagnostic markers like soluble transferrin receptor (sTfR), reticulocyte hemoglobin concentration, red blood cell distribution width, sTfR: log (ferritin) ratio and serum hepcidin levels may help to diagnose ID more accurately in the setting of HF. The intravenous (IV) iron formulation has shown promising results in improving the functional class and reducing recurrent hospitalization in patients with HF and ID. Futuristic therapies like nanosized iron preparations, hepcidin inhibitors and hepcidin antagonists may help manage ID more efficiently and conveniently in HF. This manuscript explores the relationship between ID and HF. It also provides the latest information related to the diagnosis and treatment of ID in HF patients.

Keywords: Iron deficiency, heart failure, intravenous iron formulation

Iron is essential to executing several physiological processes, such as oxygen transport and storage, cellular respiration, energy metabolism, and control of vascular tone[1]. Like all other chronic inflammatory diseases, iron deficiency (ID) frequently afflicts patients with heart failure (HF). ID is a common comorbidity in patients with HF, affecting up to 50% of all ambulatory patients[2]. Prevalence varies depending on the criteria used to diagnose ID in the cohort analyzed[3]. ID is associated with worsening of the signs and symptoms of HF, poor quality of life, and increased risk of recurrent hospitalization and death[4]. Strategies targeting ID in the HF cohort significantly improve clinical outcomes, New York Heart Association (NYHA) functional class, exercise capacity, and quality of life[5-10].

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IRON HOMEOSTASIS

Iron is vital for the human body. In free form, iron causes oxidative injury and may lead to premature cell death. Iron, therefore, must remain bound to protein to ensure safety and stability. Iron is stored as an iron-protein complex in the liver, spleen, and reticuloendothelial cells (storage pool). In the bloodstream, it is transported conjugated with apo-transferrin as transferrin. Transferrin carries iron around the body, which is physiologically usable by cells after uptake by transferrin receptor-1 (functional pool). Three key regulators are crucial in iron homeostasis. Ferroportin regulates iron absorption from the gut and its discharge from the stored pool. Hepcidin induces internalization and degradation of ferroportin and acts as a master regulator of iron metabolism. Lastly, erythroferrone is a negative regulator of iron metabolism. It inhibits hepcidin production, thus ensuring iron availability for erythropoiesis[11-13]. All these proteins work in a coordinated manner to maintain a stable level of iron in the body.

EFFECT OF HF ON IRON HOMEOSTASIS

Heart failure is a proinflammatory condition. It is associated with elevated levels of inflammatory cytokines, which result in elevated hepcidin levels. Hepcidin negatively interacts with ferroportin, hindering iron

absorption from the gut and its release from the storage pool. In this way, patients with HF are at risk of both absolute (depleted iron stores) and functional ID (sufficient iron not available at the cellular level despite normal total body iron)[13]. Within the framework of HF, many other factors may precipitate the state of ID (Table 1). Some of these factors include nutritional deficiency, poor bioavailability of dietary iron, edematous gut, blood loss secondary to antiplatelet or anticoagulant medication and associated comorbidities[2].

EFFECT OF IRON DEFICIENCY ON HF OUTCOMES

Iron is crucial for synthesizing hemoglobin, myoglobin, cytochrome *c*, and many other proteins. It acts as a cofactor of several enzymes, including nitric oxide synthase. ID, therefore, has a deleterious effect on oxygen transportation (hemoglobin) and aerobic respiration of muscles (myoglobin), oxidative phosphorylation (cytochrome *c*), and other processes dependent on a sufficient level of iron (Table 2)[1,13]. Patients with HF and ID exhibit a high prevalence of anemia, adverse remodeling, and worse muscular symptoms (such as muscle pain, fatigue, cramps, shortness of breath, and poor exercise capacity) secondary to insufficient heme production. ID disturbs oxidative phosphorylation and reduces adenosine triphosphate (ATP) production. Therefore, tissues with higher energy requirements (such as the myocardium, skeletal muscle, and the central nervous system) are affected most by ID. Lastly, ID disrupts the production of nitric oxide synthase (NOS), resulting in vasoconstriction. This, in turn, worsens symptoms like difficulty breathing and fatigue, which also result in recurrent hospitalization[1,13].

DEFINING IRON DEFICIENCY IN HEART FAILURE

Iron deficiency in HF can be absolute iron deficiency (AID) or functional iron deficiency (FID). In AID iron, the total body stores of iron get depleted. Conversely, FID typifies a situation where iron stores are normal or elevated (Table 3)[14-16]. However, the downregulation of ferroportin and upregulation of hepcidin and other inflammatory cytokines hinder iron mobilization from the storage pool. Ferritin levels (reflection of storage pool) and transferrin saturation (reflection of iron bioavailability) are the two most commonly used laboratory parameters to define ID in routine clinical settings (Fig. 1). Serum ferritin <30 µg/L and transferrin saturation (TSAT) <16% suggest a state of ID[14]. However, considering the effect of HF on serum ferritin and TSAT, it is imperative to change the criterion of diagnosing ID in the setting of HF. Serum ferritin is an acute phase

Table 1. Fundamental Causes of Iron Deficiency in Heart Failure

Poor absorption due to increased gut thickness
Poor absorption due to gut edema
Poor bioavailability of dietary iron
Blood loss due to antiplatelets or anticoagulants
Associated comorbidities
Elevated hepcidin levels
Elevated inflammatory cytokines

Table 2. Critical Substrates Affected by Iron Deficiency[1,13]

Substrate	Essential role	Impact of ID on patients with HF
Hemoglobin	Oxygen transportation	Anemia, adverse remodeling of the left ventricle, fatigue, shortness of breath, recurrent hospitalization, increased cardiovascular death.
Myoglobin	Oxygen storage in skeletal muscle	Muscle pain, fatigue, cramps, shortness of breath, and poor exercise capacity.
Cytochrome *c*	Electron transport chain for ATP generation	Adverse impact on tissues with higher energy requirements such as the myocardium, skeletal muscle, and the central nervous system.
Nitric oxide synthase	Control of vascular tone	Worsens symptoms like difficulty breathing, fatigue, and recurrent hospitalization.

Table 3. Absolute and Functional Iron Deficiency in Heart Failure[14-16]

Absolute iron deficiency

- Depletion of both storage and functional pool of iron.
- Diagnosed as serum ferritin (a marker of storage pool) <100 µg/L and transferrin saturation (a marker of the functional pool) <20%.

Functional iron deficiency

- Normal or elevated storage pool but sequestration of the functional pool of iron.
- Diagnosed as serum ferritin (a marker of storage pool) 100-300 µg/L and transferrin saturation (a marker of the functional pool) <20%.

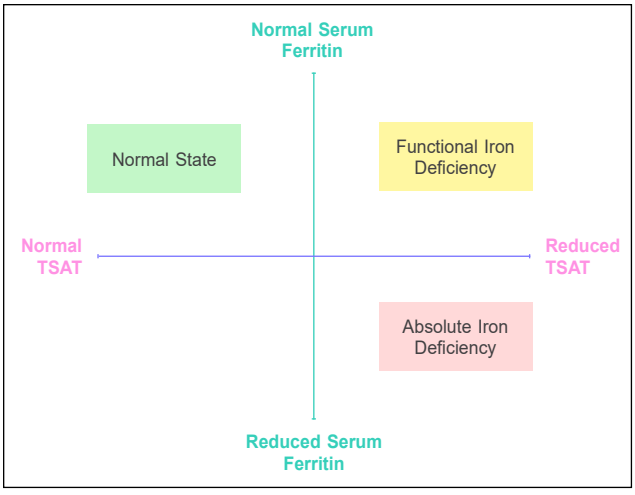

Figure 1. Absolute and functional iron deficiency in patients of heart failure. In AID, both iron storage and functional pools are depleted. However, in FID, the storage pool remains normal or even elevated, but the iron cannot move out of the storage pool. This may be due to the impact of the altered hepcidin-ferroportin axis in HF. This leads to improper iron availability to erythroid and nonerythroid tissue despite a regular storage pool.

reactant and gets nonspecifically elevated in conditions with activated inflammatory pathways such as HF. This change correlates with the extent of inflammation. Conversely, transferrin is a negative phase reactant and may get suppressed in HF[15].

Although there is no precise serum ferritin and TSAT cut-off, serum ferritin levels <100 μg/L or 100-300 μg/L if TSAT is <20% diagnose ID in HF with 82% sensitivity and 72% specificity[16]. Novel markers such as soluble transferrin receptor (sTfR), reticulocyte hemoglobin concentration, and red blood cell distribution width (RDW) can diagnose ID more accurately in patients with HF. However, these markers have yet to be routinely used. Additionally, measuring sTfR, sTfR: log (ferritin) ratio or hepcidin levels could be more effective in discriminating AID from FID[17]. A detailed description of all these investigations is beyond the scope of this manuscript.

MANAGEMENT OF IRON DEFICIENCY IN HEART FAILURE

Review of Literature

Clinical trials and meta-analyses have suggested beneficial effect of IV iron in patients with ID (Table 4)[5-10,18-20]. In the FAIR-HF (Ferinject Assessment in patient with IRon deficiency and chronic Heart Failure) trial, the use of IV ferric carboxymaltose in patients of HF

Table 4. Conclusion of Major Clinical Trials and Meta-analyses Related to the Role of Intravenous Iron Therapy in Patients with Heart Failure[5-10,18-20]

Study	Year	Conclusion
FAIR-HF[5]	2009	• Treatment with intravenous (IV) ferric carboxymaltose improves symptoms, functional capacity and quality of life in patients with chronic HF and ID, regardless of anemia. • IV ferric carboxymaltose has an acceptable side-effect profile.
CONFIRM-HF[6]	2015	• IV ferric carboxymaltose over 1 year in symptomatic iron deficient HF patients resulted in sustainable improvement in functional capacity, symptoms, and quality of life. • It may be associated with a risk reduction of hospitalization for worsening HF.
IRONOUT-HF[7]	2017	• High-dose oral iron over 16 weeks did not improve exercise capacity among participants with HF with reduced ejection fraction (HFrEF) with ID.
AFFIRM-AHF[8]	2020	• Treatment with IV ferric carboxymaltose in patients with left ventricular ejection fraction (LVEF) of <50%, ID and who were stabilized after an episode of acute HF resulted in reduced risk of HF hospitalizations. • There was no apparent effect on the risk of cardiovascular death.
IRONMAN[19]	2022	• In patients with HF, reduced LVEF, and ID, IV ferric derisomaltose administration was associated with a lower risk of hospital admissions for HF and cardiovascular death.
HEART-FID[18]	2023	• Ambulatory patients of HFrEF and ID, did not demonstrate any benefit in hierarchical composite of death, hospitalizations for HF, or 6-minute walk distance with IV ferric carboxymaltose.
Meta-analysis by Myint et al[20]	2022	• Patients with HF and ID demonstrated lower HF hospitalizations with IV iron therapy. • IV iron therapy improves the quality of life and decreases health care expenditure.
Meta-analysis by Graham et al[9]	2023	• In HF patients with ID, IV iron therapy reduces the risk of hospitalization for HF. • Its effect on cardiovascular or all-cause mortality remains inconclusive.
Meta-analysis by Salah et al[10]	2023	• IV iron therapy in patients with HF reduces the composite risk of first hospitalization for HF and cardiovascular mortality. • There was a reduction in first and recurrent hospitalizations for HF. • No effect on all-cause mortality or cardiovascular mortality.

with ID showed significant improvement in NYHA classification, functional capacity, and quality of live[5]. The results were similar in patients with anemia and without anemia. AFFIRM-AHF, a randomized, double-blind, placebo-controlled trial comparing the effect of IV ferric carboxymaltose on hospitalizations and mortality in iron deficient subjects admitted for acute HF, investigated the effect of IV ferric carboxymaltose on outcomes in patients who were stabilized after an episode of acute HF. Patients who received IV ferric carboxymaltose, showed a significant reduction in HF hospitalization compared to placebo (relative risk [RR], 0.74; 95% confidence interval [CI], 0.58-0.94) but no reduction in cardiovascular death[8]. IRONMAN (Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency) trial investigated the long-term safety and efficacy of IV ferric derisomaltose in a predominately outpatient HF population. Data suggested numerically lower HF hospitalizations and cardiovascular death in patients who received the ferric derisomaltose arm (22.4 per 100 patient-years) than in the placebo arm (27.5 per 100 patient-years). However, it failed to reach significance (p = 0.07)[19].

A meta-analysis conducted by Myint et al revealed a 13.8% decreased risk of HF hospitalizations (odds ratio [OR] 0.59; 0.35-0.98, p = 0.040) and a 17.5% reduction in the composite outcome of HF hospitalizations or cardiovascular mortality. All-cause and cardiovascular mortality were not different between IV iron and placebo groups[20].

Similar results were observed in a meta-analysis of 10 randomized controlled trials by Graham et al. It suggested a significant reduction in composite outcomes of recurrent hospitalizations for HF and cardiovascular mortality (rate ratio 0.75, 95% CI 0.61-0.93; p < 0.01) and first hospitalization for HF or cardiovascular death (OR 0.72, 95% CI 0.53-0.99; p = 0.04) in the group of patients who received IV iron as compared to those who received placebo or standard care. Similar to the prior meta-analysis, effects on cardiovascular (OR 0.86, 95% CI 0.70-1.05; p = 0.14) and all-cause mortality (OR 0.93, 95% CI 0.78-1.12; p = 0.47) were inconclusive[9].

Calculating Iron Deficit

Conventionally, the total iron deficit is estimated using the modified Ganzoni formula[21]. This equation estimates iron deficit by calculating iron attached to deficit hemoglobin. In healthy individuals, blood volume is 7% (0.07) of body weight. Iron content in hemoglobin is 0.34% (0.0034) g/dL. So, the total iron deficit in mg/L will be as below.

Iron deficit = weight (kg) × (target Hb - actual Hb) × 0.0034*0.07*10,000 + Depot iron.

Depot iron here represents an extra depot dose to replenish iron stores. This is usually kept at 500 mg. Notably, the above-mentioned formula may not accurately reflect the actual iron needs of the patient. It is crucial to consider other factors, such as inflammation, comorbidities and medication while estimating iron deficits in HF patients.

Selection of Iron Formulation

Oral iron formulations are not the preferred choice to treat ID in patients with HF. The IRONOUT HF (Iron Repletion effects ON Oxygen UpTake in Heart Failure) trial investigated the effects of oral iron therapy on exercise capacity and quality of life score in patients with HF with reduced ejection fraction and ID. Despite improvement in iron biomarkers such as transferrin saturation and ferritin levels, exercise capacity was not improved compared to placebo[7]. Unlike oral iron therapy, IV iron therapy benefits the 6-minute walk test distance, peak oxygen consumption, quality of life, and improvement in NYHA class[9]. IV iron formulations contain a core of iron hydroxide enveloped by variable carbohydrate complexes[22]. The carbohydrate envelope in the earlier formulation was composed of high molecular weight dextran. These formulations are no longer preferred due to the high risk of serious drug events associated with them[4]. Iron sucrose, ferric carboxymaltose, and ferric derisomaltose are the three most commonly studied nondextran IV iron formulations to treat ID in patients with HF (Table 5)[5,6,8,18,19,23,24]. Data from a recent meta-analysis demonstrated no significant difference in outcome

Table 5. Intravenous Iron Formulation Available for Management of Iron Deficiency in Heart Failure[5,6,8,18,19,23,24]

Formulation	Maximum dose (in single setting)	Duration of administration	Evidence in HF
Iron sucrose	200 mg	30 min	Toblli et al[23] FERRIC-HF[24]
Ferric carboxymaltose	1,000 mg	15 min	FAIR-HF[5], AFFIRM-AHF[8], HEART-FID[18], CONFIRM-HF[6]
Ferric derisomaltose	20 mg/kg up to 2,000 mg	20 min	IRONMAN[19]

Table 6. Clinical Guidelines for the Management of Iron Deficiency in Heart Failure

	European Society of Cardiology Guidelines	ACC/AHA Guideline
Recommendation of screening	All patients with HF (COR I; LOE C)	All patients with HF
Target population	Symptomatic patients with LVEF <45% (COR II; LOE A) Patients recently hospitalized for HF with LVEF <50% to reduce risk of hospitalization (COR II; LOE B)	Patients with HFrEF and ID (COR II; LOE A)
Treatment effect	Symptomatic patients with LVEF <45%: Alleviate HF symptoms, improve exercise capacity and QOL (COR II; LOE A) Symptomatic patients recently hospitalized for HF with LVEF <50%: Reduce the risk of hospitalization (COR II; LOE B)	Improve exercise capacity and QOL (COR II; LOE A)
Diagnosis	Serum ferritin <100 or Serum ferritin 100-300, if TSAT <20%	Serum ferritin <100 or Serum ferritin 100-300, if TSAT <20%
Management	Iron replacement with IV ferric carboxymaltose	IV iron replacement

between different IV iron-carbohydrate formulations when similar end points were measured[25].

Current Guidelines

Based on ample evidence, the 2021 European Society for Cardiology guidelines and the 2022 AHA/ACC/HFSA guidelines recommend using IV iron to improve functional status and quality of life in groups of patients with HF and ID (Table 6)[26,27].

FUTURE PROSPECTS

Novel markers and therapeutic options for managing ID are in the research spotlight. Newer diagnostic markers diagnose ID more accurately in the HF setting and can differentiate AID from FID. Some key diagnostic markers are sTfR, reticulocyte hemoglobin concentration, RDW, sTfR: log (ferritin) ratio, and serum hepcidin levels. sTfR levels increase in response to ID to absorb more iron. sTfR, therefore, may diagnose functional iron status more accurately than traditional markers.

Reticulocyte hemoglobin concentration represents iron available for new red blood cell production. Low levels of reticulocyte hemoglobin concentration are a clear sign of ID. RDW measures the red blood cell size variation. Higher RDW values suggest disrupted red cell production, which could indicate ID. sTfR: log (ferritin) ratio is another marker that helps distinguish FID from AID. Higher levels are consistent with FID. Lastly, the estimation of hepcidin levels helps to understand iron homeostasis. Hepcidin inhibits iron's release from body stores. Thus, elevated levels are consistent with FID[17].

Nanosized iron preparations are emerging oral iron therapies that may help to resolve concerns of poor absorption and gastrointestinal side effects related to traditional oral iron therapy[28].

Compounds that antagonize hepcidin or its effects could help ameliorate HF-associated ID and are in the research phase. The use of such compounds in clinical settings warrants further investigation and testing[29]. While more research is needed to fully understand the safety and efficacy of these newer therapeutic options, they represent exciting advances in cardiovascular medicine.

CONCLUSION

Iron deficiency is a frequent comorbidity in HF patients. HF adversely affects iron homeostasis, leading to states ranging from AID to FID. According to current guidelines, ID in HF is diagnosed using serum ferritin and transferrin. However, upcoming markers such as sTfR, reticulocyte hemoglobin concentration and RDW may help diagnose ID more accurately in patients with HF. Further, novel investigations such as sTfR, sTfR: log (ferritin) ratio, or hepcidin levels could more effectively discriminate AID from FID. Once diagnosed, nondextran IV iron therapy is safe and effective in improving functional class and quality of life in patients of ID with HF.

Although current therapy does not offer cardiovascular mortality benefits, innovative therapies (hepcidin inhibitor, nanoparticle and gene therapy) may be more effective for treating ID.

Key Messages of the Current Manuscript

- Iron deficiency worsens the clinical symptoms and functional class related to HF.
- Patients with HF may suffer from absolute or functional ID. These two conditions may happen independently or simultaneously.
- Serum ferritin and transferrin saturation can diagnose ID with modest sensitivity and specificity in the HF setting. Novel markers for a more accurate diagnosis of ID and distinguishing the two types are in the research phase.
- Nondextran IV iron formulation therapy is currently approved for managing ID in HF. Newer therapies like nanosized iron preparation and therapy targeting hepcidin are under clinical trials.

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During the preparation of this work the authors used Grammarly AI tool in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

REFERENCES

1. Dunn LL, Suryo Rahmanto Y, Richardson DR. Iron uptake and metabolism in the new millennium. Trends Cell Biol. 2007;17(2):93-100.
2. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2013;165(4):575-82.e3.
3. Yeo TJ, Yeo PS, Ching-Chiew Wong R, Ong HY, Leong KT, Jaufeerally F, et al. Iron deficiency in a multi-ethnic Asian population with and without heart failure: prevalence, clinical correlates, functional significance, and prognosis. Eur J Heart Fail. 2014;16(10):1125-32.
4. Beavers CJ, Ambrosy AP, Butler J, Davidson BT, Gale SE, Mastoris I, et al. Iron deficiency in heart failure: a scientific statement from the Heart Failure Society of America. J Card Fail. 2023;29(7):1059-77.
5. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. New Engl J Med. 2009;361(25): 2436-48.
6. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015;36(11):657-68.
7. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, et al; NHLBI Heart Failure Clinical Research Network. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. JAMA. 2017;317(19):1958-66.
8. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, et al; AFFIRM-AHF investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet. 2020;396(10266): 1895-904.
9. Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. Eur J Heart Fail. 2023;25(4):528-37.
10. Salah HM, Savarese G, Rosano GMC, Ambrosy AP, Mentz RJ, Fudim M. Intravenous iron infusion in patients with heart failure: a systematic review and study-level meta-analysis. ESC Heart Fail. 2023;10(2):1473-80.
11. Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. Blood. 2003;101(7):2461-3.
12. Franchini M, Montagnana M, Lippi G. Hepcidin and iron metabolism: from laboratory to clinical implications. Clin Chim Acta. 2010;411(21-22):1565-9.
13. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. Circulation. 2018;138(1):80-98.
14. Andrews NC. Disorders of iron metabolism. N Engl J Med. 1999;341(26):1986-95.
15. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(11):1324-40.
16. Grote Beverborg N, Klip IT, Meijers WC, Voors AA, Vegter EL, van der Wal HH, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. Circ Heart Fail. 2018;11(2):e004519.
17. Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. Clin J Am Soc Nephrol. 2006;1 Suppl 1:S4-8.
18. Mentz RJ, Garg J, Rockhold FW, Butler J, De Pasquale CG, Ezekowitz JA, et al; HEART-FID Investigators. Ferric carboxymaltose in heart failure with iron deficiency. N Engl J Med. 2023;389(11):975-86.
19. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, et al; IRONMAN Study Group. Intravenous

ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet. 2022;400(10369):2199-209.

20. Myint PT, Nandar PP, Thet AM, Orasanu G. Cost-effective heart failure management: Meta-analysis of IV iron therapy in iron-deficient heart failure patients. Am Heart J Plus Cardiol Res Pract. 2022;22:100204.
21. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. Schweiz Med Wochenschr. 1970;100(7):301-3.
22. Von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. JACC Heart Fail. 2019;7(1):36-46.
23. Toblli JE, Lombraña A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol. 2007;50(17):1657-65.
24. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency: FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol. 2008;51(2): 103-12.
25. Sindone A, Doehner W, Comin-Colet J. Systematic review and meta-analysis of intravenous iron-carbohydrate complexes in HFrEF patients with iron deficiency. ESC Heart Fail. 2023;10(1):44-56.
26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
27. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):e263-421.
28. Singh K, Chopra DS, Singh D, Singh N. Nano-formulations in treatment of iron deficiency anaemia: an overview. Clin Nutr ESPEN. 2022;52:12-9.
29. Sagar P, Angmo S, Sandhir R, Rishi V, Yadav H, Singhal NK. Effect of hepcidin antagonists on anemia during inflammatory disorders. Pharmacol Ther. 2021;226:107877.

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CLINICAL STUDY

A Controlled Clinical Study to Evaluate the Comparative Effect of Anuloma DS Tablet and Lactitol + Ispaghula Powder in Functional Constipation

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ABSTRACT

Background: The International Classification of Diseases (ICD) has described constipation as decrease in normal frequency of defecation accompanied by difficult or incomplete passage of stool and/or passage of excessively hard, dry stool (ICD10-CM-K59). Overall, the average prevalence of constipation in adults has been estimated as 16% worldwide (varies between 0.7% and 79%); in adults aged 60 to 110 years, the prevalence has been estimated to be 33.5%. **Objective:** To evaluate and compare the efficacy of tablet Anuloma DS and lactitol + ispaghula powder in constipation. **Materials and methods:** Sixty-two subjects with constipation were divided into two groups: Group A with 32 subjects and Group B with 30 subjects. Group A received 1 Anuloma DS tablet at bedtime and Group B received lactitol + ispaghula powder 5 g at bedtime for 15 days. **Results:** Twenty-eight patients in Group A showed significant improvement in stool consistency of stool, whereas just 8 patients showed improvement in consistency of stool in Group B. Twenty patients showed improvement in frequency of stool in Group A, whereas only 3 patients showed this improvement in Group B. Twenty-nine patients in Group A reported good improvement in feeling after defecation compared to 9 patients in Group B. Pain in abdomen improved in 21 patients in Group A versus 9 patients in Group B. Improvements were also seen in scores on the Constipation Assessment Scale, Patient Assessment Scale, and Quality of Life Questionnaire. **Conclusion:** Anuloma DS showed significant clinical benefits in the treatment of constipation compared to lactitol + ispaghula powder.

Keywords: Anuloma DS, constipation, Constipation Assessment Scale, ispaghula, lactitol

The fast-paced, lifestyle adopted by many individuals in today's competitive society has had a significant impact on the health of the gastrointestinal tract resulting in a rising prevalence of gastrointestinal disorders.

Constipation, or *Vibandha*, is one such outcome. *Vibandha* is not mentioned in Ayurvedic texts as a specific disease but has been mentioned as a *Nidana* (causative factor), *Lakshana* (symptoms), and *Upadrava* (complications) of several diseases. It can be considered as a *Lakshana* in *Udavarta* (retention of feces, flatus, and urine) like *Anaha* (obstruction), *Adhmana* (distension), *Malaavastamba* (hardness of feces) due to the *Pratiloma Gati* (reverse flow) of *Apana Vayu*[1].

Vibandha (constipation) is the obstruction of the *Purisha* (feces) in the *Purishavaha Srotas* (excretory system). Constipation is a warning sign for many current or imminent disorders.

The International Classification of Diseases, (ICD10-CM-K59), defines constipation as the decrease in normal frequency of defecation accompanied by difficult or incomplete passage of stool and or passage of excessively hard and dry stool. The prevalence of constipation in India is estimated to be 16.8% and that of self-reported constipation is 24.8%[2]. Overall, the average prevalence of constipation in adults has been estimated to be 16% worldwide (varies between 0.7% and 79%), whereas the prevalence in adults aged 60 to

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110 years was 33.5%[3]. Epidemiological studies show that the prevalence of constipation increases with the age and is more common in women than in men[4].

Various pharmacological agents such as bulk laxatives, stimulant laxatives, stool softeners, osmotic agents, lubricant laxatives, suppositories, and enema are used in clinical practice to treat constipation. However, their long-term use may cause electrolyte disturbance, dehydration and mineral deficiencies, and may even produce drug dependency.

Hence, there is a need for an alternative therapeutic approach, which not only manages the condition, but also minimizes the recurrence of symptoms.

Anuloma DS is an Ayurvedic proprietary medicine that contains different medicinal plants such as *Cassia lanceolata* (Senna), *Apium leptophyllum* (Ajamoda), *Cuminum cyminum* (Cumin or Jeeraka), *Terminalia chebula* (Haritaki), *Glycyrrhiza glabra* (Liquorice), *Zingiber officinale* (Ginger or Shunti), and Halite (Rock salt). These drugs are *Agnideepaka* (increase the digestive fire), *Katu Rasa* (pungent taste), *Ushna Veerya* (hot potency), and *Katu Vipaka*[5].

The primary objective of this comparative study was to evaluate the efficacy of Anuloma DS tablet and lactitol + ispaghula powder in relieving constipation. Improvements in the Quality of Life Questionnaire, Constipation Assessment Scale, and Patient Assessment Scale were the secondary objectives of the study.

METHODS

The study designed as an open-label comparative double arm clinical study enrolled 62 subjects visiting medicine OPDs of our hospital for the treatment of constipation. After screening, eligible subjects were instructed to take either Anuloma DS 1 tablet at bedtime with warm water or lactitol + ispaghula powder 5 g at bedtime with warm milk for a period of 15 days. Written informed consent was obtained from all participants on Day 1. The study was undertaken after approval by the Institutional Ethics Committee.

The inclusion criteria were male and female adults aged 18 to 70 years, who were suffering from functional constipation, were willing to sign consent form and were able to present for follow-ups.

The primary study objective assessed changes in symptoms of constipation such as consistency of stool, frequency of stool, nature of evacuation, pain in abdomen, generalized weakness, headache, body ache, and muscle cramps. Secondary end points were changes in the Constipation Assessment Scale, which evaluates 8 domains such as abdominal distension, change in amount of gas pass rectally, less frequent bowel movement, oozing of liquid stool, rectal fullness, rectal pain, small stool size, and urge but inability to pass stool. Patient assessment of constipation contain 12 domains such as discomfort- pain-bloating in abdomen, stomach cramp, painful bowel movement, rectal burning, rectal bleeding, incomplete bowel movement, hard bowel movement, small bowel movement, straining to pass bowel movement, and false alarm. And the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire is a brief but comprehensive tool, which evaluates constipation through daily individual health assessment and functioning.

Constipation was diagnosed based on the Rome IV criteria[6] as follows:

- Fewer than 3 spontaneous bowel movements per week.
- Straining for more than 25% of defecation attempts.
- Lumpy or hard stools for more than 25% defecation attempts.
- Sensation of anorectal obstruction or blockage for more than 25% of defecation attempts.
- Sensation of incomplete defecation for more than 25% of defecation attempts.
- Manual maneuvering required to defecate for more than 25% of defection attempts.

Exclusion criteria were the presence of irritable bowel syndrome, inflammatory bowel disorder, colon carcinoma, medication known to cause constipation (opioid analgesics, antidepressants, anticonvulsants, amitriptyline), uncontrolled systemic ailments or neurological illness, pregnancy and lactation.

The study participants were evaluated at baseline and two assessment points (Visit 1- Day 1 and Visit 2- Day 15). Patients underwent history and physical examination at all assessments points. They were also enquired about constipation signs and symptoms and evaluated with the Constipation Assessment Scale, Patient Assessment Scale, and Quality of Life Questionnaire. Concomitant medication and adverse events were also assessed.

Data comparison between baseline and follow-up visit was performed using a Friedman test, Wilcoxon signed rank test, Mann-Whitney test, unpaired and paired *t*-tests. A p value of 0.05 was considered statistically significant. Statistical analysis was done using statistical software SPSS 21.0.

RESULTS

A total of 62 subjects were enrolled in the study. Two subjects were dropped as they did not come for follow-up. Hence, 60 subjects were included in the final analysis. Age-wise distribution of subject shows that 28 subjects belong to the age group 18 to 27 years, while 10 subjects belonged to 48 to 57 years. Out of 60 subjects, 34 were females and 26 were males. Thirty-eight subjects belonged to middle class and the diet-wise distribution showed equal number in both vegetarian and mixed diet. Table 1 describes the demographic characteristics of the participants.

Table 1. Demographic Data of the Enrolled Subjects (n = 60)

Age (years)	Group A (Anuloma DS)	Group B (Lactitol + Ispaghula)
18-27	15	13
28-37	2	4
38-47	3	4
48-57	3	7
58-67	7	2
Gender	**Group A**	**Group B**
Male	13	13
Female	17	17
Diet	**Group A**	**Group B**
Mixed	15	18
Vegetarian	15	12

Assessment of Signs and Symptoms of Constipation

Constipation symptoms such as reduced appetite, distension of abdomen, pain in abdomen, general weakness, headache, body ache, muscle cramps, consistency of stool, frequency of stool, nature of evacuation, feeling after defecation were assessed on a 4-point scale. The mean symptom scores were significantly improved in Group A compared to Group B as shown in Tables 2 & 3 and Figure 1.

Constipation Assessment Scale and Patient Assessment Scale

Significant improvements were observed in the Constipation Assessment Scale and Patient Assessment Scale in Group A (Anuloma DS) ($p < 0.00$) (Table 4 and Fig. 2).

Assessment of Quality of Life

Group A had significantly greater improvement in quality of life than Group B as assessed via the Quality of Life Questionnaire (Table 5).

DISCUSSION

Constipation is a common condition that affects people of all ages. It is often erroneously attributed to the natural aging process. Although aging is associated with changes in the gastrointestinal tract and may predispose one to develop constipation, the disorder usually has a multifactorial etiology.

Etiologically, constipation can be broadly divided into two main groups: primary and secondary[7]. Primary or functional constipation is defined as constipation for more than 6 months[8], which is not due to any underlying cause such as medication side effect or an underlying medical condition. It can be distinguished from irritable bowel syndrome based on the absence of abdominal pain. It is the most prevalent type of constipation and frequently has multiple causes. Diets, such as consuming too little fiber or water, or behaviors such as engaging in less physical activity are the main culprits[9].

The incidence of gastrointestinal diseases had an unprecedented hike in recent years. This is mainly due to changes in lifestyle, food habits, behavioral changes, etc. *Annavaha Sroto dushti Vikaras* (disease of gastrointestinal system) explained in Ayurveda classics share similarity with gastrointestinal disorders in terms of etiopathogenesis and symptomatology. *Vibandha* (constipation) is a disease of *Annavaha Srotas* (gastrointestinal system) caused by disturbances of *Agni* (digestive fire). Irregular dietary habits, behavioral changes, stress, etc. lead to *Agnimandya* (weakened digestive fire), which causes *Ajeerna* (indigestion) and then constipation.

Abnormalities of *Samana* (kindling *vata*) – *Apana Vayu* (descending *vata*), *Pachaka Pitta* (digesting *pitta*), and *Kledaka Kapha* (moistening *kapha*) also play significant roles in causing constipation. Along with the difficulty in passing stools, other symptoms like pain in abdomen, flatulence, rectal pain, hemorrhoids, headache can also be associated with constipation. Chronic uncontrolled cases of constipation can lead to complications like *Udavarta*, *Vataja* gulma, *Vatodara*.

Management of constipation includes correction of *Agni*, movement of *Apana Vata* and normalizing the vitiated *Pachaka Pitta* and *Kledaka Kapha*. Different formulations like *Churna*, *Kashaya*, *Arishta*, *Ghrita* are indicated in the management of *Vibandha.*

Management of constipation in contemporary medicine includes lifestyle modifications such as introduction

Table 2. Comparison of Mean Changes in Symptom Score from V1 and V2 (n = 60)

Parameters	Group A (Study Group)			Group B (Control Group)		
	Visit	Mean score (Mean ± SD)	P value	Visit	Mean score (Mean ± SD)	P value
Reduced appetite	V1	1.40 ± 0.724	0.00	V1	1.17 ± 0.747	0.317
	V2	0.47 ± 0.507		V2	1.13 ± 0.730	
Distension of abdomen	V1	1.43 ± 0.626	0.00	V1	1.33 ± 0.711	0.01
	V2	0.40 ± 0.498		V2	1.10 ± 0.712	
Pain in abdomen	V1	0.93 ± 0.785	0.00	V1	0.70 ± 0.750	0.003
	V2	0.20 ± 0.484		V2	0.40 ± 0.498	
Generalized weakness	V1	1.03 ± 0.850	0.00	V1	0.90 ± 0.885	0.002
	V2	0.23 ± 0.430		V2	0.57 ± 0.679	
Headache	V1	0.57 ± 0.858	0.00	V1	0.50 ± 0.777	0.03
	V2	0.10 ± 0.403		V2	0.33 ± 0.606	
Body ache	V1	0.60 ± 0.770	0.00	V1	0.53 ± 0.937	0.03
	V2	0.10 ± 0.305		V2	0.37 ± 0.669	
Muscle cramps	V1	0.57 ± 0.898	0.00	V1	0.80 ± 1.031	0.01
	V2	0.17 ± 0.461		V2	0.60 ± 0.814	
Stool consistency	V1	2.27 ± 0.583	0.00	V1	2.17 ± 0.531	0.01
	V2	1.10 ± 0.305		V2	1.90 ± 0.607	
Stool frequency	V1	1.37 ± 0.556	0.00	V1	1.20 ± 0.407	0.08
	V2	1.00 ± 0.00		V2	1.10 ± 0.305	
Nature of evacuation	V1	2.33 ± 0.479	0.00	V1	2.30 ± 0.535	0.01
	V2	1.27 ± 0.450		V2	2.07 ± 0.640	
Feeling after defecation	V1	2.30 ± 0.466	0.00	V1	2.30 ± 0.596	0.01
	V2	1.20 ± 0.407		V2	2.00 ± 0.695	

Table 3. Comparison of Mean Changes in Symptom Score (n = 60)

	Reduced appetite		Distension of abdomen		Pain in abdomen		Generalized weakness		Headache	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
MR	23.2	37.8	22.7	38.3	27.2	33.8	26.65	34.35	27.5	33.4
SR	695.0	1135.0	681.0	1149.0	816.0	1014.0	799.5	1030.0	827.0	1003.0
P	0.0		0.00		0.06		0.04		0.05	

	Body ache		Muscle cramps		Stool consistency		Stool frequency		Nature of evacuation		Feeling of defecation	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
MR	27.8	33.1	26.3	34.7	20.3	40.7	29.0	32.0	21.1	39.9	21.3	39.3
SR	835.5	994.5	789.0	1041.0	609.0	1221.0	870.0	960.0	632.0	1198.0	639.0	1191.0
P	0.08		0.02		0.00		0.08		0.00		0.00	

MR: Mean Rank; SR: Sum Rank; P: P value

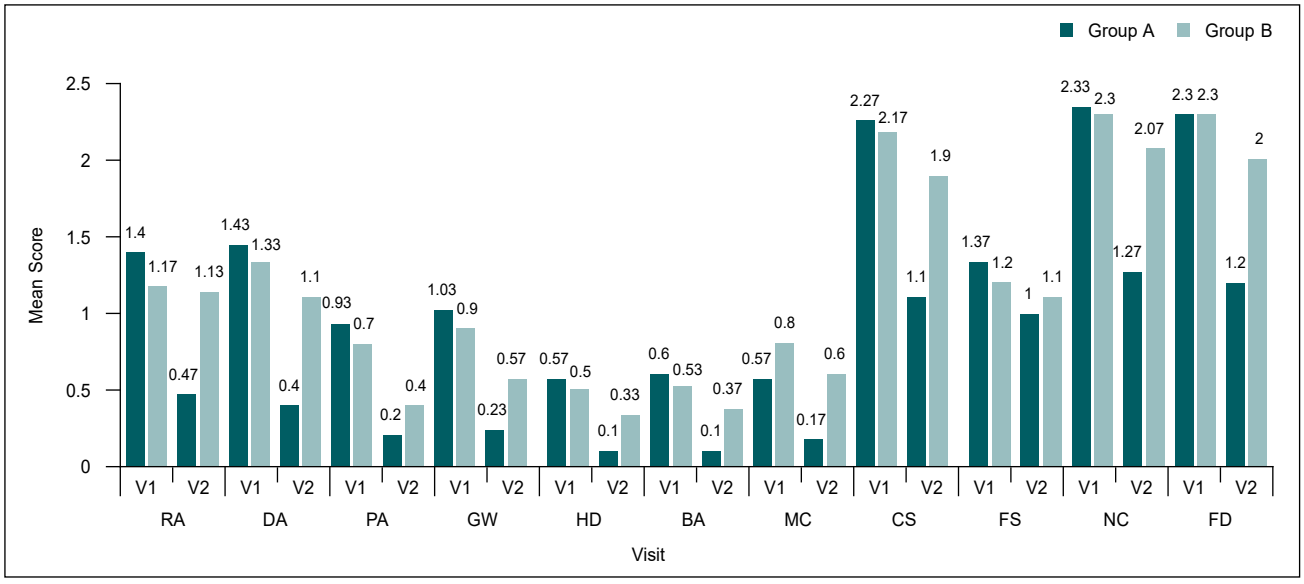

Figure 1. Comparison of mean changes in symptom score from V1 to V2 (n = 60).

RA: Reduced appetite; DA: Distension of abdomen; PA: Pain in abdomen; GW: Generalized weakness; HD: Headache; BA: Body ache; MC: Muscle cramps; CS: Stool consistency; FS: Stool frequency; NC: Nature of evacuation; FD: Feeling after defecation.

Table 4. Comparison of Mean Changes in Constipation Assessment Scale and Patient Assessment Scale from V1 to V2 (n = 60)

Parameters	Group A				Group B			
	Visit	Mean ± SD	SE	P value	Visit	Mean ± SD	SE	P value
Constipation Assessment Scale	V1	5.03 ± 2.13	0.388	<0.00	V1	5.77 ± 2.72	0.498	0.02
	V2	1.73 ± 1.20	0.225		V2	5.60 ± 2.64	0.483	
Patient Assessment Scale	V1	11.8 ± 6.08	1.110	<0.00	V1	12.3 ± 5.37	0.981	0.002
	V2	6.0 ± 3.37	0.061		V2	11.9 ± 5.10	0.931	

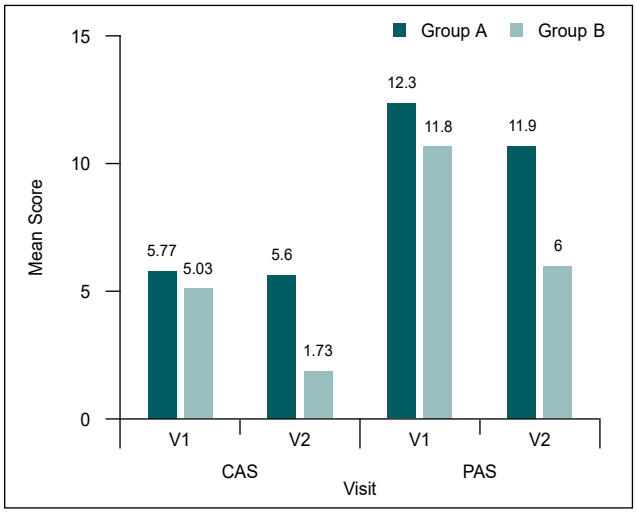

Figure 2. Comparison of mean changes in Constipation Assessment Scale and Patient Assessment Scale from V1 to V2 (n = 60).

CAS: Constipation Assessment Scale; PAS: Patient Assessment Scale.

of high-fiber diet, plenty of water intake, physical exercise, and good bowel habits. Various classes of laxative medications include fiber supplements, osmotic laxatives, stimulant laxatives, lubricants, stool softeners, etc. Enemas and suppositories are used when the above treatments yield no result[10].

Various studies report that women are more than twice as likely to develop constipation as men. This is attributed to the slower gut transit in women due to the changing levels of progesterone and estrogen or damage to the pelvic floor in a women's obstetric history.

Considering the socioeconomical background and dietary habits of the locality, it is not possible to draw any conclusions. Out of 60 subjects, 22 were of *Vata-Kapha Prakriti* and 16 were of *Vata-Pitta Prakriti*. *Vibandha* (constipation) is a *Vata-Dosha Pradhana Vyadhi* (main disease), which may be common among people with *Vata*-predominant *Prakriti*.

Table 5. Comparison of Mean Changes in Quality of Life (PAC-QOL) from V1 to V2 (n = 60)

Parameters	Group A				Group B			
	Visit	Mean ± SD	SE	P value	Visit	Mean ± SD	SE	P value
Quality of life	V1	50.6 ± 13.2	2.404	<0.00	V1	49.5 ± 12.4	2.235	0.001
	V2	29.9 ± 10.3	1.886		V2	33.8 ± 11.4	2.083	

SD = Standard deviation; SE = Standard error.

In this study, patients in Group A (Anuloma DS tablet) showed significant improvement in primary and secondary outcome measures compared to Group B (lactitol + ispaghula powder) after 15 days of intervention.

Appetite was improved in 26 subjects of the study group and remained same in 4 subjects. In the control group, appetite improved in 1 subject, but remained same in 29 subjects of the control group. Anuloma DS contains *Agnideepaka* herbs like *Ajamoda*, *Shunti* and *Jeeraka, Katu Rasa, Ushna Veerya*, and *Katu Vipaka*, which help in improving the appetite.

Distention of abdomen was found to be reduced in 28 subjects of study group and 7 subjects in control group after intervention. This can be attributed to the *Vata Anulomana* property of Haritaki, which properly digests the *Mala* and facilitates the passage of *Apana Vata*.

Pain in abdomen was reduced in 21 subjects and remained same in 9 subjects of study group and 9 subjects showed reduced symptoms and remained same in 21 subjects in control group. *Shunti* and *Ajamoda* possess *Shoolaghna* property, which helped reduced the abdominal pain.

Generalized weakness was reduced in 20 subjects and remained same in 10 patients. *Agnideepaka* drugs helped in normalizing the *Agni* thereby facilitating digestion and absorption. This might have helped in reducing the generalized weakness. Reduction in generalized weakness is also attributed to *Yashtimadhu*, which is a *Jeevaniya dravya* having *Balya, Glanihara*, and *Kshayahara* properties.

Headache was reduced in 11 subjects, but remained the same in 19 subjects in Group A. Body ache was reduced in 13 subjects and remained same in 17 subjects. Muscle cramp was reduced in 8 subjects and remained same in 22 subjects.

Consistency of stool was improved in 28 subjects and remained same only in 2 subjects and 8 subjects improved and 22 subjects remained in control group. Haritaki is *Anulomana dravya*, which does the *Malapaka* resulting in improved consistency of stool.

Frequency of stool was improved in 20 subjects and remained same in 10 subjects and 3 subjects showed improvement and 27 subjects remain in control group. Sonamukhi is *Adhoshodhaka* (laxative) dravya and *Saindhava Lavana* is *Vibandha Hara dravya*. Both helped in improving the stool frequency.

Nature of evacuation was improved in 27 subjects and 7 subjects in study and control group, respectively. Feeling after defecation was improved in 29 subjects and 9 subjects in study group and control, respectively. This was due to the improvements observed in appetite, digestion, consistency, and frequency of stool. Ingredients of tablet Anuloma DS were not only effective in facilitating defecation, but also helped in increasing appetite and digestion. This helped in proper absorption, formation and elimination of stools. This was significantly evident in secondary outcome measures such as Constipation Assessment Scale, Patient Assessment Scale of constipation and Quality of Life Scale.

CONCLUSION

Functional constipation refers to a condition where individuals experience hard, infrequent bowel movements that are often difficult or painful to pass. It is not caused by any apparent physical abnormalities or specific diseases; instead, it is diagnosed by ruling out other potential causes. The current study as demonstrated significant improvement in signs and symptom of constipation such as stool consistency and frequency, nature of evacuation, feeling of defecation, reduced appetite, pain and distention of abdomen, general weakness, headache, body ache, and muscle cramps with Anuloma DS tablets compared to the lactitol + ispaghula powder in patients with functional constipation. The improvement observed in PAC-QOL, Constipation Assessment Scale, Patient Assessment Scale show that Anuloma DS was highly effective for the treatment in functional constipation vis-à-vis lactitol + ispaghula powder. It was also safe as no treatment-related adverse effects were reported by any of the study participants. This beneficial effect can be attributed to the synergistic therapeutic action of its constituent herbs.

REFERENCES

1. Murthy Shrikantha KR (editor). *Sushruta Samhita* of Vol. III. Reprint ed. (India, Varanasi: Chaukhambha Orientalia), Uttara Tantra 2017, 55/7.
2. Rajput M, Saini SK. Prevalence of constipation among the general population: a community-based survey from India. Gastroenterol Nurs. 2014;37(6): 425-9.
3. Forootan M, Bagheri N, Darvishi M. Chronic constipation: a review of literature. Medicine (Baltimore). 2018;97(20):e10631.
4. Wald A, Scarpignato C, Mueller-Lissner S, Kamm MA, Hinkel U, Helfrich I, et al. A multinational survey of prevalence and patterns of laxative use among adults with self-defined constipation. Aliment Pharmacol Ther. 2008;28(7):917-30.
5. Varuni BG. An open-labeled clinical study to evaluate the safety and efficacy of "Anuloma DS" in improving constipation. Indian J Clin Pract. 2023;34(2):15-22.
6. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. J Clin Med. 2017;6(11):99.
7. Jani B, Marsicano E. Constipation: evaluation and management. Mo Med. 2018;115(3):236-40.
8. Chatoor D, Emmnauel A. Constipation and evacuation disorders. Best Pract Res Clin Gastroenterol. 2009;23(4): 517-30.
9. Locke GR 3rd, Pemberton JH, Phillips SF. American Gastroenterological Association Medical Position Statement: guidelines on constipation. Gastroenterology. 2000;119(6):1761-6.
10. Portalatin M, Winstead N. Medical management of constipation. Clin Colon Rectal Surg. 2012;25(1):12-9.

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CASE REPORT

Myocarditis with Unidigital Gangrene in Scrub Typhus Patient – Rare Case

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ABSTRACT

Introduction: Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium. The disease is of greatest public health importance in rural areas of Asia and the Western Pacific Islands. The clinical manifestations range from subclinical disease to organ failure. The chief target of organism is the vascular endothelium of various organs. There is inflammation in and around the blood vessels that causes endothelial damage resulting in vascular leakage and organ dysfunction. **Case report:** A 70-year-old female patient, farmer by occupation, presented to us with features of acute febrile illness and shortness of breath and was diagnosed as scrub typhus with myocarditis. She subsequently developed gangrene of right little finger. The patient was investigated for infectious and noninfectious causes of vasculitis leading to gangrene. We established that the cause for gangrene was scrub typhus as evidenced by presence of eschar and positive serology. **Conclusion:** We report for the first time a case of scrub typhus complicated by both myocarditis and gangrene. Both myocarditis and unidigital gangrene are unusual complications of scrub typhus. Hence, scrub typhus should be ruled out in patients who present with these complications.

Keywords: Scrub typhus, *Orientia tsutsugamushi*, vasculitis, eschar, myocarditis, unidigital gangrene

Scrub typhus, also known as bush typhus, is a zoonotic disease caused by the bacterium *Orientia tsutsugamushi*. It is an obligate, intracellular, Gram-negative coccobacilli and is transmitted to humans by an arthropod vector of Trombiculidae family.

Scrub typhus spreads to people through bite of infected chiggers (infected larval mites)[1]. Mites remain infected throughout different stages (egg, larva, nymph and adult) of their life cycle[2]. Around a billion people are at risk and nearly million cases are reported every year[3]. Scrub typhus was first described in China in 313 AD; it later re-emerged during the Second World War[4].

Scrub typhus is seen worldwide but it is endemic to a part of world known as "Tsutsugamushi Triangle", which extends from Japan and eastern Russia to Australia in south and to Pakistan and Afghanistan in the west[5]. In India, the highest numbers of cases are reported from West Bengal, Assam, Meghalaya, Rajasthan, Maharashtra, and Madhya Pradesh.

Clinically, scrub typhus varies from mild and self-limiting to fatal disease. The incubation period ranges from 6 to 21 days. The onset of the disease is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. The classic case description includes an eschar at the site of chigger bite, regional lymphadenopathy, and maculopapular rashes.[2]

Severe cases typically manifest with encephalitis, meningoencephalitis, myocarditis, pericardial effusion, acute renal failure, multiorgan dysfunction, and focal or pan digital gangrene.

Focal or pan digital gangrene is one among the rare complications that may occur during the acute phase or in the recovery phase of scrub typhus caused due to focal or disseminated vasculitis or perivasculitis of digital blood vessels.[5]

Concomitant presentation of myocarditis with digital gangrene in scrub typhus is very rare; hence, we are reporting this case.

CASE REPORT

A 70-year-old female patient, farmer by occupation, admitted to medical ICU, Maharana Bhupal Government

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Hospital and RNT Medical College, Udaipur, Rajasthan with the complaint of high-grade fever and chills, generalized bodyache, nausea and vomiting, and shortness of breath for last 5 days.

On general examination, the pulse rate was 118 bpm, blood pressure (BP) was 80/60 mmHg, oxygen saturation (SpO_2) was 86% on room air and 96% on 6 liters of oxygen (on the day of admission). She had pallor, icterus, and fever of 100°F orally. An eschar mark was present on the back in the region of left scapula (Fig. 1).

On systemic examination, examination of the cardiovascular system revealed tachycardia, hypotension with muffling of heart sounds without any murmur. Other systemic examination was normal. No organomegaly in the form of hepatosplenomegaly was seen.

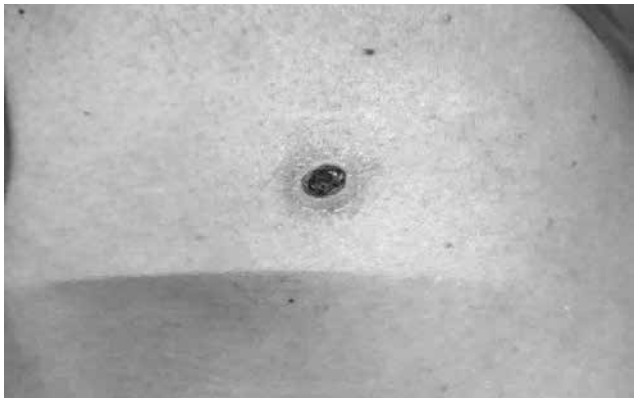

Figure 1. Showing eschar on back of chest.

Clinically, we diagnosed the patient as acute fertile illness with eschar without organomegally suspected to be scrub typhus with cardiogenic shock.

Patient was investigated for acute febrile illness. Laboratory investigations showed hemoglobin (Hb) - 7.6 g/dL, total leukocyte count (TLC) - 8,400 /μL, platelet count - 58,000/μL, blood urea - 182 mg/dL, serum creatinine - 2.7 mg/dL, total bilirubin - 2.07 mg/dL, and direct bilirubin - 1.2 mg/dL.

ECG showed T wave inversion from V2 to V6 (Fig. 2). Trop T on the day of admission was 0.4. Both were monitored daily. Trop T initially increased to 0.7 on the second day. But on the fifth day, both ECG (Figs. 3 and 4) and Trop T were normal.

Chest X-ray, ultrasound abdomen and pelvis were normal. 2D Echocardiogram showed diastolic dysfunction with mild mitral regurgitation. Human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) and hepatitis C virus antibodies (anti-HCV), venereal disease research laboratory (VDRL) tests were negative. Urine analysis was normal.

Specific investigations for acute febrile illness were performed. Dengue IgM, IgG antibodies and NS1 antigen were negative.

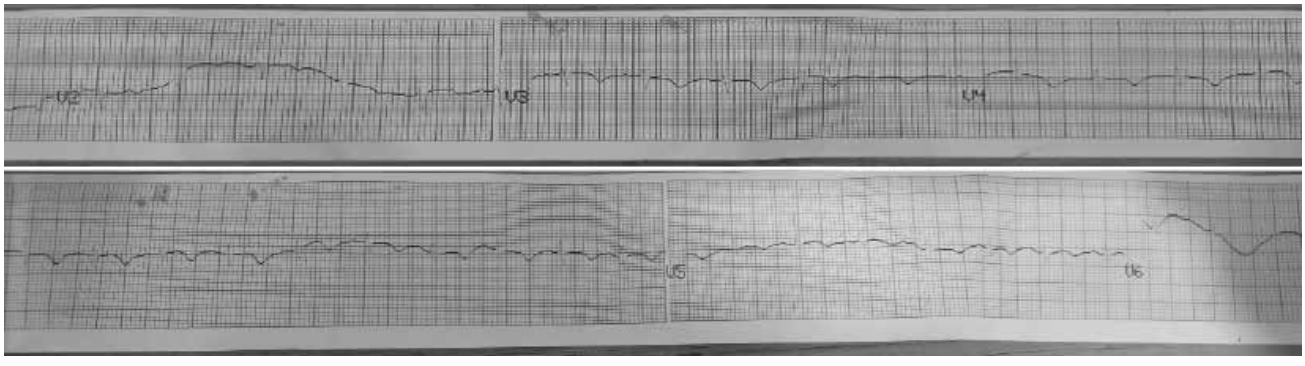

Figure 2. Showing T wave inversion from V2 to V6 (day 1).

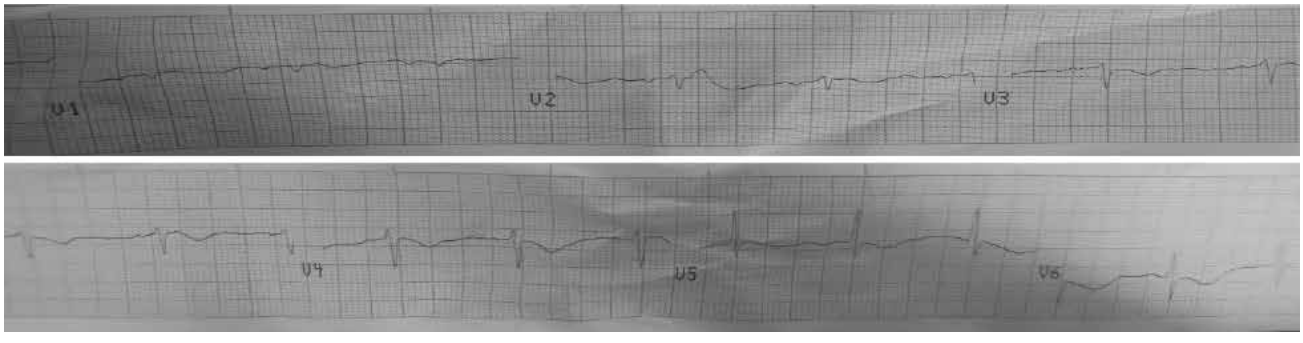

Figure 3. Showing T wave inversion reverting to normal (day 3).

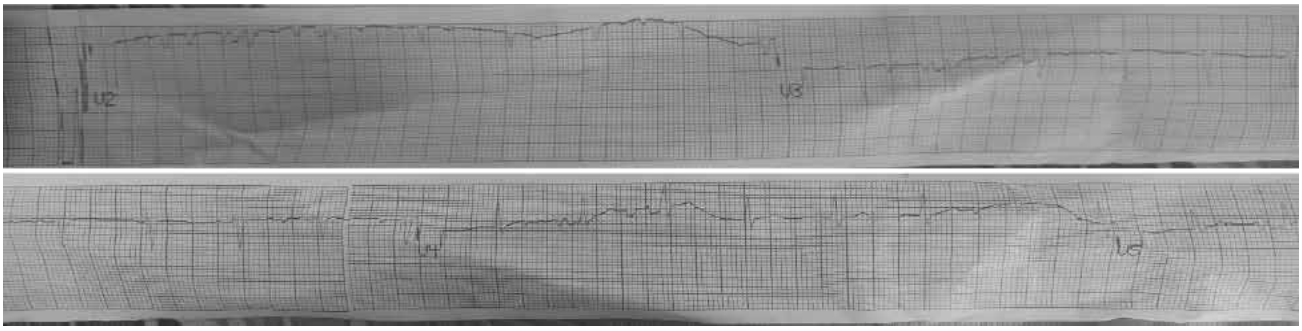

Figure 4. Showing T wave inversion reverted to normal (day 5).

Figure 5. Showing dry gangrene of little finger.

Blood smear and quantitative buffy coat test for malaria parasite were negative. But IgM ELISA (enzyme-linked immunosorbent assay) for scrub typhus was positive. Hence, etiological diagnosis of scrub typhus with myocarditis with multiorgan dysfunction was made.

Patient was put on symptomatic management with antibiotics (doxycycline 100 twice daily), antimalarial drugs, antipyretics, intravenous (IV) fluids and inotrope support.

Despite treatment, the patient complained of burning sensation and blackish discoloration of fingers of the right hand. On examination, we found dry gangrene of the little finger and blackish discoloration of other fingers with a line of demarcation (Fig. 5); peripheral pulses were normal. The patient was referred to a cardiothoracic surgeon, who advised color Doppler of arteries of all four limbs and to also rule out other causes of gangrene such as infectious and autoimmune diseases. HIV, HBsAg, VDRL were nonreactive; the antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), lupus erythematosus cell, cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) tests were also negative. Color Doppler of arteries of all four limbs was normal. Hence, we concluded that scrub typhus was the cause for gangrene.

The patient was treated with antiplatelets, anticoagulants and steroids. When the patient improved clinically, the ionotrope support was tapered and stopped. The patient was discharged and asked to come for review in Medicine as well as Cardiothoracic Vascular Surgery (CTVS) OPDs.

DISCUSSION

Scrub typhus is a serious public health problem of Asia-Pacific region. With involvement of multiple organs, serious complications may develop, which could make the disease potentially fatal.

Myocarditis can be a clinical manifestation of scrub typhus but has rarely been reported. It is usually subclinical and therefore ignored many times[6]. Patient may present with chest pain, shortness of breath, palpitation, cardiogenic shock, congestive heart failure, ECG changes of myocarditis and elevated cardiac enzymes.

Digital gangrene is sign of systemic disease, which can be seen in infectious diseases such as syphilis, leprosy, viral hepatitis, HIV meningococcemia, leptospirosis, and other noninfectious diseases like autoimmune disease such as polyarteritis nodosa, Wegener's granulomatosis (now called granulomatosis with polyangiitis), Churg-Strauss syndrome (involvement of medium-sized artery and systemic lupus erythematosus [SLE]), rheumatoid arthritis, scleroderma, and antiphospholipid syndrome, which may commonly involve small vessels and present with digital gangrene[7].

Gangrene is an uncommon complication of rickettsial disease and very few cases have seen reported worldwide yet. The distribution of gangrene may be due to selective proliferation of these bacteria in cooler body regions leading to vasculitis, perivasculitis, tissue hypoperfusion and gangrene development[8].

Rijhwani et al[9] reported pan-digital gangrene in scrub typhus as a rare case. Avasthi et al[10] reported acute

fulminant myocarditis in scrub typhus as a rare case. Bharathi et al[11] also reported similar cases. But to the best of our knowledge, no case reports have been found on scrub typhus complicated by both myocarditis and digital gangrene in the same patient.

CONCLUSION

Scrub typhus is a re-emerging zoonotic disease in the Indian subcontinent. It is a multiorgan disease as it involves endothelial dysfunction of small blood vessels. Vasculitis is among the serious complications of scrub typhus, which can lead to digital ischemia, gangrene, and myocarditis.

Proper evaluation and early diagnosis and treatment with doxycycline and steroids can help to prevent the development of complications. Our patient showed improvement in the form of disappearance of discoloration of other fingers of right hand at the time of discharge. While going through literature, we found out that a case of concomitant myocarditis and unidigital gangrene in scrub typhus had not yet been reported.

REFERENCES

1. Traub R, Wisseman CL Jr. The ecology of chigger-borne rickettsiosis (scrub typhus). J Med Entomol. 1974;11(3):237-303.
2. Luce-Fedrow A, Lehman ML, Kelly DJ, Mullins K, Maina AN, Stewart RL, et al. A review of scrub typhus (*Orientia tsutsugamushi* and related organisms): then, now, and tomorrow. Trop Med Infect Dis. 2018;3(1):8.
3. Watt G, Parola P. Scrub typhus and tropical rickettsioses. Curr Opin Infect Dis. 2003;16(5):429-36.
4. Scrub typhus. Dated September 29, 2023. Available at: https://emedicine.medscape.com/article/971797-overview#a1. Accessed October 2, 2023.
5. Dave M, Jain S, Nath H, Nagraj. Digital gangrene: a rare complication in scrub typhus. JIACM. 2020;21(3-4):187-9.
6. Soerjomataram I, Bray F. Planning for tomorrow: global cancer incidence and the role of prevention 2020–2070. Nat Rev Clin Oncol. 2021;18(10):663-72.
7. Cracco C, Delafosse C, Baril L, Lefort Y, Morelot C, Derenne JP, et al. Multiple organ failure complicating probable scrub typhus. Clin Infect Dis. 2000;31(1):191-2.
8. Premaratna R, Chandrasena TG, Dassayake AS, Loftis AD, Dasch GA, de Silva HJ. Acute hearing loss due to scrub typhus: a forgotten complication of a reemerging disease. Clin Infect Dis. 2006;42(1):e6-8.
9. Rijhwani P, Charan A, Agrawal CM, Pahadia MR, Gupta S, Anand H. Pan digital gangrene: a rare phenomenon in scrub typhus. J Mahatma Gandhi Univ Med Sci Tech. 2017;2(1):35-7.
10. Avasthi GI, Patel P, Kuka R, Mahajan R. Acute fulminant myocarditis as a rare manifestation in complicated scrub typhus: a case report. IHJ Cardiovasc Case Rep. 2018;2(Suppl):S18-S20.
11. Bharathi SL, Jayachandran S, Senthil N, Sujatha S. Scrub typhus causing myocarditis and ARDS: a case report. Heart India. 2013;1(3):85-6.

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CASE REPORT

Hypokalemia Secondary to Distal Renal Tubular Acidosis as a Manifestation of Primary Sjögren Syndrome

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ABSTRACT

The classical symptoms of primary Sjögren syndrome such as dry eyes and mouth are not always the initial manifestations. Herein, we report the case of a middle-aged female with documented multiple hypokalemic paralytic episodes along with nonspecific symptoms. Upon evaluation, she was found to have type 1 – distal renal tubular acidosis (RTA), which is an extraglandular manifestation of Sjögren syndrome. She was administered oral alkali salts of sodium along with potassium citrate and oral prednisolone. Both hypokalemia and acidosis recovered on 6th week follow-up. She was advised to continue alkali supplementation.

Keywords: Hypokalemic paralysis, urine anion gap, type 1 distal RTA, RTA, primary Sjögren syndrome

Primary Sjögren syndrome is a common chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, mainly salivary and lacrimal, resulting in oral and ocular dryness, although virtually any organ system can be affected[1]. Extraglandular manifestations of Sjogren's syndrome include palpable purpura, interstitial lung disease, distal renal tubular acidosis (RTA); membranoproliferative glomerulonephritis and peripheral neuropathy[2]. Clinical renal disease is unusual in primary Sjögren syndrome, being reported in 5% of patients, but it is probably underestimated. Chronic tubulointerstitial nephritis is the predominant form of primary Sjögren syndrome-associated renal involvement, which clinically translates mostly into distal RTA[2].

Furthermore, type 1 distal RTA is characterized by a cortical collecting duct dysfunction leading to an impaired elimination of hydrogen (H^+) ion. Secondary to tubular defects, patients develop systemic metabolic acidosis or the inability to acidify urine following an oral acid intake. Weakness or paralysis due to hypokalemia, renal calculi, or osteomalacia may be present in primary Sjögren syndrome patients with distal RTA[2].

CASE REPORT

A 45-year-old female presented with complaints of generalized weakness and tiredness since 5 years. She had generalized muscle pain over hands and legs for the past 4 years along with tingling and numbness for past 9 months. She also gave a history of occasional cough for 15 years and oral ulcers for past 1 year. She had no co-existing comorbid illness and there were no symptoms such as chest pain, palpitation, loss of weight or appetite, decreased urine output, shortness of breath or excessive menstrual flow. She had a history of recurrent hypokalemia paralytic attacks for past 3 years, which was not evaluated for the cause. She was not on any diuretics or other potassium-lowering drugs. Physical examination was normal except for oral ulcers and dry eyes. Skin and joint movements were normal. She ate the usual Indian diet. Vitals were stable and neurological examination was unremarkable.

Her complete blood count (CBC) was normal with hemoglobin of 13.9 g/dL, total white blood cell counts of 7,140 cells/mm^3 with normal differential counts; platelet count of 3,45,000; erythrocyte sedimentation rate (ESR) at 1 hour was 26 mm. Renal and liver function parameters were normal. Serum electrolyte

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assay showed hypokalemia 2.7 mEq/L (normal range 3.5-4 mEq/L); low serum bicarbonate 19 mEq/L (normal range 22-26 mEq/L); normal serum sodium 139 mEq/L and mildly raised serum chloride 112 mEq/L (normal range 98-107 mEq/L). Fasting thyroid-stimulating hormone (TSH) levels were normal 1.3 μIU/mL. Serum total vitamin D was deficient at 17.2 ng/mL (Table 1).

Urine routine examination showed pH of 7.5 with trace proteinuria without glucosuria or hematuria or sterile pyuria. The 12-lead electrocardiogram was normal with sinus rhythm and heart rate of 87 beats per minute with no T-wave morphological changes. 2D echocardiogram was normal with no regional wall motion abnormality or valvular pathology. Except for oral ulcers with dry eyes and hypokalemia with acidosis, the patient did not have any other pathology.

Table 1. Investigations Done for the Patient

Parameter	Patient's value	Normal value
Hemoglobin	13.9 g/dL	12-16 g/dL
White cell count	7,140/mm^3	4,000-11,000/mm^3
Platelet count	345 10^3/mm^3	150-450 10^3/mm^3
Neutrophils	45	40-80
Lymphocytes	44	20-40
Eosinophils	6	1-6
Monocytes	4	2-10
Blood urea	19 mg/dL	13-43 mg/dL
Serum creatinine	0.7 mg/dL	0.7-1.3 mg/dL
Alanine transaminase (ALT)	27 U/L	<34 U/L
Aspartate transaminase (AST)	30 U/L	<31 U/L
Alkaline phosphatase (ALP)	174 U/L	<141 U/L
Gamma-glutamyl transpeptidase (GGTP)	29 U/L	<38 U/L
Total bilirubin	0.8 mg/dL	0.0-1.3 mg/dL
Direct bilirubin	0.2 mg/dL	0.0-0.5 mg/dL
Indirect bilirubin	0.6 mg/dL	0-1.2 mg/dL
Serum albumin	4.2 g/dL	3.5-5.2 g/dL
Serum globulin	4.0 g/dL	2.0-3.5 g/dL
Serum sodium	139 mEq/L	136-145 mEq/L
Serum potassium	2.7 mEq/L	3.5-5.1 mEq/L
Serum chloride	112 mEq/L	98-107 mEq/L
Serum bicarbonate	19 mEq/L	22-26 mEq/L
Vitamin D Total	17.2 ng/mL	>30 ng/mL

She was having normal anion gap metabolic acidosis with hypokalemia and history of hypokalemic paralytic attacks. As she did not have any gastrointestinal causes of bicarbonate loss such as diarrhea and normal serum magnesium levels (1.55), urine electrolytes were done to evaluate renal losses. Spot urine sodium was 63.9 mmol/L; spot urine potassium was 32 mmol/L (normal range 17-80 mmol/L); spot urine chloride was 90 mmol/L (normal range 46-168 mmol/L); and spot urine creatinine was 49.53 mg/dL.

Urine anion gap, which is an indirect measure of urinary ammonium excretion, is calculated by the formula: Urine anion gap = (urine sodium + urine potassium) – urine chloride. In normal healthy individuals with no renal pathology, the urine anion gap is negative. Application of the above-mentioned formula to this patient yielded a positive urine anion gap of 6 mmol/L. Positive urine anion gap is suggestive of failure of urine acidification. Hence, a provisional diagnosis of RTA was made. Hypokalemia is present in type 1 (distal) and type 2 (proximal) RTA. Patient tested strongly positive for SSA (Ro) and Ro-52 antibodies (Table 2). With normal calcium, magnesium, and phosphorous levels, a final diagnosis of type 1 distal RTA secondary to Sjögren syndrome was made. Urinary potassium creatinine ratio was suggestive of renal potassium loss. Renal biopsy is not mandatory, and since our patient had normal renal function, it was not performed.

Treatment was started with oral sodium bicarbonate 1 g thrice daily, potassium citrate, oral vitamin D/calcium supplementation, and oral prednisolone 50 mg (tapering dose weekly). On a 6-week follow-up, serum electrolytes were rechecked. Serum bicarbonate levels were - 22.4 mEq/L; serum potassium - 4.1 mEq/L. There were no abdominal or neurological symptoms from initiation of treatment till follow-up. She was advised to continue potassium citrate and dosage of oral sodium bicarbonate reduced to 500 mg twice daily.

Table 2. Extractable Nuclear Antigens (ENA)-7 IgG Panel by IMMUNOBLOT Technique

Anti-Sm	Negative
Anti-Sm/RNP	Negative
SSA (Ro)	Strongly positive 3+
Anti-Ro-52	Strongly positive 3+
SSB (La)	Negative
Scl-70	Negative
Anti-Jo-1	Negative

DISCUSSION

Sjögren syndrome is an autoimmune disease characterized by chronic lymphocytic infiltration of exocrine glands resulting in clinical manifestations such as xerostomia, dry eyes[1]. The extraglandular manifestations of primary Sjögren syndrome are usually less frequent but can affect virtually any organ. They can occur at presentation or during the course of primary Sjögren syndrome, and if present can impact prognosis[3]. Renal involvement is estimated to occur in up to 10% of patients, more frequently as tubulointerstitial nephritis (TIN) and rarely as glomerulonephritis[4]. TIN is manifested as distal RTA, nephrogenic diabetes insipidus, proximal tubular dysfunction, normally without renal failure. Distal RTA is the most frequent renal manifestation, it is incomplete when there is a urinary acidification defect with normal serum bicarbonate and pH, and complete when there is a urinary acidification defect, low serum bicarbonate and acidosis[5]. Most laboratories cannot measure urinary ammonium; therefore, estimations can be made from urinary anion gap or osmolar gap. Positive urinary anion gap suggests reduced urine ammonium excretion, reflecting a primary defect in distal urine acidification, which characterizes distal RTA[4]. Despite being an extraglandular manifestation, distal RTA is not an indication for immunomodulatory therapy in primary Sjögren syndrome. However, steroid therapy can be considered when replacement therapy alone is unable to correct the imbalances, and in cases of recurring hypokalemic paralysis episodes. Early diagnosis and life-long alkali supplementation can prevent both acute hypokalemia and chronic complications like osteomalacia, renal stones, and progression to chronic kidney disease[4].

Metabolic acidosis also leads to enhanced proximal tubular reabsorption of citrate, resulting in hypocitraturia. Alkaline urine in combination with hypocitraturia and hyperphosphaturia promotes calcium phosphate precipitation leading to nephrocalcinosis and/or kidney stones[6]. The pathophysiological mechanism of distal RTA in relation to autoimmunity remains unclear. Several reports suggest that autoantibodies against the carbonic anhydrase enzyme[7].

Correction of the metabolic acidosis is by starting alkali in amount slightly greater than daily acid production. Correction of acidosis with sodium salts of such as sodium bicarbonate, can further aggravate hypokalemia. So, potassium supplementation should begin even before acidosis correction[8]. IgG4-related disease is often confused with Sjogren's syndrome, as the former can similarly affect the lacrimal and salivary glands, and present with tubulointerstitial nephritis[9].

CONCLUSION

Currently, there is no universal agreement on the diagnostic criteria for the diverse spectrum of extraglandular involvement in primary Sjögren's syndrome. This leads to significant underdiagnosis of extraglandular manifestations, resulting in inadequate treatment and progression to severe organ dysfunction in affected individuals[2]. It is crucial to establish correlations between the nonspecific presentations of systemic autoimmune diseases and initiate timely treatment to mitigate chronic debilitating outcomes.

Declaration

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Patient's Consent: Telephonic consent was obtained from the patient for research purposes.

Conflict of Interest: None.

Ethical Approval: Not required.

REFERENCES

1. Mavragani CP, Moutsopoulos HM. Sjögren's syndrome: Old and new therapeutic targets. J Autoimmun. 2020;110: 102364.
2. Mihai A, Caruntu C, Jurcut C, Blajut FC, Casian M, Opris-Belinski D, et al. The spectrum of extraglandular manifestations in primary Sjögren's syndrome. J Pers Med. 2023;13(6):961.
3. Mariette X, Criswell LA. Primary Sjögren's syndrome. N Engl J Med. 2018;378(10):931-9.
4. Garza-Alpirez A, Arana-Guajardo AC, Esquivel-Valerio JA, Villarreal-Alarcón MA, Galarza-Delgado DA. Hypokalemic paralysis due to primary Sjögren syndrome: case report and review of the literature. Case Rep Rheumatol. 2017;2017:7509238.
5. Evans R, Zdebik A, Ciurtin C, Walsh SB. Renal involvement in primary Sjögren's syndrome. Rheumatology (Oxford). 2015;54(9):1541-8.
6. Both T, Zietse R, Hoorn EJ, van Hagen PM, Dalm VA, van Laar JA, et al. Everything you need to know about distal renal tubular acidosis in autoimmune disease. Rheumatol Int. 2014;34(8):1037-45.
7. Takemoto F, Hoshino J, Sawa N, Tamura Y, Tagami T, Yokota M, et al. Autoantibodies against carbonic anhydrase II are increased in renal tubular acidosis associated with Sjogren syndrome. Am J Med. 2005;118(2):181-4.
8. Palmer BF, Kelepouris E, Clegg DJ. Renal tubular acidosis and management strategies: a narrative review. Adv Ther. 2021;38(2):949-68.
9. Maślińska M, Przygodzka M, Kwiatkowska B, Sikorska-Siudek K. Sjögren's syndrome: still not fully understood disease. Rheumatol Int. 2015;35(2):233-41.

BRIEF COMMUNICATION

Person-centered Pharmaceutical Business

SANJAY KALRA*, ATUL DHINGRA†

ABSTRACT

Person-centered care is a phrase, which seems omnipresent in medical discourse. Can pharmaceutical businesses and industries be person-centric? This article explores the various facets of person-centered pharmaceutical businesses, it suggests ways of incorporating and measuring person-centricity in the business milieu, and describes best practices shared by leading pharmaceutical houses.

Keywords: Chronic disease, corporate social responsibility, patient-centered care, person-centered care, psychosocial aspects

The phrase 'person-centered' has entrenched itself in modern medical praxis, and rightfully so. Person-centered care is the right of every person or individual who wishes to promote and optimize health, and prevent or manage disease[1]. It is also the responsibility of all stakeholders. These include not only physicians and policymakers, but the pharmaceutical industry as well.

DEFINITION

Person-centered care has been defined in various ways. The Institute of Medicine, Washington DC, USA, defines person-centered care as "care that is respectful of and responsive to individual patient preferences, needs, and values" and which ensures "that patient values guide all clinical decisions"[2]. South Asian thought leaders have highlighted the need for responsible person-centered care, and included the health care ecosystem, apart from doctors, as stakeholders who need to practice responsible person-centered care[3,4]. To this, we add the pharmaceutical industry.

THE ROLE OF PHARMACEUTICAL INDUSTRY

As Atreya points out, in his eponymously named Quadruple, the physician is but one of the four aspects of therapeutics[3]. Equal attention must be paid to the person living with disease, drugs and their attendants. The drug, and the drug manufacturer, need to work in collaboration with the person living with disease, and their caregivers, in order to achieve optimal outcomes. This calls for integration of person-centered care in each and every step of pharmaceutical development and delivery.

There is increasing recognition of the need to enhance person-centricity amongst the pharmaceutical industry. This is required to ensure sustainability, and improve satisfaction among the customers that the business serves. As Batla et al quote Robinson, person-centricity is the right thing to do, it makes commercial sense, and will soon be expected by regulators[5]. In fact, person-centricity is being considered as a part of corporate social responsibility as well[6].

MESAUREMENT AND MONITORING

The International Alliance of Patients' Organizations (IAPO) is a global leader in advocating for person-centered care. In its review of person-centered health care indicators[7], IAPO cites Carlson EH (2009). She lists five factors that pharmaceutical companies need in order to become more patient-centered. She suggests that companies should put the patient at the center of every decision, right from the beginning of commercialization; translate clinical benefits to real-world health gains; facilitate a collaborative relationship between doctor and patient; improve patient and carer experience through their journey; and take nothing for granted[7]. The review also mentions Patient View, which has used six indicators to rate company performance: the presence of an effective patient-centered strategy;

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quality of information provided; patient safety record; usefulness of products; transparency with external stakeholders; and integrity[7].

TANGIBLE TOOLS AND TARGETS

Person-centricity is required not only in public-facing verticals of business, but also within internal domains of organizations. Box 1 lists eight alliteratively crafted aspects of person-centricity for pharmaceutical businesses. These can be used as targets or goals, and also as tools and techniques to achieve these targets. We hope that this will motivate discussion and debate regarding person-centered pharmaceutical processes, and lead to better health for humankind.

Box 1. Eight Principles of Person-centered Pharmaceutical Business

- Insert person-centeredness into one's vision/mission statement
- Inform all stakeholders about one's person-centered aim and ambition
- Involve person living with disease/disability in all relevant decision making, e.g., style of packaging
- Include person-centered/patient reported outcomes as part of all clinical trials/research
- Integrate person-centered care in all educational events
- Initiate steps to engage and empower persons living with disease through digital/social/other media
- Introspect about the spirit and spectrum of person-centered care
- Improve continually. There is always scope to do better

BEST PRACTICES

We list here a few best practices, shared by colleagues from the pharmaceutical industry:

Bayer is committed to patient centricity, prioritizing the needs of individuals living with health conditions and their care partners. Patient engagement at Bayer involves partnering with people with lived experience at every stage of the product lifecycle, from preclinical to commercialization. This approach aims to enhance decision-making and generate measurable value across the entire value chain. By fostering open communication based on trust, Bayer seeks to improve health outcomes and treatment satisfaction for patients. The company's mission is to advance health for all by partnering with people with lived experience to shape the future of care standards. Bayer's patient engagement focus includes amplifying the patient voice, democratizing access to patient and care partner analytics, and collaborating to deliver customer-centric solutions. The Patient Insights & Engagement (PIE) Community plays a crucial role in ensuring a dedicated and consistent approach to engaging patients and care partners across Bayer's Patient Engagement ecosystem.

KareIndia is a patient-centered program launched by Bayer India in 2023 to support patients of chronic kidney disease (CKD) associated with type 2 diabetes. The program aims to address two major challenges in disease management: Lower diagnosis rates and nonadherence to the treatment. Through unique tie-ups with pathology lab-networks and mobile based point of care kits, KareIndia program facilitates awareness and usage of urine albumin-creatinine ratio/albuminuria testing enabling early diagnosis. Till date >5,000 undiagnosed patients have been detected through this initiative. KareIndia patient counseling program aims to improve adherence through tele-counseling services by handholding the patients throughout the CKD journey with dietary and lifestyle tips, therapy awareness and pill-reminders.

Forum for Injection Technique (FITTER) India, supported by Embecta, educates health care professionals (HCPs) and patients, publishes in leading national and international journals, and conducts media awareness sessions every January, to advocate for optimal insulin injection practices to support people living with diabetes on insulin therapy. Since 2012, over 3,00,000 HCPs and 4,00,000 individuals with diabetes have undergone training[8]. In 2020, FITTER launched its educational initiative IGNITE "Insulin optimization Guidelines 'N' Injection Technique Expertise" in partnership with reputed medical institutes, led by FITTER members and eminent national speakers in the field of endocrinology and diabetology, with the aim to sensitize physicians at the early stage of their practice around optimizing insulin injection technique and its impact on glycemic control[8].

Lupin works hard to integrate person-centricity in its endeavors. It runs HumRahi, a patient support program designed to increase awareness, adherence, and access to diabetes care. Over 27,000 persons living with diabetes have benefited from this. Lupin has taken the lead in creating a national task force on person-centered endocrinology, and hopes to incorporate this aspect of management in its continuing medical education programs.

At Novo Nordisk, patient-centricity is the cornerstone of operations, driving innovation, quality, and health care

provider education through groundbreaking formats. The robust research and development (R&D) expenditure fuels a dynamic product pipeline, ensuring early innovation and the swift transition from product discovery to patient solutions. It addresses unmet needs with pioneering products, including modern insulins, new generation insulins, and once-weekly formulations, alongside the invention of glucagon-like peptide-1 therapies.

Their commitment extends beyond product development. Initiatives like the DiabetesWhatNext (DWN) website, the Digital Patient Support Program, and the MISHTI chatbot benefit thousands of patients in India, providing support and educational materials within regulatory frameworks. Novo Nordisk also backs numerous patient education programs solicited by doctors, reflecting their dedication to empowering patients and enhancing their health outcomes. At Novo Nordisk, patient-centricity is not just a concept; it is a practice embedded in the DNA, driving innovations for a better tomorrow.

Sanofi chases the miracles of science to improve people's lives. It is an organization that listens, acts, and leads with patients. Sanofi relentlessly pursues scientific advancements to deliver life-changing medicines and vaccines and prioritizes patient needs by collaborating with patients, advocates, and utilizing real-world data. This patient-centric approach fuels the R&D, ensuring that the innovations address critical health goals. Sanofi empowers patients and families through comprehensive support programs, educational resources, and disease awareness initiatives within the regulatory framework. Programs like Sanofi India's Patient Support Programme, Diabetes Dialogue have already impacted thousands of lives. At Sanofi, the aim is to help the patients to break through the complexities of diabetes management by developing a simplified novel combination of two antidiabetic drugs in a single injection.

USV prioritizes person-centered activities by providing patient education in regional languages using audio and video formats, and leveraging social media, apps, and websites for health awareness. They develop innovative formulations with flexible dosage forms, fixed-dose combinations, and user-friendly packaging; ensuring affordable medicines are accessible omnichannel. Their patient support programs offer counseling and follow-up care. USV focuses on upskilling health care staff, HCPs, and paramedics through regular training to enhance patient interactions and care delivery. By implementing digital health solutions like telemedicine and mobile apps, their aim is to improve accessibility and patient outcomes across India.

Acknowledgments

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REFERENCES

1. Mezzich JE, Appleyard WJ, Glare P, Snaedal J, Wilson CR (Eds.). Person centered medicine. Springer Nature; 2023 Apr 13.
2. Institute of Medicine (US) Committee on Quality of Health Care in America. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington (DC): National Academies Press (US); 2001.
3. Kalra S. The history of person-centred medicine: a South Asian perspective. Int J Person Centered Med. 2022;12(1):41-6.
4. Kalra S, Baruah MP, Unnikrishnan AG. Responsible patient-centered care. Indian J Endocrinol Metabol. 2017;21(3):365-6.
5. Balta A, Soon J, Morton R. Person-centred healthcare versus patient centricity - what is the difference and how are pharmaceutical companies aiming to secure internal representation of the patient voice? Europ J Person Centered Healthc. 2020;8(3):277-81.
6. Macassa G, da Cruz Francisco J, McGrath C. Corporate social responsibility and population health. Health Sci J. 2017;11(5):528.
7. International Alliance of Patients' Organizations (IAPO). Patient-Centred Healthcare Indicators Review. Available from: https://www.iapo.org.uk/sites/default/files/files/IAPO%20Patient-Centred%20Healthcare%20Indicators%20Review.pdf. Last accessed June 10, 2024.
8. Kalra S, Pathan F, Kshanti IAM, Bay NQ, Nagase T, Oliveria T, et al. Optimising insulin injection techniques to improve diabetes outcomes. Diabetes Ther. 2023;14(11):1785-99.

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EXPERT OPINION

Role of Nutrition in the Management of PCOS

ANITA GOYAL

INTRODUCTION

- Polycystic ovary syndrome (PCOS) represents the most common female endocrinopathy, affecting nearly 15% to 18% of women of reproductive age[1].
- It is defined as a heterogeneous group with different phenotypes, thus challenging the treatment[1].
- Higher hormone levels, gut microbiome composition, and plasma metabolomics are related to the PCOS phenotypes[1].
- Precise recommendations should be implemented to prevent the occurrence of metabolic complications, since women with PCOS are predisposed to developing endometrial and ovarian cancer.[1]

LIFESTYLE CHANGES

- Lifestyle changes remains the first-line of treatment for the management of women with PCOS[1].
- Regular physical activity, maintaining appropriate body weight, following healthy dietary patterns and avoiding tobacco use is important to prevent and treat metabolic disorders[1].
- Nutritional counseling remains a focus while treating patients with PCOS[1].

DIET

- Low glycemic index (LGI) diets decrease homeostatic model assessment for insulin resistance (HOMA-IR), fasting insulin, total and low-density lipoprotein (LDL) cholesterol, triglycerides, waist circumference and total testosterone without affecting fasting glucose, high-density lipoprotein (HDL) cholesterol, weight or the free androgen index.[1]
- LGI diet, punitive restrictions and/or physical activity, and the supplementation of omega-3 have shown to increase HDL, sex hormone-binding globulin (SHBG) synthesis, and reduction in body fat[1].
- LGI diets have been shown to reduce ghrelin and increased glucagon in women with PCOS[1].
- Thus LGI diet is an effective, acceptable and safe intervention for relieving insulin resistance (IR), and thus professional dietary advice is a must for patients with PCOS[1].
- The ketogenic diet (KD) improves the menstrual cycle, reduces blood glucose and body weight, improves liver function and treats fatty liver in women with PCOS, and liver dysfunction in obese individuals[1].
- The initial focus must be on the eating pattern and the macronutrient content of the diet instead of promoting healthy eating and weight loss too quickly in these patients[2].
- Limiting nutrient intake or increasing calorie expenditure will help gain an energy deficit in these patients. Calorie deficit of about 200 kcal/day will prevent weight gain and promote weight loss in the longer term. A deficit of 500 kcal/day is required for the average person to lose 0.5 kg/week, while doubling the value further double the weight loss/week[2].

SUPPLEMENTATION

Vitamin B3

- Insufficient supply of vitamin B3 causes the development of inflammatory conditions, leading to the associated diseases and the increased risk of cardiovascular syndromes[1].
- Women with PCOS who are treated with metformin chronically, to normalize glycemia may show deficiencies in thiamine and cobalamin[1].
- Thus supplementing with thiamine, activates transketolase, which inhibits the mechanisms of damaging blood vessels and reduces the risk of cardiovascular diseases[1].

CoQ10

- Coenzyme Q10 (CoQ10) supplementation for 8 weeks has a beneficial effect on inflammatory and endothelial dysfunction markers in overweight and obese patients with PCOS[1].

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Vitamin D

- Vitamin D increases insulin synthesis and release, which increases insulin receptor expression and increases the insulin response to glucose transport. It indirectly influences carbohydrate metabolism by normalizing extracellular calcium and parathyroid hormone concentration and also affects the expression of the genes of the metabolic pathways affecting systemic inflammation by inhibiting the synthesis of proinflammatory cytokines, which may contribute to the occurrence of IR[1].
- When 20,000 IU of cholecalciferol is given to women with PCOS, weekly carbohydrate metabolism is improved and fasting glucose, triglycerides, and estradiol is reduced[1].
- It also improves the menstrual frequency[1].

Inositols

- Administration of myo-inositol may bypass the side effects experienced with metformin. It increases insulin sensitivity, normalizes androgens in the blood, improves glycemia and affects numerous features of metabolic syndrome[1].
- Inositols (both isomers, both given separately and in combination) also have the potential to restore spontaneous ovulation and improve fertility in women with PCOS[1].
- Thus supplementation with inositol is a safe and effective form of PCOS therapy, which improves the development of ovarian follicles, oocyte maturation, and stimulation of pregnancy[1].

Berberine

- Berberine possesses good hypoglycemic and hypolipidemic effects, reduces body weight and is an effective insulin sensitizer.
- It decreases steroid hormone synthesis and the expression of ovarian aromatase by acting on the hypothalamic-pituitary-ovarian axis and improves the ovulation rate and the regulation of menstruation, thus increasing the pregnancy and live birth rates[1].
- Its side effects are transient and mild (constipation, nausea), thus it may be a safe and promising compound for the treatment of PCOS patients[1].

Chromium

- Chromium improves diabetes in patients with PCOS by enhancing the insulin signaling pathway, increasing the activity of adenosine monophosphate-activated protein kinase, and increasing cellular glucose uptake[1].

Zinc

- Supplementation with zinc and selenium may be beneficial in some patients with PCOS[1].
- Zinc supports lipid and glucose metabolism and fertility by intracellular signaling and structural functions[1].
- Low zinc intake in obese people can cause hyperinsulinemia, increased low-grade inflammation, and a worsened lipid profile[1].
- Zinc deficiency has a role in the pathogenesis of PCOS and thus may be a prognostic marker of PCOS[1].

Selenium

- Selenium causes a lower level of C-reactive protein (CRP) and has anti-inflammatory and antioxidant properties[1].

Omega-3 Fatty Acid

- Omega-3 fatty acid lacks in the diet of PCOS women. Polyunsaturated fatty acids (PUFAs) improve the reproductive performance in PCOS by boosting the expression of steroidogenesis enzymes[1].

Thus, a balanced diet and a healthy lifestyle should be the first element of PCOS therapy[1].

HERBS SUPPORTING TREATMENT

Since a balanced diet is the most important treatment for PCOS, herbs infusions such as *Aloe vera*, cinnamon (*Cinnamomum verum*), green tea (*Camellia sinensis*), and chamomile (*Matricaria chamomilla*), and white mulberry (*Morus alba*) would complement the therapy[1].

As these herbs can regulate lipid and carbohydrate metabolism they can be used by all phenotypes of PCOS women[1].

Green tea and marjoram: Herbs like green tea and marjoram (*Majorana hortensis*) can improve hormonal levels, ovaries weight, insulin sensitivity, antioxidants, and anti-inflammatory parameters[1].

Green mint: Green mint (*Mentha spicata* L.) has an antiandrogenic effect and restores follicular development in ovarian tissue[1].

Licorice smooth: Licorice smooth (*Glycyrrhiza glabra*) has antiandrogen and estrogen-like activity. Its root is

effective in reducing excess testosterone as it blocks the conversion of androstenedione. However, licorice has the potential to induce hypertension, hypokalemia, and metabolic alkalosis thus not suitable for people with high cortisol levels[1].

Serenoa repens, C. sinensis, Rosmarinus officinalis,* and *G. glabra: *S. repens, C. sinensis, R. officinalis,* and *G. glabra* have also been shown to lower androgen levels and inhibit androgenetic alopecia[1].

Vitex agnus-castus: *V. agnus*-castus regulates the menstrual cycle[1].

Flaxseed lignans: Flaxseed lignans are the well-known dietary phytoestrogens. The lignan content of flaxseed (*Linum usitatissimum*) modulates relative levels of circulating sex hormones and their metabolites[1].

Turmeric: Turmeric (*Curcuma longa*), and specifically curcumin, reduces oxidative-stress-related complications in patients with PCOS[1].

REFERENCES

1. Szczuko M, Kikut J, Szczuko U, Szydłowska I, Nawrocka-Rutkowska J, Ziętek M, et al. Nutrition strategy and life style in polycystic ovary syndrome—narrative review. Nutrients. 2021;13(7):2452.
2. Farshchi H, Rane A, Love A, Kennedy RL. Diet and nutrition in polycystic ovary syndrome (PCOS): pointers for nutritional management. J Obstet Gynaecol. 2007;27(8):762-73.

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Euthanasia

The English philosopher Sir Francis Bacon coined the phrase "euthanasia" early in the 17th century. Euthanasia is derived from the Greek word "eu", meaning "good" and thanatos meaning "death", and early on signified a "good" or "easy" death. It is commonly called "mercy killing".

Euthanasia is defined as the administration of a lethal agent by another person to a patient for the purpose of relieving the patient's intolerable and incurable suffering.

TYPES OF EUTHANASIA

Euthanasia has been further defined as "active" or "passive".

- Active euthanasia refers to a physician deliberately acting in a way to end a patient's life. There are three types of active euthanasia.
  - Voluntary euthanasia is one form of active euthanasia which is performed at the request of the patient.
  - Involuntary euthanasia, also known as "mercy killing", involves taking the life of a patient who has not requested for it, with the intent of relieving his pain and suffering.
  - In nonvoluntary euthanasia, the process is carried out even though the patient is not in a position to give consent.
- Passive euthanasia pertains to withholding or withdrawing treatment necessary to maintain life.

ETHICAL DEBATE ON EUTHANASIA

It is a controversial issue that has been exposed to debate throughout the world as it involves deliberate termination of human life. This matter has witnessed heated debates not only within the premises of court but also among the elites, intelligentsia and academicians alike. There are two crucial paradigms around which the public discussions on euthanasia have been shaped.

- The first one revolves around sanctity of life and the impermissibility to end the same.
- The other one revolves around the principle of autonomy or choices and the belief that individuals have a right to end their life, when in misery.

Article 21 of the Constitution guarantees 'Right to Life', which is an inalienable right. However, the essence of human life is not merely restricted to breathing rather it is more about living a dignified life. To die with dignity is a concept that has led to major modifications in this field.

Recognizing this, in the landmark judgment in the matter of **Common Cause (A Regd. Society) vs. Union of India**, the Hon'ble Supreme Court of India also stated "*An inquiry into common law jurisdictions reveals that all adults with capacity to consent have the right of self-determination and autonomy. The said rights pave the way for the right to refuse medical treatment which has acclaimed universal recognition. A competent person who has come of age has the right to refuse specific treatment or all treatment or opt for an alternative treatment, even if such decision entails a risk of death*".

EVOLUTION OF LAW ON WITHDRAWAL OF LIFE SUPPORT IN INDIA

Active euthanasia is an offence under Section 302 (punishment for murder) of the Indian Penal Code (IPC) or at least under Section 304 (punishment for culpable homicide not amounting to murder).

- **302. Punishment for murder.** — Whoever commits murder shall be punished with death, or imprisonment for life, and shall also be liable to fine.
- **304. Punishment for culpable homicide not amounting to murder.** — Whoever commits culpable homicide not amounting to murder shall be punished with imprisonment for life, or imprisonment of either description for a term which may extend to 10 years, and shall also be liable to fine, if the act by which the death is caused is done with the intention of causing death, or of causing such bodily injury as is likely to cause death, or with imprisonment of either description for a term which may extend to 10 years, or with fine, or with both, if the act is done with the knowledge that it is likely to cause death, but without any intention to cause death, or to cause such bodily injury as is likely to cause death.

The following judgments of the Apex Court have played a significant role in the prevailing legal position on euthanasia:

- P Rathinam vs. Union of India in 1994

- Gian Kaur vs. State of Punjab in 1996
- Aruna Shanbaug vs. Union of India in 2011
- Common Cause vs. Union of India in 2018

In **P Rathinam vs. Union of India on 26 April, 1994**, it was held that *"Section 309 IPC deserves to be effaced from the Statute Book to humanise the Penal Laws… suicide or attempt to commit it causes no harm to others, because of which State's interference with the personal liberty of the persons concerned is not called for… Section 309 violates Article 21, and so, it is void."* The Bench said that if a person has a Right to Live, he also has a Right to Die. However, this ruling was overturned in **Gian Kaur vs. State of Punjab on 21 March, 1996** where appellants were convicted by the court u/s 306 IPC and conversion was attacked on the ground that Section 306 IPC is unconstitutional violative of Article 21 – the constitutionality of Section 306 was questioned. The Court said that the Right to Life is a natural right embodied in Article 21, but suicide is an unnatural termination of life and declared Section 309 IPC as constitutional. It said that Article 21 does not include the 'Right to Die'.

Section 306 prescribes punishment for abetment of suicide, while Section 309 punishes attempt to commit suicide.

The issue of euthanasia was again raised before the Supreme Court in 2011 in "**Aruna Ramchandra Shanbaug vs. Union of India**", which for the first time allowed passive euthanasia for a patient in a permanent vegetative state, but it had to have the sanction of the High Court. The Apex Court noted the lack of a law with regard to withdrawing life support for a person in permanent vegetative state or who is otherwise incompetent to take a decision in this connection.

"*A decision has to be taken to discontinue life support either by the parents or the spouse or other close relatives, or in the absence of any of them, such a decision can be taken even by a person or a body of persons acting as a next friend. It can also be taken by the doctors attending the patient. However, the decision should be taken bona fide in the best interest of the patient"…"Hence, even if a decision is taken by the near relatives or doctors or next friend to withdraw life support, such a decision requires approval from the High Court concerned as laid down in Airedale's case (supra). In our opinion, this is even more necessary in our country as we cannot rule out the possibility of mischief being done by relatives or others for inheriting the property of the patient."* It further stated as follows *"…in the case of an incompetent person who is unable to take a decision whether to withdraw life support or not, it is the Court alone, as parens patriae, which ultimately must take this decision, though, no doubt, the views of the near relatives, next friend and doctors must be given due weight*".

In the landmark judgment "**Common Cause (A Regd. Society) vs. Union of India, delivered in 2018**, the Hon'ble Supreme Court of India held that the Right to Die with dignity is now a fundamental right under Article 21 of Constitution of India. Through this judgment, it has legalized passive euthanasia and advance medical directive/living will. The Bench also drew a distinction between active and passive euthanasia. "In active euthanasia, a specific overt act is done to end the patient's life whereas in passive euthanasia, something is not done which is necessary for preserving a patient's life." This difference has led to legalization of passive euthanasia by making a law or by judicial interpretation.

The Court was of the opinion that *"Advance Medical Directive would serve as a fruitful means to facilitate the fructification of the sacrosanct right to life with dignity. The said directive, we think, will dispel many a doubt at the relevant time of need during the course of treatment of the patient. That apart, it will strengthen the mind of the treating doctors as they will be in a position to ensure, after being satisfied, that they are acting in a lawful manner."*

Four Terminologies Need to be Understood in Context of this Judgment

Advance directive: This is a legal document made when the person is alive and still in possession of decisional capacity about how treatment decisions should be made on her or his behalf if they are no longer able to make decisions for themselves or lose the capacity to make such decisions. Advanced directives are acted upon only when the patient has lost the ability to make decisions for himself. They can be revoked orally or in writing by the patient at any time (so long as he or she has maintained decisional capacity).

Living will: A living will is a document that summarizes a person's preferences for future medical care and addresses resuscitation and life support. It is a document in which patients give clear instructions about treatment to be administered or state their wishes for end-of-life medical care, when they are no longer able to communicate their decisions. It comes into play if the person is terminally ill without chance of recovery, and outlines the desire to withhold heroic measures.

The living will gives a general sense of the patient's wishes, and can be modified by the patient to include

specific interventions such as cardiopulmonary resuscitation (CPR), ventilatory support, or enteral feeding.

Proxy will: In a proxy will, the patient identifies the person/s who will take decision with regard to treatment on his/her behalf in case he/she is incapacitated. Simply put, it can be called as giving "power of attorney" for medical decisions.

DNR or Do not resuscitate: This document talks of resuscitation only, whether the patient wishes for all efforts to be made to revive him by CPR and to be put on lifesaving ventilator.

However, the Bench cautioned about the need for safeguards and laid down strict guidelines on execution of the advance directive/living will to prevent its misuse. These guidelines remain in force since the Parliament is yet to enact a legislation on passive euthanasia.

Supreme Court Guidelines on Advanced Directive and Living Will

Who can execute the advance directive and how?

As directed by the Supreme Court, the advanced directive can be executed only an adult of sound and healthy state of mind, who can communicate, related and comprehend the purpose and consequences of executing the document. It must be voluntarily executed without any coercion or inducement or compulsion. It should be with informed consent without any undue influence or constraint. It should be written clearly when medical treatment may be withdrawn.

What should it contain?

The advanced directive should clearly indicate the decision relating to circumstances in which treatment is withdrawn. It should have absolutely clear instructions in specific terms.

The executor may revoke at any time but the executor must understand the consequence of executing such document. It should specify the name of the guardian or close relative who in the event of executor becomes incapable of making decisions, to authorize and to give consent. If there are more than one valid advanced directives, the most recently signed is considered.

How should it be recorded and preserved?

The document should be signed by the executor in the presence of two independent witnesses and countersigned by local Judicial Magistrate of First Class (JMFC) designated by concerned District Judge. The witnesses and the Magistrate record that the document is executed voluntarily without any coercion or compulsion with relevant information. The Magistrate shall preserve one copy in his office and also keep it in a digital format.

The Magistrate forwards one copy to jurisdictional District Court for registration. The Magistrate informs the immediate family members about the document. A copy is handed over to competent officer of local government, Municipality or Panchayat. The Magistrate shall hand over the copy to family physician if any.

When and by whom can it be given effect to?

If the executor (patient) becomes terminally ill and is undergoing prolonged medical treatment with no hope of recovery and cure of the ailment, the treating physician, when made aware about the advance directive, should ascertain the genuineness and authenticity thereof from the jurisdictional JMFC.

The physician/hospital where the executor has been admitted for medical treatment shall then constitute a Medical Board consisting of the Head of the treating Department and at least three experts from the fields of general medicine, cardiology, neurology, nephrology, psychiatry, or oncology with experience in critical care and with overall standing in the medical profession of at least 20 years.

Once the hospital medical board certifies that the instructions contained in the advance directive ought to be carried out, the jurisdictional Collector is informed, who then constitutes a second Medical Board comprising the Chief District Medical Officer of the concerned district as the Chairman and three expert doctors from the fields of general medicine, cardiology, neurology, nephrology, psychiatry, or oncology with experience in critical care and with overall standing in the medical profession of at least 20 years (who were not members of the previous Medical Board of the hospital).

This Board will visit the patient before implementing the decision of the Court. The JMFC shall visit the patient at the earliest and, after examining all aspects, authorize the implementation of the decision of the Board.

The executor can revoke the document at any stage before implementation.

What if permission is refused by the medical board?

If permission to withdraw treatment is refused by hospital medical board or the secondary medical board constituted by the Collector, the executor can approach the High Court by a writ petition under Article 226 of Constitution. The High Court constitutes an independent committee with three doctors from general medicine, cardiology, neurology, nephrology, psychiatry, or oncology with experience in critical care and at least 20 years of experience. The committee will submit the report about the feasibility of acting upon the instructions contained in the advance directive. The High Court is however expected to expedite the hearing and "shall render its decision at the earliest" acting in "the best interests of the patient".

Revocation or inapplicability of advance directive

At any time, the executor may withdraw the advance directive and it should be in writing. The advance directive shall not be applicable to the circumstances, which the person did not anticipate. If the advance directive is not clear and ambiguous, it is not applicable. If the hospital medical board decides not to follow advance directive, then the executor shall make an application to the medical board constituted by the collector.

If there is no advanced directive, the person cannot be alienated. The same procedure is followed as in cases where advanced directives are in existence.

EUTHANASIA GUIDELINES MODIFIED

The Indian Society for Critical Care Medicine (ISCCM) filed a petition in July 2019, describing the 2018 guidelines as "cumbersome". In a bid to streamline the steps of removal of life support from terminally ill patients, on 24th January 2023, the Supreme Court modified its 2018 order on passive euthanasia.

- While the modified guidelines have retained the requirement of two medical boards, the second review board will also be constituted by the hospital where the patient is undergoing treatment and not the District Collector as was mandated earlier. The review board will have a doctor nominated by the District Medical Officer.
- Earlier doctors with at least 20 years of experience were selected for the medical board. But now doctors with 5 years of experience can be included in the medical board.
- The Apex Court imposed a time limit of 48 hours (preferably) for the boards to come to a decision in order to hasten the process and not delay it any more than required.
- The new order does not require the sanction of the judicial magistrate for withholding treatment or withdrawal of life support. The Magistrate just needs to be informed.
- The living will or advance directive had to be made in the presence of two witnesses who would attest the document which had to be then countersigned by the Judicial Magistrate. But now the living will can be attested by a notary or a gazetted officer.

■■■■

HCFI Dr KK Aggarwal Research Fund

Minutes of an International Weekly Meeting on "Acute Pyelonephritis: Diagnosis & Treatment"

Speaker: Dr Ratan Jha, *FISN, DM, DNB, MD, DTCD.*
Senior Consultant Nephrologist, Care Hospitals, Hyderabad

June 1, 2024 (Saturday 9.30-10.30 am)

- Pyuria is often taken as *sine qua non* of urinary tract infection (UTI), but this is not true. Also, inappropriate use of antibiotics can cause side effects and emergence of drug resistance (extended-spectrum beta-lactamase/multidrug resistance [ESBL/MDR]).
- Pyuria is not equivalent to UTI unless the clinical picture is compatible.
- UTI is the presence of organisms >10^5 mL in urine with or without symptoms. Lower counts 10^2/10^3/ could also be UTI if the patient has symptoms that are appropriate for the clinical setting.
- The bacterial count has to be supported by urine microscopy, urine test strip (leukocyte esterase/ Griess nitrate test), and clinical features (history).
- The types of UTI include cystitis (mostly uncomplicated), acute pyelonephritis (complicated if risk factors such as diabetes, stone, prostatitis are present), acute bacterial prostatitis is considered complicated as there is no risk of recurrence, catheter-associated UTI (CAUTI), and asymptomatic bacteriuria.
- UTI may present as lower urinary symptoms, upper urinary tract symptoms. Sometimes, there is fever with no localization; this is urosepsis (occult pyelonephritis). Few patients may have vague chronic ill health due to pyelonephritis of subacute nature.
- The purple urinary bag syndrome is due to chronic stasis in the urinary catheter giving the picture of hematuria with associated asymptomatic bacteriuria.
- Upper UTI can be clinically recognized by symptoms such as lumbar pain, shaking chills, loin tenderness, hematuria.
- Lower UTI is characterized by frequency, dysuria, urgency, frank hematuria, suprapubic pain; small void, foul smell, cloudy urine, or asymptomatic (covert)/sepsis syndrome.
- Acute pyelonephritis can also be precipitated by heat stress if the water intake is inadequate.
- The possible symptoms of acute uncomplicated cystitis include dysuria, urinary frequency, urinary urgency, suprapubic pain, absence of vaginal symptoms/upper tract symptoms/systemic symptoms (rigors, shaking chills). May require only urine analysis or urine dipstick to support the diagnosis. Culture may not be required and may be treated empirically.
- Fifty percent of patients will have classical picture of bacterial cystitis with colony count >10^5 CFU/mL, while 20% with the same clinical picture may have low colony count (10^2-10^4). This will still be considered as true UTI.
- About 15% of patients may have urethritis, 5% may have vaginitis. In less than 1% patients, the symptoms may be due to noninfectious causes (chemical irritation or estrogen deficiency).
- There are few overlooked causes of UTI such as less fluid intake, spicy diet, neurological problems (neurogenic bladder, normal pressure hydrocephalous), bladder outlet obstruction (benign prostatic hyperplasia [BPH], prostate cancer, urethral stenosis, bladder calculus/cancer), or drugs (caffeine, diuretics).
- In the elderly, children, immunosuppressed, diabetics, the presentation may be atypical in the form of vomiting, loose motions, shock, mental obtundation, and jaundice. One must have high index of suspicion.
- Clinically, pyelonephritis can present as acute pyelonephritis with classical symptoms of loin pain, rigors, fever. But it can have other presentations too such as emphysematous pyelonephritis, papillary necrosis, occult or subacute pyelonephritis, recurrent/ relapsing pyelonephritis, or xanthogranulomatous pyelonephritis/malakoplakia.
- Diagnosis is based on positive urine analysis (≥10 WBC per HPF, leukocyte esterase, nitrites) and positive urine culture; no catheter (≥10,000-1,00,000 CFU/mL of a urinary pathogen, catheter ≥1,000 CFU/mL of a urinary pathogen). Blood cultures must be obtained if pyelonephritis or urosepsis is suspected.

- In symptomatic patients, bacteriuria + pyuria is true UTI. Pyuria is 10 cells/HPF of spun urine (10 mL, 2000 rpm, 5 min).
- If only pyuria with symptoms and less significant bacteriuria, this could still be true UTI (likely to be cystitis).
- If pyuria with insignificant bacteriuria ($<10^2$) + pyuria, this could be chlamydia or nongonococcal urethritis.
- Symptomatic but no bacteriuria/pyuria could be acute urethral syndrome.
- In asymptomatic patients, no bacteriuria + pyuria is sterile pyuria (analgesic nephropathy, tuberculosis, steroid, chronic prostatitis).
- Some factors predispose to the risk of recurrence. These include obstruction (stricture, BPH, stone, neoplasm), diabetes, nonsteroidal anti-inflammatory drug abuse, vesicoureteral reflux, catheterization/instrumentation, renal disease (polycystic kidney disease, medullary sponge kidney, horse shoe kidney, ectopic kidney), hypokalemia, hypocalcemia.
- Any male patient, any female with recurrent UTI, any complicated UTI, history of hematuria/stone/voiding disturbance and any child with pyelonephritis (high incidence of cakut – congenital abnormalities of kidney and urinary tract).
- Investigate the patient radiologically with X-ray KUB. Now contrast CT is done, instead of intravenous pyelogram. Voiding cystourethrogram is done in young patients with recurrent UTIs to exclude possibility of posterior urethral valves or vesicourethral reflux. Ultrasound is the first radiological test.
- Purple urinary bag syndrome can occur due to metabolic byproducts of bacteria such as *Providencia stuartii, Providencia rettgeri, Klebsiella pneumoniae, Proteus mirabilis, Escherichia coli, Morganella morganii*, and *Pseudomonas aeruginosa*. Risk factors include bacteriuria, constipation and female gender. It is a benign condition.
- Asymptomatic bacteriuria is common and it is generally benign. Treat only in pregnant women at 12 to 16 weeks of gestation or in case of an impending urologic procedure (this does not include placement of a urinary catheter) in which mucosal bleeding is expected.
- As per the ICMR-AMRSN (Indian Council of Medical Research-Antimicrobial Resistance Research and Surveillance Network) data 2017, the common organisms causing UTI include *E. coli* (49.2%), *Klebsiella* spp. (17.4%), *Proteus* spp. (1.4%), *Citrobacter* (1.3%), *Enterococcus* spp. (10.9%), *Staphylococcus aureus* (0.9%), and nonfermented Gram-negative bacilli (8.2%).
- Based on resistance pattern, the ICMR recommends that initial empiric therapy for infections caused by Enterobacteriaceae (*E. coli* and *Klebsiella*) (pyelonephritis) should be with an agent active against ESBL producers, e.g., a carbapenem or with a β-lactam/β-lactamase inhibitor for less severely ill patients.
- ICMR has defined standard doses of antimicrobial agents in its 2019 guidelines. It says that drugs should be given in the appropriate dose.
- In a study published in the *Indian Journal of Nephrology*, 89% organisms in acute pyelonephritis were *E. coli* and 09% were *Klebsiella*. In this study, the drug with 100% benefit was ertapenem, while the drug with 0% benefit was ceftriaxone.
- The Centers for Disease Control and Prevention (CDC) has defined three criteria for a CAUTI: Indwelling catheter in place for more than 2 consecutive days in an inpatient location, urine culture with no more than 2 organisms present and 1 organism with bacterial count of $>10^5$ CFU/mL and presence of at least 1 of the following: fever (38^oC), suprapubic tenderness, costovertebral angle pain/tenderness, urinary urgency, frequency, or dysuria.
- If all the three criteria are met, only then it is CAUTI and has to be treated appropriately. In the absence of these, it is considered asymptomatic bacteriuria.
- The 2018 guideline for CAUTI recommends against urine culture in an asymptomatic catheterized patient. Do not try to treat it.
- To prevent UTI, increase fluid intake, regularity in taking drugs, last dose of the day after urination, voiding after sex, careful removal of sanitary pads, avoid constipation, use 16F catheter in adult males and look at predisposing factors.
- Other palliative measures for symptomatic relief are cranberry extract, local estrogens, probiotics, alkalizers/analgesics, anticholinergics, avoid spicy/nonveg diet, and plenty of water.
- New antibiotics are available such as ceftazidime-avibactam, ceftriaxone-sulbactam/disodium edetate (1.5-3 g OD), aminoglycosides (isepamicin 400 OD, arbekacin 200 OD), and biapenem (300 mg BID).

- Patients with cystitis can be treated empirically with 5 days of antibiotics (no culture) – nitrite and leukocyte esterase test.
- Acute pyelonephritis – culture is needed – 7 days treatment in most or 14 days. No radiology tests unless extra risk.
- Do not culture in catheterized patient unless symptoms. Asymptomatic bacteriuria is common, no treatment. Treat CAUTI for 10 days, if needed, based on CDC criteria.
- Suspect acute bacterial prostatitis in males who come with voiding pattern. Do digital rectal examination/transrectal ultrasound and treat for 14 to 28 days.
- Treat recurrent cystitis with vaginal cream or postcoital antibiotics.
- In cases of candida growth in urine, repeat after catheter removal and treat as per clinical sense.
- Sodium-glucose cotransporter 2 can be continued if no additional risk of recurrence.
- Treat infection not colonization/contamination.
- Be aware of antimicrobial resistance patterns.

Participants: Dr Yeh Woei Chong, Singapore, Chair of Council-CMAAO; Dr Akhtar Hussain, South Africa; Dr Qaisar Sajjad, Pakistan; Dr Ashraf Nizami, Pakistan; Dr Benito Atienza, Philippines

Invitees: Dr Monica Vasudev, USA; Dr Mulazim Hussain Bukhari, Pakistan; Dr Poonam Chablani; Dr Poonam Saith; Dr Sanjay Shah; Dr Tan Wan Ghee; Dr Anjali Agarwal; Dr S Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

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CSI NIC Mid Term Meet: NIC 2024

THE POWER OF SUSTAINED LDL-C REDUCTION: INCLISIRAN AND THE 'LOWER FOR LONGER' APPROACH

Dr Viveka Kumar, Delhi

As a cardiologist, I strongly advocate for the "lower for longer" approach to LDL-C (low-density lipoprotein cholesterol) control as a pivotal strategy in preventing the recurrence of cardiovascular events. Achieving and maintaining low LDL-C levels over an extended period significantly diminishes the risk of these events recurring. The prolonged reduction in LDL-C helps stabilize atherosclerotic plaques, reduces inflammation, and overall contributes to improved cardiovascular outcomes.

Inclisiran has emerged as a groundbreaking therapy in this context, with its ability to maintain an LDL-C reduction of more than 50% from baseline for more than a year with just twice-yearly dosing regimen. The sustained LDL-C lowering effect of Inclisiran is highly compatible with the "lower for longer" approach, offering a reliable and convenient means to maintain low LDL-C levels.

WE GROW BY LEARNING FROM EACH OTHER

Dr Anil Dhall, New Delhi

Networking and community building are good watch-words, but it is largely peer interaction. Sometimes, we have more than one right answer for a clinical problem. So, we need to keep an open mind and we need to learn from each other…learn techniques, learn appropriate utilization of technology, learn how we can handle clinical events, how we can be prepared for disasters, which may happen. This is how this meeting helps us grow not only as individuals but also as a cardiovascular community.

We are running a very active Fellow's program this year with a lot of international representation. The live case transmissions from overseas not only help in fostering a relationship with our global peers but also help us to understand their techniques and how we can improve our technique with the resources available in our country. India is known to adapt to less advantaged situations and turn disadvantage into an advantage by a process which we call "jugad". Because we can actually innovate and think. But the whole problem is that modern medicine is not what I think or I feel. It is based on global data.

And today we have the opportunity to use multiple touch points to collect data. Over 1,200 centers have collaborated for this year's NIC Chairman's Report, which is colossal and shows a very active, ready mindset of people to collaborate and give data, for which there was a reticence to share data till now. But today, with global acceptance, and once we start generating our own data, we will be able to understand our solutions, our problems, and how we can adapt, even with marginally less resources.

So, I think collecting data in modern evidence-based medicine is the only way by which you can demonstrate that something brings value to what you do.

We have designed the Fellow's program this year on the most vexing problems, which fellows face, and that is how to deal with complications, how to think through them, how to prevent them and if they actually happen, how to deal with them. These will be exciting times and we will learn from each other's mistakes and solutions and innovations and out of the box ideation, which actually bails us out of difficult situations.

TAVI COMPLICATIONS AND MANAGEMENT

Dr Sengottuvelu G, Chennai

Chance favors the prepared mind

- Key transcatheter aortic valve implantation (TAVI) complications are device embolization, aortic root injury, paravalvular AI, coronary occlusion, stroke, pericardial tamponade, valve thrombosis, endo-carditis, myocardial stunning, and hemodynamic collapse.
- Incidence of coronary occlusion post-TAVI is low but can be catastrophic.
- Low coronary arteries, small SOV and TAV in SAV are the most common risk factors.
- Complete and detailed assessment of the CT is essential.
- In patients at high risk of coronary occlusion, consider: predilatation + contrast to assess, coronary protection with guide and stent in position, Basilica

procedure, not performing TAVI and re-discuss at Heart Team meeting regarding AVR.

Key Messages

- Complications will occur!!
- Be prepared!
- Patient selection is vital – the CT is the key!
- See as many cases as possible.
- Do as many cases as possible…. as a team!

IMAGING IN COMPLICATIONS: OPTICAL COHERENCE TOMOGRAPHY

Dr Darshan Doshi, USA

Optical coherence tomography (OCT) is an advanced imaging technology used to assess the microstructure of coronary arteries with an axial resolution of approximately 10-15 μm. Compared to intravascular ultrasound (IVUS), OCT provides superior resolution, enabling detailed characterization of the vessel wall's superficial structure. The efficacy of OCT hinges on accurate image acquisition and interpretation.

In interventional cardiology, OCT guides procedures by facilitating precise stent placement, ensuring optimal expansion and alignment. Its capacity to visualize intricate coronary details has established OCT as a vital tool in clinical settings, elevating diagnostic precision, and enhancing patient care in cardiology.

OCT images can be displayed in three primary modes: the traditional cross-sectional image, which provides a view perpendicular to the vessel wall; the longitudinal view, which shows a lengthwise section along the artery; and 3-dimensional visualization, offering a comprehensive spatial representation of the coronary anatomy. Each mode serves distinct purposes in clinical assessment, allowing cardiologists to analyze plaque morphology, assess stent deployment, and visualize vascular structures precisely. These imaging modalities enhance the utility of OCT in diagnosing and guiding interventions for coronary artery disease (CAD), contributing to improved patient outcomes in cardiology practice.

ALTERNATE ACCESSES IN TRANSCATHETER AORTIC VALVE REPLACEMENT

Dr S Nagendra Boopathy, Chennai

- Transcatheter aortic valve replacement (TAVR) has become a viable treatment option for patients with severe aortic stenosis; it is especially beneficial for those at high or prohibitive risk.
- The femoral artery is the most widely used vascular access route. Evidence is evolving in favor of transcarotid and transcaval access routes.
- TF access is key to the success of TAVR. It is essential to learn at least one alternate access route. Maintain adequate volume with one alternate access before moving on to others.
- TAVR is never a one-person procedure; it always requires a team approach.
- Keep three stents handy, each sized according to the common femoral artery, external iliac artery, and common iliac artery. Master one route and become comfortable with it before adapting to others.
- Perform a final angiogram, use a safety wire, have bailout equipment ready, and be competent in individual peripheral skills. Always call for help in cases of urgency.
- Utilize intravascular lithotripsy-assisted peripheral angioplasty to facilitate TF-TAVR, which is crucial for the success of TAVR.

LARGE-BORE VASCULAR ACCESS: CHALLENGES IN MANAGEMENT

Dr Ashishkumar Mandalay, Kozhikode

- Currently, larger bore access is employed for TAVR, left atrial appendage (LAA) occluders, MitraClip device, transcatheter mitral valve repair (TMVR) devices, aortic stent grafts, and hemodynamic support systems such as the Impella and extra-corporeal membrane oxygenation (ECMO). The incidence of vascular access site complications is 20% after TAVI and 12% to 25% after endovascular aneurysm repair (EVAR).
- Access site complications include bleeding and hematoma, vessel dissection and occlusion, pseudo-aneurysm, infection and nerve injury.
- Risk factors for vascular access site complications are female sex, extremes of weight, renal insufficiency, and anticoagulant use. The advantages of USG-guided access are differentiation between artery and vein, identification of bifurcation, avoid calcification, and posterior wall puncture.
- Manual compression is easy to learn, is safe and effective and does not require any special equipment but it is painful with prolonged mean time to achieve hemostasis. It is associated with prolonged time to ambulation, hand and arm fatigue, vascular complications and longer duration of hospitalization.

- Vascular closure device (VCD) are suture-based or collagen-based. The benefits of VCD are increased patient comfort, immediate/early mobility, reduced bleeding, and other vascular complications.
- Proglide VCD has the broadest arterial and venous indication. There is minimum inflammatory response, less blood transfusion, infection, mortality, and shorter hospital stay with minimum intravascular footprint. There are no re-access restrictions.
- MANTA VCD is the first commercially available biomechanical VCD. It is specifically designed for large-bore femoral access. It is available in two sizes: 14 Fr and 18 Fr; they can close access ranging from 12 to 15 Fr OD. No pre-closure is required.

COULD YOU ARTICULATE WHY CSI-NIC 2024 IS CRUCIAL IN ADVANCING THE FIELD OF INTERVENTIONAL CARDIOLOGY AND SHAPING ITS FUTURE TRAJECTORY?

Dr N Prathap Kumar, Kollam

Since the last 2 years, the NIC meeting has been moving to a different level, where participation as well as the people's engagement in the conference is much higher. Last year in Ahmedabad and then in Hyderabad, the total participation was over 2,500. This year we are expecting nearly 2,500 to 3,000 people. Two highlights of the scientific agenda this year are a Fellow's Course dedicated only for the complications. Secondly, for the first time in the history of interventional cardiology, we have "Death on Table". This is to understand why patients in crisis die on the table and can this be prevented in the next generation.

In 2022 and 2023, I was NIC chair. In 2022, nearly 640 senders gave NIC data, whereas in 2023, this number was 740. This year, Dr PK Sahoo got data from 1,200 hospitals. This means that people are interested in sharing data. Data is the initial entrance to the research programs in the country. This will create a lot of research activity in the country.

Lot of collaborations will happen in this NIC. One is with SCAI; we are also planning to collaborate with SOLACI in South America. We already have a collaboration with the Gulf Interventional Society. Such collaborations not only attract people from across the globe, but also facilitate exchange of knowledge.

There are 12 to 15 live cases from across the world in this meeting, except from India since Indian guidelines do not permit a live case. So globally, we are also associating to enhance the knowledge of the young crowd through live cases. From India, we have "Case in a Box" this time to attract the young people.

EMPOWERING POST-PCI CARE: INCLISIRAN FOR AGGRESSIVE LDL CONTROL IN INDIAN POPULATIONS

Dr Sarita Rao, Indore

Intensive lipid control among patients after percutaneous coronary intervention (PCI) is crucial, particularly for the Indian population. Indians often have smaller coronary arteries and experience CAD at a younger age compared to their Western counterparts. The "LOWER FOR LONGER IS BETTER" concept for LDL-C levels is a well-established principle in managing high-risk patient populations.

As a cardiologist, I emphasize that controlling LDL-C levels is paramount in preventing future cardiac complications and recurrence of cardiovascular events-which improve the quality of life of a patient. Through lifestyle modifications, **high-intensity statins**, and **innovative therapies like Inclisiran**, we can significantly reduce the risk of atherosclerosis progression, enhancing long-term cardiovascular health, and patient outcomes.

NIGHTMARE WITH ROTABLATION

Dr Yoshifumi Kashima, Japan

- Rotablation, also known as rotational atherectomy, is an advanced technique employed in PCI for patients.
- Due to its complexity and associated risks, meticulous care is essential during its execution.
  - External factors, such as cardiac motion, can affect the stability of intravascular devices like rotablation wires.
  - It is important to verify the location of the rotablation wire when the guiding catheter is removed. This checkpoint helps ensure proper wire placement and prevents potential complications during PCI.
- Even minor oversights can lead to severe complications. Hence, vigilance is crucial. Any deviations during follow-ups should prompt thorough investigation to prevent potential complications from progressing unnoticed.
- Surgical intervention may be required if the wire displacement worsens.

FEMORAL VASCULAR ACCESS: TECHNIQUE, CLOSURE DEVICES, AND COMPLICATIONS

Dr Rajaram Anantharaman, Chennai

- Access is important as arterial access starts every case and access closure ends every case. It may be

a source of unintended complication and dissatisfaction to the patient after a successful procedure.

- Consequences of non-common femoral artery (CFA) access are increased risk of RPH (high stick), PSA (low stick) but procedure can be completed. Current access techniques are not satisfactory for 100% CFA access.
- Assess the multidetector computed tomography (MDCT) thoroughly (vessel size, tortuosity, calcification, bifurcation, soft plaque burden). Predict the challenges that will be posed in that particular case. Use angiographic, guidewire, and ultrasound (AGU) technique.
- Prepare adequately technique, device, and support as required. Have the tool kit for all access complications ready (check before starting the case). Majority of the access site complications can be managed percutaneously (safely), but do not hesitate to call your vascular interventional/surgical colleague.

THE POWER OF PRECISION: MANAGING DYSLIPIDEMIA IN INDIANS WITH INCLISIRAN

Dr Dilip Kumar, Kolkata

Dyslipidemia management among the Indian population presents unique challenges due to distinct morphological and genetic factors. **Indians tend to have a more multivessel, more diffuse and multiple CAD compared to western population.** The prevalence of central obesity, insulin resistance, and atherogenic dyslipidemia, significantly high than to Western counterparts. Traditional treatment including Statin proven to be significant reduction in LDL-C control but often fall short in achieving optimal lipid levels and reducing cardiovascular risk in this demographic. Therefore, it is crucial to adopt tailored strategies that address the specific lipid abnormalities prevalent among Indians.

One promising advancement in the treatment of dyslipidemia is the use of **Inclisiran, a novel small interfering RNA (siRNA) therapy** that targets PCSK9 synthesis. It provides sustained LDL-C reduction with just **biannual dosing**, aligning well with the lipid goals for high-risk patients. Embracing such innovative treatments can potentially bridge the gap in cardiovascular disease management and improve outcomes for the Indian population.

RADIAL CHALLENGES

Dr Sanjay Kumar Chugh, Gurgaon

- The European and American Guidelines for PCI recommend transradial access (TRA) as the default procedure because of the overwhelming and irrefutable evidence of reduced risk of vascular complications, bleeding, and mortality, especially in acute and high-risk patients undergoing PCI using TRA.
- Vasovagal is common to all cath lab procedures but most relevant and crucial to radial access because of early mobilization and discharge.
- Radial artery spasms are better prevented than treated. They are responsible for up to 38% of all transradial procedure failures.
- Radial artery occlusion occurs in 3% to 10% of all transradial interventions and can be prevented by appropriate anticoagulation, proper sheath selection and nonocclusive/patient hemostasis.
- To prevent nonaccess site forearm bleed/hematoma, clinicians should have a low threshold for performing a radial artery arteriogram when any resistance to the guidewire or catheter insertion is encountered.
- Be cautious when taking a guide catheter and crossing the cubital fossa to the subclavian artery.
- Transradial procedures have low complications rates, but more complications occur in small RA-diameters. Access arteries with a diameter of ≥1.7 mm have lesser complications. A larger catheter curve size is required for aortic root. Preventing pseudoneural artery occlusion rarely requires surgery and is an outpatient procedure under local anesthesia.

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News and Views

Integrating Diabetes and Cognitive Care

Diabetes is strongly associated with a faster rate of cognitive decline in patients with mild cognitive impairment (MCI). This decline was most pronounced within the first year of diagnosis. Also, patients with diabetes had a higher likelihood of progressing from MCI to Alzheimer's disease (AD) compared to those without diabetes. Diabetes mellitus also negatively affects brain areas involved in cognitive functioning. These findings were published online June 12, 2024 in the journal *Alzheimer's & Dementia*[1].

This study used the Alzheimer's Disease Neuroimaging Initiative dataset to determine the optimal time window to intervene to slow or prevent the transition from MCI to AD as well as to identify the neurobiological targets that could be targeted to prevent or slow down the progression from MCI to AD. A total of 980 participants diagnosed with MCI were included in the study were categorized based on their diabetes status. They underwent neuroimaging and cognitive evaluation to assess the rate of conversion from MCI to AD, neuroimaging changes and cognitive changes. One hundred-two diabetes patients were matched with 2 patients without diabetes (n = 204).

A strong correlation between diabetes and cognitive deterioration as well as an elevated risk of AD progression, particularly during the first year of MCI follow-up was observed. It has a negative impact on several brain regions, most notably on the nucleus accumbens where it hastened significant atrophy and a decrease in the gray matter volume and sulcal depth.

Researchers found no statistically significant difference in conversion to AD between patients with and without diabetes over the follow-up period of 11 years. Nonetheless, more diabetic patients (8.82%) progressed to AD within the first 12 months following the diagnosis of MCI than those without DM (2.45%). According to absolute differences in the Participant-reported Everyday Cognition Scale Plan (EcogPtPlan), Rey's Auditory Verbal Learning Test immediate recall (RAVLT-immediate), Alzheimer's Disease Assessment Scale task 4 (ADASQ4) and relative differences in RAVLT-immediate outcomes, patients with diabetes mellitus were found to have worse cognitive impairment at year 1 relative to baseline compared to those who did not have diabetes.

Compared to the subjects without diabetes mellitus, patients with diabetes had a marked inwardly concave surface and mild atrophy of the left nucleus accumbens at the start of the study. At 12 months, atrophy of the left nucleus accumbens was found to persist. Additionally, they also displayed atrophy in the right nucleus accumbens. Over the follow-up period, patients with diabetes also had changes in cortical thickness and gyrification index along with decreased sulcal depth.

These findings highlight the first year following the diagnosis of MCI in patients with diabetes as a crucial window for therapeutic intervention. Early and aggressive diabetes care in patients with MCI with regular cognitive assessments and monitoring are essential to detect and address changes promptly. This includes implementing lifestyle changes such as diet and exercise together with maintaining blood sugar levels and managing comorbid conditions to mitigate the impact of diabetes on cognitive health. Further, understanding the specific brain structures affected by diabetes mellitus can guide the development of targeted neuroprotective therapies.

Reference

1. Ding X, et al; Alzheimer's Disease Neuroimaging Initiative. Diabetes accelerates Alzheimer's disease progression in the first year post mild cognitive impairment diagnosis. Alzheimers Dement. 2024 Jun 12. doi: 10.1002/alz.13882.

Predicting Respiratory Morbidity after Early-Life RSV Infection

Lower gestational age and age at first respiratory syncytial virus (RSV) infection are linked to a higher incidence of subsequent respiratory morbidity following early-life RSV infection, according to a study published in the journal *Open Forum Infectious Diseases*[1]. Maternal history of asthma and low socioeconomic status were also associated with later respiratory morbidity.

For this study, the investigators employed a whole-of-population birth cohort that was probabilistically linked, and consisted of 2,52,287 children born in Western Australia between 2000 and 2009, and was examined up to the end of 2012. The associations between different risk factors and the first respiratory episode of asthma, wheezing, and an unspecified acute lower respiratory infection after the age of 2 years. The study also examined

the prenatal and sociodemographic characteristics linked to respiratory illness in later childhood that required secondary treatment after exposure to an RSV episode that was confirmed in the laboratory during the first 2 years of life.

A total of 4,151 children who had a confirmed RSV test before the age of 2 years were included in the analysis.

The highest incidence of subsequent respiratory morbidity following early-life RSV infection was observed in children aged 2 to <4 years, with an incidence rate of 41.8 per 1,000 child-years. The incidence of respiratory morbidity increased with the age at which the child was infected with RSV. For children infected at the age of 6 to <12 months, the incidence rate was 23.6 per 1,000 child-years. For children infected at 12 to <24 months age, the incidence rate was 22.4 per 1,000 child-years.

The incidence of respiratory morbidity decreased with gestational age. The incidence rate was 50.8 per 1,000 child-years among children who were born extremely premature (<28 weeks gestation).

The study also identified several risk factors for subsequent respiratory morbidity following an early-life RSV infection. Children who experienced their first RSV episode between 6 to <12 months of age had a higher risk of subsequent respiratory morbidity with adjusted hazard ratio (aHR) of 1.42. Children born extremely premature (<28 weeks gestation) and those with maternal history of asthma were at a significantly higher risk with aHRs of 2.22 and 1.33, respectively. Low socioeconomic index was another significant risk factor (aHR 1.76).

This study therefore suggests that the recommendations for RSV prevention such as vaccination can be extended beyond preterm and very young infants to also include older children, between the ages of 12 and <24 months, in order to lessen the burden of subsequent respiratory morbidities linked to RSV. Parents should be educated about the importance of RSV prevention in children up to 24 months old.

Reference

1. Sarna M, et al. Factors predicting secondary respiratory morbidity following early-life respiratory syncytial virus infections: population-based cohort study. Open Forum Infect Dis. 2023;10(10):ofad450.

Long-term Safety of Metformin Use in Pregnancy

Use of metformin to treat gestational diabetes or diabetes during pregnancy did not have any negative impact on the long-term outcomes for both children and mothers, according to the results of a study recently published online June 12, 2024 in the journal *Endocrine Practice*[1]. Exposure to metformin did not adversely affect the metabolic health or development of children, 5 to 11 years of age, compared to insulin exposure. It also did not increase the risk of adverse metabolic outcomes postpartum in mothers.

The study designed as a meta-analysis and systematic review undertook to assess the long-term effects of metformin use during pregnancy on mothers and their offspring at the age of 9 years compared to insulin use. Relevant studies comparing metformin against insulin for the treatment of gestational diabetes mellitus or diabetes were identified following a comprehensive search of several electronic databases. Seven randomized controlled trials and cohort studies were included in the final analysis. Any change in the body mass index (BMI) in children at 5 and 11 years of age was the primary study endpoint. The secondary outcomes were the changes in other anthropometric parameters, obesity prevalence, and metabolic parameters (lipids and adipocytokines) in mothers and children.

At 9 years of age, no significant difference was observed in BMI between children whose mothers were treated with metformin and those treated with insulin. The mean difference (MD) was 1.09 kg/m^2. They also had comparable waist circumference-to-height ratio (MD 0.13), total fat mass measured by dual-energy X-ray absorptiometry (MD 0.68 kg) and total fat percent (MD 0.04%), total fat-free mass (MD 0.81 kg), visceral adipose tissue volume (MD 80.97 cm^3), and liver fat percentage (MD 0.27%).

The levels of ferritin, alanine aminotransferase, leptin, and serum adiponectin were similar between the two groups. The prevalence of obesity, diabetes, or difficulties with motor and social development in children between the ages of 9 and 11 years did not show any significant difference between the two groups. Showing a similar trend, no differences in BMI or the risk of developing diabetes in mothers were observed between metformin and insulin groups at 9 years postpartum.

This meta-analysis has for the first time analyzed the long-term outcomes of use of metformin vis-a-vis insulin during pregnancy. Metformin was as safe as insulin for the treatment of gestational diabetes or diabetes during pregnancy, with no significant differences in the long-term health of both mothers or the infants. The ease of administration and positive metabolic effects further reinforce the potential benefits of metformin use during pregnancy. Hence, metformin may be considered as

a safe and effective alternative to insulin. However, further research is needed to elucidate on outcomes into adulthood.

Reference

1. Dutta D, et al. Long-term impact on offspring (5 to 11 years of age) of metformin use in pregnancy in mothers with diabetes: a systematic review and meta-analysis. Endocr Pract. 2024 Jun 12:S1530-891X(24)00559-7.

Predisposing Factors for Pneumomediastinum in COVID-19 Pneumonia Patients

Although the COVID-19 pandemic has officially ended, there are still many unknowns about the virus and its impact. Ongoing research continues to delve into various aspects of the disease to enhance our understanding and improve future responses to public health challenges of such nature.

Adding to the growing evidence, a team of researchers from Italy undertook a multicenter case-control study to identify risk factors for COVID-19-associated pneumomediastinum and to also investigate its impact on the clinical outcomes of patients[1]. Patients hospitalized with COVID-19 pneumonia and pneumomediastinum from March 2020 to July 2020 at 10 centers were included in the study. Another group of inpatients with COVID-19 pneumonia and respiratory failure who did not develop pneumomediastinum during the same period were also included as controls. Data were gathered and compared between the two groups for respiratory support, radiologic features, laboratory findings, clinical characteristics, and clinical outcomes.

The analysis was performed on a cohort of 139 patients with pneumomediastinum and 153 patients without pneumomediastinum.

Results published in the journal *Respiratory Medicine* show that pneumomediastinum was independently linked with lung involvement of ≥75%, presence of consolidation, BMI <22 kg/m^2, C-reactive protein (CRP) >150 mg/L, D-dimer >3,000 ng/mL fibrinogen equivalent units, and smoking exposure of >20 pack-years.

Over half of the patients (52.5%) with pneumomediastinum required intubation compared to 17.6% patients in the control group. Likewise, pneumomediastinum patients had higher rates of in-hospital mortality (48.9% vs. 23.5%) along with longer mean duration of hospitalization (31.2 days vs. 19.6 days) versus controls.

The study has identified various risk factors for the development of pneumomediastinum in patients with COVID-19 pneumonia. These include extensive lung involvement, presence of consolidation, low BMI, elevated inflammatory markers (CRP and D-dimer) and significant smoking history. Patients with these risk factors have worse clinical outcomes with regard to in-hospital mortality and duration of hospitalization. Clinicians should be vigilant in identifying patients at higher risk for pneumomediastinum based on the identified risk factors. The high-risk patients may benefit from enhanced monitoring and early intervention to mitigate the impact of pneumomediastinum. Hence, there is the need for adoption of strategies to mitigate severe lung involvement and control inflammation in patients with COVID-19 pneumonia.

Reference

1. Negri S, et al. Pneumomediastinum in COVID-19: Risk factors and outcomes from a multicentre case-control study. Respir Med. 2024;230:107684.

Timely Antibiotic Administration Mitigates Mortality Risk in Pediatric Sepsis

Administration of antibiotics at 330 minutes or later (>5.5 hours) to children with sepsis presenting to the emergency department (ED) is associated with more than threefold increase in mortality at 3 days and 30 days, according to findings of a study from the US published in *JAMA Network Open*[1].

Data from 51 children's hospitals in the US participating in the Improving Pediatric Sepsis Outcomes collaborative was analyzed for this multicenter, retrospective cohort study. Patients diagnosed with sepsis within an hour of arriving at the emergency room from January 2017 to December 2021 were included. Their ages ranged from 29 days to <18 years.

The period of data analysis was March 2022 to February 2024. The objective of the study was to identify a critical time point at which antibiotic administration was linked to a higher risk of death in children with sepsis. The main outcome of the study was 3-day mortality due to sepsis. The secondary endpoint was 30-day death attributable to sepsis.

This retrospective cohort study included a total of 19,515 pediatric cases with sepsis, with a median age of 6 years. The median time before antibiotics were administered was 69 minutes. The results showed that the estimated median time to antibiotic administration, which resulted in an increase in 3-day sepsis-related mortality was 330 minutes (5.5 hours). For every increase of 30 minutes beyond this cut-off point, the risk of mortality significantly increased with odds ratio (OR) of 2.44.

A total of 19,164 patients received an antibiotic in <330 minutes. Of these, 93 patients had a sepsis-related 3-day mortality of 0.5%, while 163 patients had a 30-day mortality of 0.9%.

The 3-day mortality due to sepsis in those who received antibiotics at 330 minutes or later was 1.2% (vs. 0.5%). The 30-day mortality rate was 2.0% (vs. 0.9%) in the delayed treatment group.

In adjusted analysis, those who received antibiotics at or any time after 330 minutes (351 patients) had higher adjusted odds of sepsis-attributable mortality at 3 days (OR 3.44) and 30 days (OR 3.63) compared with antibiotics given before 330 minutes.

The presence of bacteremia (aOR 2.78), lactate levels above 36 mg/dL (aOR 9.38), IPSO-defined critical sepsis (aOR 5.06), the existence of high-risk conditions (aOR 2.29), and receiving long-term ventilation (aOR 2.13), were among the factors associated with an increased risk of sepsis-attributable mortality at 3 and 30 days.

This study demonstrates significant differences in the adjusted odds of sepsis-related mortality based on the timing of antibiotic administration in pediatric patients with sepsis. These findings align with existing literature and guidelines, which highlight that delay in antibiotic treatment are associated with adverse outcomes in cases of pediatric sepsis. Hence, these conclusions underscore the critical importance of timely antibiotic treatment in improving outcomes in this high-risk group of patients.

Reference

1. Lane RD, et al. Delays to antibiotics in the emergency department and risk of mortality in children with sepsis. JAMA Netw Open. 2024;7(6):e2413955.

Outcomes in Pregnancy with Uterine Fibroids

The size of the uterine fibroids, and not their number, increases the risks for adverse pregnancy and obstetric outcomes including breech presentation, postpartum hemorrhage (PPH), and placenta previa, according to a recent study published in the journal *BMC Pregnancy and Childbirth*[1].

This meta-analysis was conducted to ascertain the impact of uterine fibroids on adverse consequences, with particular focus on the multiple or big fibroids measuring ≥5 cm in size. Li and colleagues looked through the databases of PubMed, Embase, Web of Science, ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI), and SinoMed to find relevant research on the impact of uterine fibroids on unfavorable pregnancy outcomes. Twenty-four studies with a total of 2,37,509 participants were included in the analysis.

Pooled analysis revealed that uterine fibroids significantly increased the risks of a number of unfavorable pregnancy and obstetric outcomes, such as low birth weight (relative risk [RR] 1.72), breech presentation (RR 2.26), preterm birth (RR 1.72), placenta previa (RR 2.99), miscarriage (RR 4.51), preterm premature rupture of membranes (PPROM) (RR 1.37), placental abruption (RR 1.85), PPH (RR 3.52), and fetal distress (RR 3.61).

Adverse effects, however, were only observed for preterm birth, cesarean delivery, placenta previa, placental abruption, PPH, intrauterine fetal mortality, breech presentation, and pre-eclampsia after correcting for the potential confounding factors.

A subgroup analysis further revealed that compared to smaller fibroids (<5 cm), larger fibroids (>5 cm) significantly increased the risks for PPH (RR 5.04), breech presentation (RR 1.5), and placenta previa (RR 1.62).

The risk of breech presentation, placental abruption, cesarean delivery, PPH, placenta previa, PPROM, preterm birth, and intrauterine growth restriction (IUGR) was not increased by the presence of multiple fibroids. On meta-regression analysis, the relationship between uterine fibroids and intrauterine fetal death was influenced by BMI, while the association between uterine fibroids and preterm birth was solely impacted by the age of the mother. Outcomes such as malposition, fetal discomfort, placenta previa, placental abruption, PPROM, miscarriage, and PPH were unaffected by other potential confounding factors.

These findings highlight the importance of considering individual factors like maternal age and BMI when assessing the risks associated with uterine fibroids in pregnancy. This helps in managing and counseling patients with uterine fibroids during pregnancy to diminish the impact of these risks. "Our results provide valuable information for the identification of the risks of breech presentation, PPH, and placenta previa," write the authors.

Reference

1. Li H, et al. The influence of uterine fibroids on adverse outcomes in pregnant women: a meta-analysis. BMC Pregnancy Childbirth. 2024;24(1):345.

■■■■

The Buddha Description of a Disease: Desire, Hatred, and Ignorance

According to Buddhism, three negative emotions cause a disease and they are "ignorance, hatred, and desire". According to the Buddhist philosophy, physical sicknesses are classified into three main types:

- Disorders of the desire (Ayurvedic equivalent *Vata* imbalance): These are disharmony of the wind or energy. The seed of these disorders is located in the lower part of the body. It has cold preferences and affected by mental desires. A person suffers from the disorders of movement functions.
- Disorders of the hatred (Ayurveda equivalent *Pitta* imbalance): It is due to disharmony of the bile. The seed of these disorders is centered in the middle and upper part of the body and is caused by the mental emotion hatred. In Ayurveda text, it is equivalent to "*Pitta*" disorder. The person suffers from metabolic and digestive abnormalities.
- Disorders of the ignorance (Ayurveda equivalent *Kapha* imbalance): It is due to the disharmony of phlegm, which is generally centered in the chest or in the head and is cold in nature. It is caused by the mental emotion *ignorance*.

Desire, hatred and ignorance are the main negativities mentioned in Buddhist philosophy. They are all produced in the mind. Once produced, they behave like a slow poison. The *Udanavarga* once said, "From iron appears rust, and rust eats the iron", "Likewise, the careless actions (*karma*) that we perform, lead us to hellish lives".

According to other scriptures, six afflictions are most troublesome - ignorance, hatred, desire, miserliness, jealousy, and arrogance. Patience is the most potent virtue a person can acquire. According to the Shantideva, "There is no evil like hatred, and there is no marriage like patience. Therefore, dedicate your life to the practice of patience".

Bhagavad Gita mentions the enemies as *Kama, Krodha, Lobh, Moh,* and *Ahankar* and out of these, *Kama, Lobh,* and *Ahankar* as the three gateways to hell.

■■■■

Just Listen...

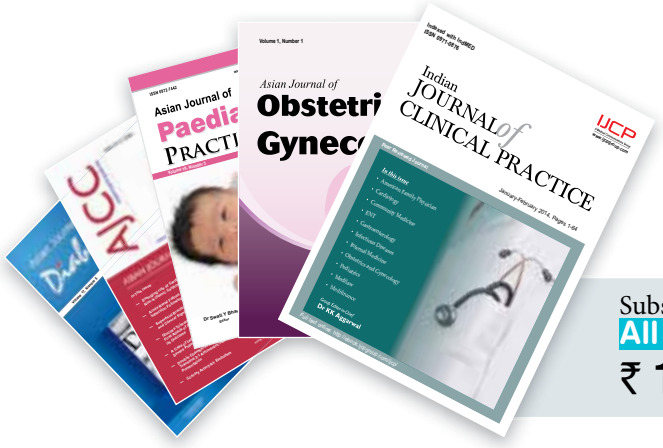
I suspect that the most basic and powerful way to connect to another person is to listen. Just listen. Perhaps the most important thing we ever give each other is our attention. And especially if it's given from the heart. When people are talking, there's no need to do anything but receive them. Just take them in. Listen to what they're saying. Care about it. Most times caring about it is even more important than understanding it. Most of us don't value ourselves or our love enough to know this. It has taken me a long time to believe in the power of simple saying, "I'm so sorry," when someone is in pain. And meaning it.

One of my patients told me that when she tried to tell her story people often interrupted to tell her that they once had something just like that happen to them. Subtly her pain became a story about themselves. Eventually, she stopped talking to most people. It was just too lonely. We connect through listening. When we interrupt what someone is saying to let them know that we understand, we move the focus of attention to ourselves. When we listen, they know we care. Many people with cancer can talk about the relief of having someone just listen.

I have even learned to respond to someone crying by just listening. In the old days, I used to reach for the tissues, until I realized that passing a person a tissue may be just another way to shut them down, to take them out of their experience of sadness and grief. Now I just listen. When they have cried all they need to cry, they find me there with them.

This simple thing has not been that easy to learn. It certainly went against everything I had been taught since I was very young. I thought people listened only because they were too timid to speak or did not know the answer. A loving silence often has far more power to heal and to connect than the most well intentioned words.

■■■■



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Lighter Side of Medicine

HUMOR

WHO DISCOVERED AMERICA?

Teacher: George, go to the map and find North America.

George: Here it is!

Teacher: Correct. Now, class, who discovered America?

Class: George!

AND THE MAN SAID

There was this man driving along in his car when he suddenly got a flat tire. When he pulled over, he was at the fence of a mental hospital. When he got out of the car one of the patients came to the fence and asked "Can I help you?" And the man said "No, I need to figure out how to make it home with only 2 lugs on this wheel." The patient asked again "Are you sure you do not need any help?" And the man said "No." The man tried to figure it out when all of a sudden, the patient said "If I were you, I would take one lug off the other 3 wheels and put them on that wheel and you should be able to get home." The man asked "How did you think of that?" The patient replied "I am in here because I'm crazy not because I'm stupid."

ORGANIZED CRIME

No matter how much the government fights it, organized crime just seems to get more organized every day. The police pulled in a Mob kingpin recently and reminded him he had the right to make a phone call.

"Just fax the arrest report to my lawyer," the mobster said calmly.

SOME ANSWERS

Antibody – One who hates his body

Artery – Study of fine paintings

Bacteria – Back door of a cafeteria

Coma – Punctuation mark

Gallbladder – Bladder of a girl

Genes – Blue denim

Labor Pain – Hurt at work

Liposuction – A French Kiss

Ultrasound – Radical sound

Cardiology – Advanced study of playing cards

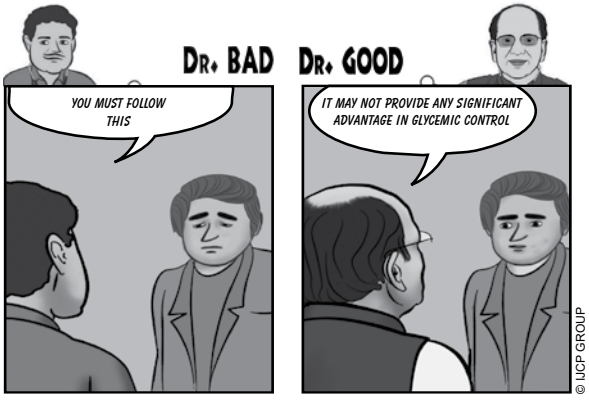
KIDNEYS AND LIVERS

Two old men were arguing the merits of their doctors. The first one said, "I don't trust your fancy doctor. He treated old Jake Waxman for a kidney ailment for nearly a year, and then Jake died of a liver ailment." "So what makes you think your doctor is any better?" asked his friend.

"Because when my doctor treats you for a kidney ailment, you can be sure you'll die of a kidney ailment.

Dr. Good and Dr. Bad

SITUATION: A 32-year-old male with noninsulin-treated T2DM, HbA1c level 7% was asked to perform SMBG.



LESSON: The researchers have shown no clinically or statistically significant differences at 1 year in glycemic control or health related quality-of-life between non-insulin-treated T2DM patients who performed SMBG and those who did not perform it.

JAMA Intern Med. 2017;177(7):920-9.

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Articles

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

Books

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

Articles in Books

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

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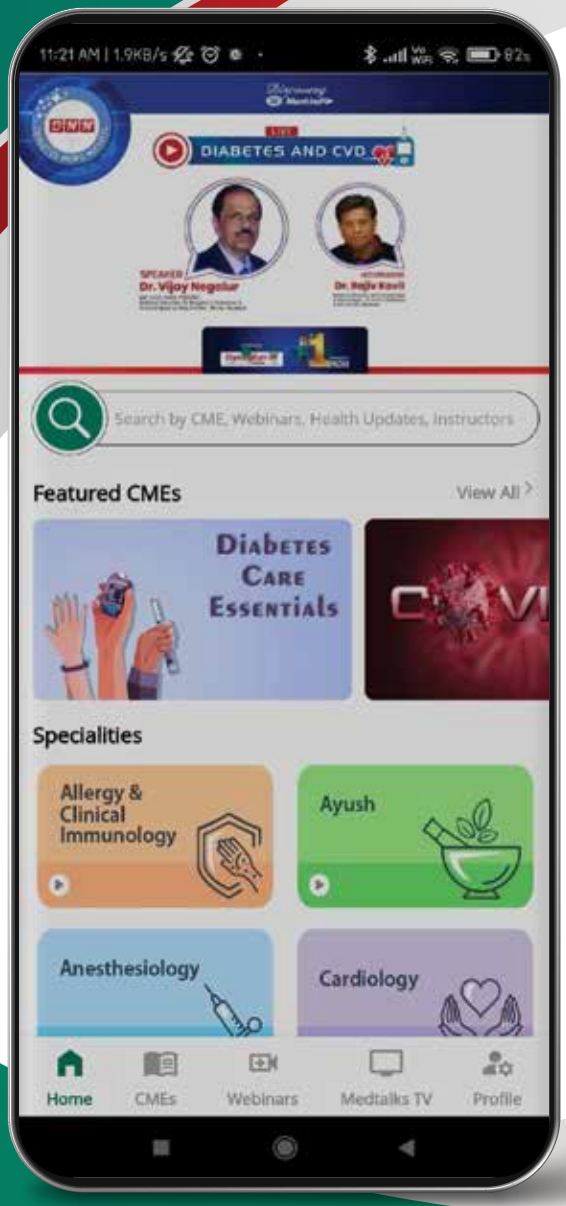

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