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Journal of Associations of Clinicians of India



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153, Block - B, Lake Town, Kolkata 700089

JOURNAL OF THE ASSOCIATIONS OF CLINICIANS OF INDIA

Volume – 2, September 2026



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Published by

The Associations of Clinicians of India

153, Block-B, Lake Town, Kolkata 700 089

Email: rcpi.indianchapter@gmail.com

Website: www.indchaptrcpi.org

Printed by

Unique Phototype

49, Guru Prosad Chowdhury Lane

Kolkata 700 006

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From Chairman's Desk

It's my great pleasure to write for the 2nd edition of JACI (2026) to be published in September.

In the previous edition I mentioned, President, Royal College of Physicians of Ireland (RCPI), Dr. Diarmuid O'Shea and Dr. Geoff Chadwick, Senior Fellow of College Council along with RCPI officials Sinead Lucey and Sinead Freeman will be in Kolkata for upcoming MRCPI Clinical examination in General Medicine on 7th March 26 and participate in master class ceremony on 8th March 26. Unfortunately, the examination had to be withheld at the last minute due to sudden unrest in West Asia. However, the day long Masterclass ceremony program was a grand success with virtual participation of Dr. O'Shea, Dr. Chadwick and RCPI officials, felicitation of dignitaries, introduction of ACI members with and launching of JACI March edition was held on 8th March at Altair Hotel auditorium, Kolkata. Over 250 delegates attended the meeting.

I am delighted to inform that after a significant improvement of west Asian disruption, RCPI team have rescheduled global calendar of MRCPI clinical examination and new examination will be held in Kolkata on 6th December 26 and the President with RCPI team will visit India at that time.

I would like to extend heartfelt thanks and gratitude to the editorial team lead by the Editorial in Chief Prof Kanjaksha Ghosh along with Joint editors Dr. Kaushik Ghosh and Mainak Mukhopadhyay and secretaries Mr Debasish Chakraborty and Ms Basabpriya Das for their enormous endeavour to publish this edition on time.

I would like to extend my best wishes to all of you for a series of festivities ahead this year.

dr. Sabyasachi Ray
Chairman

Association of Clinicians of India

(A unit of Fellows & Members of Royal College of Physicians, Ireland)

Consultant Gastroenterologist, Peerless Hospital & Remedy Clinic, Kolkata

President, Laketown Scientific Research and Clinicians Association

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View Point

It is with pleasure and a sense of accomplishment I on behalf of the Editors and Editorial board present the current issue of Journals of Clinicians of India(JACI) to our readers and subscribers.

Like the past issues of the journal this journal also presents interesting case reports, original articles and reviews along with a question answer corner for the students,

The case reports were carefully picked up because of their unusual nature, chances why some diagnosis may be missed, a side effect in the form of a serious complication of a commonly used antidiabetic drug, simple modification of an ultrasound procedure to assess the extent of disease and complication in a case of carcinoma cervix and so on. Original article from Ireland nicely described how reticulocyte parameters as obtained through present day haematology counter can easily provide us with the diagnosis of Iron deficiency in dialysis dependent chronic renal disease patients.

A paper on career path in Transfusion medicine for Indian doctors may be useful for those contemplating such a career. There are several articles on various topics like relationship between Gut and Brain, echocardiography parameters to assess certain cardiac function, Wasp Envenomation and Secondary haemochromatosis etc will improve the understanding of those preparing for membership and other postgraduate examination. It will also help to brush the current understanding in the subjects covered for doctors of some seniority.

Any journal of a society can go from strength to strength only when the members of the organization utilize their journal in as many ways as they can i.e they read the articles, send their comments as correspondence, submit their own work in their own journal and cite the papers published in their journal elsewhere where feasible.

I have received substantial help from my co-editors Dr Mainak Mukhopadhyay and Dr Kaushik Ghosh as well as members of the editorial board and editorial advisory board in various ways to bring this issue on time. Editorial office with Ms Basabpriya has always been responsive and rendered secretarial help in every way possible.

No journal can boast of publishing good articles without help from its contributors and reviewers I sincerely thank all of them for their effort and times help.

Constant encouragement from Dr Diamond O'Shea, The president of the Royal College of Physicians of Ireland and from Dr Sabyasachi Roy, The chairman of the association is gratefully acknowledged.

I hope the readers will like this issue and I look forward their comments and criticisms to improve the content of the journal in future.

Prof (dr) Kanjaksha Ghosh

Editor-in-Chief

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President message form Pricedent of RCPI

Foreword from dr diarmuid O'Shea, President of the Royal College of Physicians of Ireland

It is a great honor to contribute this foreword to the forthcoming Journal of Association of Clinicians of India (JACI), a publication that exemplifies the Association's enduring commitment to academic excellence, professional development, and the advancement of clinical practice. The Royal College of Physicians of Ireland greatly values our enduring relationship with India, increasingly strengthened by our growing network of members and fellows in the region, to advance our shared ambitions in global health.

With contributions from authors in India and Ireland, this issue reflects the global nature of medical scholarship and the value of international collaboration in addressing shared healthcare challenges. These partnerships enrich professional discourse, foster the exchange of knowledge and experience, and ultimately contribute to improved patient care and outcomes.

The JACI occupies a central place within the Association's broad academic programme. With an impressive portfolio of continuing medical education activities, scientific conferences, case-based learning, and training initiatives, the journal provides an important platform for the dissemination of research, clinical insights, and emerging perspectives from across the medical community.

Progress in healthcare and medical practice is grounded in this type of rigorous inquiry, critical reflection, and scholarly engagement. Our global community of over 15,000 members and fellows play a vital role in advancing discourse, pedagogy and practice. We continue to collaborate and engage with the medical community in India through our MRCPI examinations and education programming, directly with our members and fellows in the region, and I look forward to further strengthening the bonds of collaboration between our clinical communities over the coming months and years.

My sincere congratulations to all involved in the production of this edition. The dedication of the JACI editorial team, reviewers, and contributing authors ensures that the journal remains a valuable resource for practitioners, trainees, and researchers across the course of their medical careers.

I commend the Association for its ongoing leadership in fostering academic achievement and professional growth. Your commitment and dedication to improving patient care, to the training and education of doctors, and the future generation of health care leaders in your country is inspiring.

I wish all affiliated with the Association of Clinicians of India and the JACI continued success and contentment in their careers, academic activities and the publication of this journal.

Dr. Diarmuid O'Shea



President

Royal College of Physicians of Ireland

MRCPI EXAMINATION dATES

Applications are invited from the prospective candidates for the following forthcoming Examinations. All applications are processed online at www.rcpi.ie

MRCPI Part I (General Medicine) Written : 10th December 2026

MRCPI Part I (General Medicine) Written : 15th April 2027

MRCPI Part I (General Medicine) Written : 19th August 2027

MRCPI Part I (General Medicine) Written : 9th December 2027

MRCPI Part II (General Medicine) Written : 29th October 2026

MRCPI Part II (General Medicine) Written : 19th March 2027

MRCPI Part II (General Medicine) Written : 24th June 2027

MRCPI Part II (General Medicine) Written : 28th October 2027

MRCPI Part II (General Medicine) Clinical : 26th Sept – 23rd October 2026 (Ireland)

MRCPI Part II (General Medicine) Clinical : 22th Jan - 26th Feb 2027 (Ireland)

MRCPI Part II (General Medicine) Clinical : 21th May – 25th June 2027 (Ireland)

MRCPI Part II (General Medicine) Clinical : 17th Sept – 22rd Oct 2027 (Ireland)

MRCPI Part II (General Medicine) Clinical : 31st Oct – 1st Nov 2026 (Penang)

MRCPI Part II (General Medicine) Clinical : 6th Dec 2026 (India)

MRCPI Part I (Paediatrics) Written : 22nd January 2027

MRCPI Part I (Paediatrics) Written : 7th May 2027

MRCPI Part II (Paediatrics) Written : 12th March 2027

MRCPI Part II (Paediatrics) Written : 20th August 2027

MRCPI Part II (Paediatrics) Clinical : 13th Nov & 20th Nov 2026 (Ireland)

MRCPI Part II (Paediatrics) Clinical : 20th Nov 2026 (Riyadh)

MRCPI Part II (OBGYN) Written : 5th March 2027

MRCPI Part II (OBGYN) Written : 3rd September 2027

MRCPI Part II (OBGYN) Clinical : 6th Nov & 7th Nov 2026 (Dublin)

MRCPI Part II (OBGYN) Clinical : 6th Nov & 7th Nov 2026 (Riyadh)

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Novel Reticulocyte Parameters from the Sysmex XN 9000 Analyser and the Early detection of Iron deficiency Anaemia Among dialysis Patients

*Dr. Chukwuemeka Mgbemena¹²³, Dr. Philip Murphy²,
Dr. Stephen Bergin², Dr. Fiona Crotty³*

Abstract

Background: Iron deficiency anaemia (IDA) is a common complication among dialysis patients. Novel reticulocyte parameters, including reticulocyte haemoglobin equivalent (RET-He), delta haemoglobin equivalent (Delta-He), and percentage of hypo-haemoglobinised red cell (% Hypo-He), have emerged as promising diagnostic tools for IDA. This study examines the diagnostic potential of these novel reticulocyte parameters and establishes an optimal cutoff point for diagnosing IDA among dialysis patients.

Method: This retrospective study included 139 patients undergoing haemodialysis at Beaumont Hospital in Dublin, Ireland. Receiver operator characteristic (ROC) curves were performed to assess the diagnostic performance of these parameters. The optimal cutoff point was determined using Youden's index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each cutoff point.

Results. RET-He demonstrated superior diagnostic performance, achieving an area under the curve (AUC) of 0.822 (95% CI: 0.739-0.888). With a cutoff point of ≤ 31.2 pg, it yielded a sensitivity of 81.5%, specificity of 72.4% and negative predictive value (NPV) of 80.8%. In contrast, Delta-He recorded an AUC of 0.746 (95% CI: 0.655-0.823), where a cutoff point of ≤ 0.3 pg resulted in a sensitivity of 61.1%, specificity of 81.0% and NPV of 69.1%. % Hypo-He exhibited the least diagnostic capability, presenting an AUC of 0.653 (95% CI: 0.557-0.740). At a cutoff point of $> 0.6\%$, it provided a sensitivity of 57.4%, specificity of 72.4% and NPV of 64.6%.

Conclusion: Novel reticulocyte parameters represent valuable tools in early detection of IDA among dialysis patients.

Key words

Chronic kidney disease, reticulocyte haemoglobin equivalent, percentage of hypo-haemoglobinised red cells, iron deficiency anaemia.

Introduction

Anaemia is one of the major complications of chronic kidney disease (CKD), affecting over 75.5%

of patients with end-stage renal disease (ESRD), particularly those undergoing haemodialysis treatment [1,2]. The causes of anaemia in CKD are multifactorial, with insufficient erythropoietin

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production and iron deficiency (ID) as the leading causes [3]. Early detection and treatment of iron deficiency anaemia (IDA) are crucial for managing CKD patients, as they lead to improved physical activity, enhanced cognitive and cardiovascular function, reduced mortality, and a better quality of life [4].

Bone marrow aspiration (BMA) is the gold standard for diagnosing ID [3]. However, this test involves an invasive procedure that can be traumatic for patients, thus limiting its routine application among dialysis patients [4]. Less invasive biochemical tests, such as serum ferritin, serum iron, and transferrin saturation (TSAT), are routinely used alongside haemoglobin (Hb) and red blood cell indices (mean corpuscular volume, MCV, and mean haemoglobin concentration, MCH) in the assessment of IDA.

Despite the numerous tests available, significant concerns have been raised regarding their limitations in diagnosing ID and IDA among dialysis patients. Although serum ferritin is a marker that reflects iron stores, it is an acute-phase protein that elevates in chronic inflammatory conditions. Serum iron and TSAT (Transferrin Saturation) are influenced by circadian rhythms and the patient's nutritional status [5,6]. Additionally, these biochemical markers do not correlate with bone marrow iron stores.

Since a mature red blood cell has a long lifespan of 120 days, detecting ID using Hb and red cell indices may be delayed [7]. Additionally, MCV values are influenced by conditions such as reticulocytosis, liver disease, and myelodysplastic syndrome. These limitations underscore the need for alternative diagnostic markers.

Recently, novel reticulocyte parameters to assess iron status have become available on Sysmex automated haematology analysers. RET-He measures the amount of Hb in reticulocytes [8], reflecting the availability of functional iron for erythropoiesis [11].

Delta-He is derived from the difference between Ret-He and the haemoglobin content of mature erythrocytes (RBC-He) [8]. Normally, Delta-He gives a positive value because RET-He is higher than RBC-He [8]. However, in acute ID with low Ret-He values, Delta-He shows a negative value [11]. Therefore, this marker detects rapid changes

in erythropoietic status, making it a suitable tool for diagnosing iron deficiency and monitoring response to treatment.

% Hypo-He measures the Hb content of mature red blood cells and reflects functional iron deficiency several months before the clinical manifestations of anaemia [1]. However, it is unsuitable for monitoring short-term changes in iron status [11].

These novel reticulocyte parameters offer superior diagnostic capabilities compared to traditional iron markers because they are not influenced by inflammatory or infective conditions. The clinical utility of these parameters has been thoroughly investigated as markers of iron-deficient erythropoiesis across various clinical conditions, including dialysis and pre-dialysis patients [1-13]. However, limited information exists regarding their usefulness in diagnosing IDA among dialysis patients.

Several optimal cutoff points for these novel reticulocyte parameters have been proposed by earlier studies. However, variations in these cutoff points are primarily influenced by ethnic differences and study populations [13]. Therefore, this study aims to explore the diagnostic potential of these novel reticulocyte parameters and establish an optimal cutoff point for diagnosing IDA among our population of dialysis patients.

Methods

Study design and setting

This retrospective diagnostic accuracy study was conducted on end-stage renal disease (ESRD) patients, on regular haemodialysis treatment at the Department of Nephrology, Beaumont Hospital, Dublin, Ireland, from February to December 2024. ESRD was defined based on $\text{eGFR} < 15 \text{ ml/min/1.73 m}^2$ [14].

Clinical and laboratory results of the dialysis patients were extracted from the hospital and laboratory databases retrospectively. Exclusion criteria include patients with known haemoglobinopathies, recent bleeding, blood transfusions within the three months prior to the study, infectious diseases, malignancy, and severe hyperparathyroidism ($\text{PTH} > 800$), along with vitamin B12 and folate deficiency (folate $< 3 \text{ ng/}$

ml and B12 < 200 pg/ml) [15, 16]. Additionally, patients without laboratory results for ferritin, TSAT, iron, full blood count, and reticulocyte count were also excluded.

Definition of groups and patient partitioning

Anaemia was defined as Hb < 120 g/L for women and < 130 g/L for men, while iron deficiency was described as a TSAT < 20% and ferritin < 200 µg/l [18, 14]. Participants were assigned to four clinical groups based on their iron and anaemic status: IDA group (all patients with anaemia and ID), latent iron deficiency (LID) (all patients with ID and no anaemia), control group (all iron replete patients without anaemia), and non-iron deficiency anaemia group (NIDA) (all patients with anaemia without ID).

Laboratory analysis

EDTA blood samples were analysed on the Sysmex XN 9000 modular analyser to include full blood count (FBC) as well as reticulocyte parameters Ret-He, % Hypo-He, and Delta-He. Other investigations included serum ferritin, serum iron, TSAT, C-reactive protein (CRP), vitamins B12 and folate, and serum parathyroid hormone (PTH).

Sample Size

The power calculation was based on a 30% prevalence of IDA [19], with an estimated sensitivity of 80%, an 11% margin of error, and a 5% type 1 error [20]. Therefore, 169 dialysis patients were deemed sufficient for this study.

Statistical analysis

The continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed variables were reported as means ± standard deviations, while those exhibiting an asymmetrical distribution were presented as medians and interquartile ranges (IQRs, P25%-P75%) [21]. The categorical variables were summarised as frequencies and percentages. A Kruskal-Wallis test was conducted to compare the levels of RET-He, Delta-He, Hypo-He and CRP across the groups. The Dunn-Bonferroni post hoc test was used to determine whether there was a

significant difference between the groups.

Spearman's rank correlation coefficient was used to investigate any linear correlation between these novel parameters, Hb, and red blood cell indices (MCH and MCV), as well as biochemical parameters such as ferritin, TSAT, iron, and CRP. The interpretation of the correlation coefficients (α) was based on the following criteria: α < 0.3 indicates a weak correlation, 0.3-0.5 indicates a moderate correlation, 0.5-0.7 indicates a strong correlation, and > 0.7 signifies a very strong correlation [22].

The receiver operator characteristics (ROC) and area under the curve (AUC) were used to evaluate the diagnostic capability of these novel reticulocyte parameters for detecting IDA (discriminating IDA from the non-iron-deficient anaemia population), using TSAT (< 20%) and ferritin (< 200 µg/l) as the standards. The AUC of a diagnostic test of 0.80 or higher is considered clinically useful [23]. Youden's index was employed to establish an optimal cutoff, and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at this cutoff point were also calculated. Values below the cutoff point for RET-He and Delta-He and values above the cutoff point for %Hypo-He are regarded as positive for IDA. The diagnostic potential of the novel reticulocyte parameters and red blood indices in detecting IDA was assessed by comparing their respective AUCs [24].

To verify the optimal cutoff point of Ret-He for discriminating IDA, patients were divided into two groups: IDA and NIDA, and the means of RBC, Delta-He, %Hypo-He, RBC-He, Hb, MCH, MCV, ferritin, iron, and TSAT were compared using both an independent t-test (for symmetrical data) and the Mann-Whitney U test (for asymmetrical data). Results were considered statistically significant if $P < 0.05$. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 29 and MedCalc statistical software version 29.2.

Results

139 out of a total cohort of 170 dialysis patients met the criteria for inclusion in the study. The mean age of the study group was 60.84 ± 16.25 years, with a male-to-female ratio of 1.78:1. 112

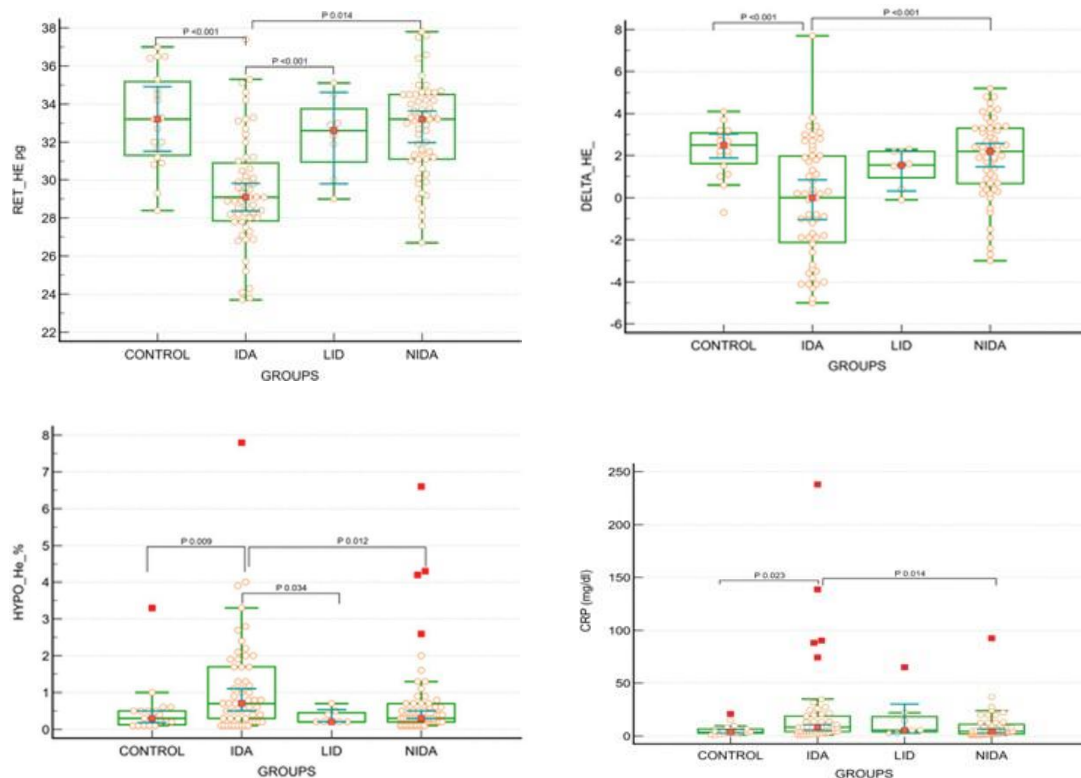


Fig. 1 Distribution of RET-He, Delta-He, % Hypo-He, and CRP across the groups. Box and whisker plots illustrate novel reticulocyte parameters and the CRP levels of four population study groups. Comparison of values between groups was performed using Kruskal-Wallis and Dunn post hoc tests. ($P < 0.05$) was considered significant. IDA, iron deficiency anaemia group; LID, latent iron deficiency group; NIDA, non-iron deficiency anaemia group. RET-He, reticulocyte haemoglobin equivalent; Delta-He, delta haemoglobin equivalent; %Hypo-He, percentage of hypo-haemoglobinised red cells.

Table 1. Correlation of novel reticulocyte parameters with other parameters of iron metabolism

Test	Ret-He	R	Hypo-He		delta-He	
	α	P-value	α	P-value	α	P-value
Hb	0.249	0.003	-0.175	0.039	0.274	0.001
MCV	0.346	<0.001	-0.245	0.004	-0.170	0.046
MCH	0.558	<0.001	-0.510	<0.001	-0.035	0.685
Iron	0.639	<0.001	-0.489	<0.001	0.475	<0.001
TSAT	0.657	<0.001	-0.296	<0.001	0.515	<0.001
Ferritin	-0.157	0.065	0.102	0.230	-0.047	0.580
CRP	-0.218	0.013	0.169	0.054	-0.219	0.012

α denotes Spearman's rank correlation coefficient. This association is statistically significant with a P value less than 0.05. RE-He, reticulocyte haemoglobin equivalent; %Hypo-He, percentage hypo-haemoglobinised red cells; Delta-He, delta haemoglobin equivalent.

patients (80.6%) were anaemic with a median haemoglobin concentration of 11.50 (10.9-12.30) g/dl. 55 (39.6%) had iron deficiency anaemia (IDA), while 57 (41%) had non-iron deficiency anaemia (NIDA). Mean serum ferritin and CRP for all patients were 569 (377.0-740) ug/L and 5.65 (2.70-12.95) mg/dl, respectively. The IDA group exhibited reduced RET-He and Delta-He levels ($P < 0.001$), along with elevated % Hypo-He ($P = 0.009$) and CRP ($P = 0.023$) compared to the control group (Figure 1).

The Spearman rank correlation revealed a significant moderate to strong correlation between novel reticulocyte parameters (positive for RET-He and Delta-He and negative for % Hypo-He) and red blood cell indices (MCH and MCV), iron and TSAT. Additionally, Ret-He and Delta-He demonstrated weak negative correlations with CRP (Table 1).

Furthermore, the ROC curve and AUC were used to evaluate the diagnostic capabilities of these

novel reticulocyte parameters in distinguishing IDA from the NIDA population. Figure 2 displays the ROC curve, illustrating the AUC, sensitivity, and specificity at the optimal diagnostic cutoff point for each parameter. RET-He and Delta-He exhibited AUCs of 0.822 (95% CI: 0.739-0.888) and 0.746 (95% CI: 0.655-0.823), respectively, while Hypo-He showed an AUC of 0.653 (95% CI: 0.557-0.740). The PPV and NPV for each parameter were also calculated. The RET-He cutoff point of ≤ 31.2 pg demonstrated a PPV of 73.3% (95% CI: 64.0-81.0) and an NPV of 80.8% (95% CI: 70.1-88.3), while Delta-He at a cutoff point of ≤ 0.3 pg exhibited a PPV of 75% (95% CI: 62.8-84.2) and an NPV of 69.1% (95% CI: 61-76.2). Additionally, % Hypo-He at a cutoff point of $> 0.6\%$ displayed a PPV of 66% (54.6-75.7) and an NPV of 64.6 % (56.3-72.1).

A significant decrease in MCH, RBC-He, RET-He, Hypo-He, Delta-He, iron, and TSAT was observed when RET-He ≤ 31.2 pg was used to

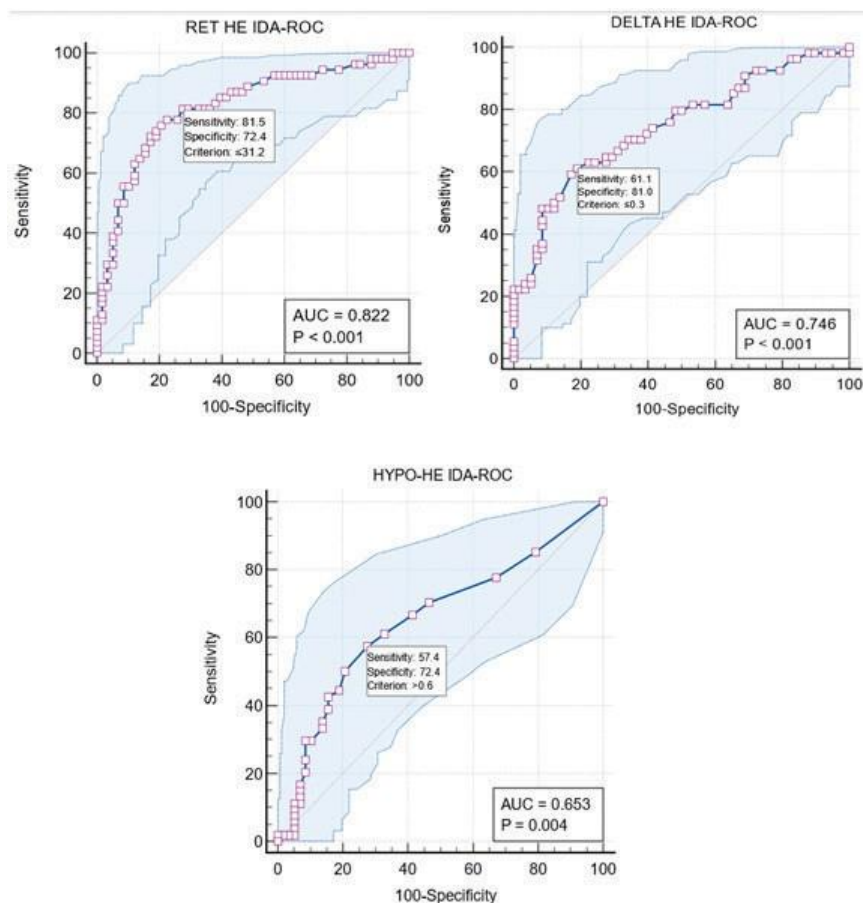


Fig. 2 An illustration of the receiver operating characteristic (ROC) curves for RET-He, Hypo-He, and Delta-He in detecting IDA. This curve also shows the calculated optimal cutoff points (criterion), the area under the curve (AUC), sensitivity, specificity, and the level of significance. A p-value < 0.05 is considered significant.

Table 2. Comparison of haematological and biochemical parameters in the diagnosis of IDA

Parameters	RET-He $\leq$ 31.2 pg (n=60)	RET-He $>$ 31.2 pg (n=52)	P-value
RBC $\times 10^{12}/L\#$	3.58 $\pm$ 0.56	3.46 $\pm$ 0.39	0.214
Hb (g/dl)*	11.35 (10.43-11.80)	11.30 (10.72-11.80)	0.744
MCV (fL)#	91.51 $\pm$ 5.92	94.45 $\pm$ 5.15	0.006
MCH (pg)#	30.60 $\pm$ 2.22	32.35 $\pm$ 1.65	$<$ 0.001
RBC-HE (pg)#	29.40 $\pm$ 2.19	31.26 $\pm$ 1.5	$<$ 0.001
Ret-He (pg)#	28.64 $\pm$ 1.87	33.92 $\pm$ 1.60	$<$ 0.001
Hypo-He (%)*	0.75 (0.30-1.98)	0.30 (0.20-0.68)	$<$ 0.001
Delta-He (pg)#	-0.76 $\pm$ 2.29	2.66 $\pm$ 1.40	$<$ 0.001
Ferritin (μ g/L)*	596.50 (431.75-766.75)	573.00 (356.50-758.75)	0.556
Fe (μ mol/L)#	7.33 $\pm$ 2.23	10.64 $\pm$ 3.00	$<$ 0.001
TSAT (%)*	18.00 (15.00-20.00)	24.50 (21.00-31.50)	$<$ 0.001

MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; HB, haemoglobin; Delta-He, delta haemoglobin equivalent; Hypo-He, percentage of hypo-haemoglobinised red cells; Ret-He, reticulocyte haemoglobin content; Fe, serum iron; TSAT, transferrin saturation; RBC-He, red blood cell haemoglobin measured in reticulocyte channel; RBC, red blood cell count. Parameters marked with # are normally distributed; thus, they are summarised as (Mean $\pm$ SD), while those marked with * are asymmetrically distributed and are reported as median (interquartile range). The interquartile the haematological and biochemical parameter levels between the subgroups. RET-He of $\leq$ 31.2 pg, Hb of $<$ 120 g/l for females and $<$ 130g/l for males were used as a cutoff point to stratify the patients into IDA and NIDA groups.

partition the patients into IDA and NIDA groups (Table 2). However, 11 of the 55 patients in the IDA group had RET-He $>$ 31.2 pg and 16 of the 57 in the NIDA group had RET-He $\leq$ 31.2 pg.

Discussion

Timely diagnosis and management of IDA are crucial for enhancing the quality of life for patients on dialysis. This study focused on determining whether the measurement of novel reticulocyte parameters (RET-HE, Delta-He, and Hypo-He) can enable prompt, accurate, and simpler detection of IDA among dialysis patients.

The prevalence of anaemia in our study was 80%, with a median Hb concentration of 11.50 g/dl. However, this Hb value was higher compared to previous studies by Alageeli et al. [25] and Karunarathne et al. [13], who reported mean Hb values of 9.8 g/dl and 9.27 g/dl, respectively. The discrepancy in Hb values could be associated with geographical location and effective anaemia management within our hospital. The Hb result of the current study aligns with the NICE guideline of maintaining an optimal Hb target between 100-120 g/l in dialysis patients [14].

Additionally, IDA constitutes approximately

39.6% of the anaemic population in our study. The findings are consistent with previous studies by Nalado et al. [4] and Clancy et al. [16], which reported a 35% and 37% prevalence for IDA and ID, respectively. Discrepancies in these values may be influenced by sample size, as prior studies utilised larger sample sizes in comparison to the current study. Consistent with previous studies [1,8,26], IDA groups demonstrated a depressed RET-He and Delta-He, along with an increased % Hypo-He. Our results, therefore, indicate that these novel reticulocyte parameters are good predictors of IDA.

Consistent with previous studies [1,4], our results demonstrated weak to strong correlations with Hb, MCH, MCV, and biochemical parameters such as iron and TSAT. These findings indicate that any imbalance between the supply and demand for iron during erythropoiesis decreases the haemoglobin content of mature erythrocytes and reticulocytes. Haemodialysis treatment triggers an inflammatory reaction, leading to increased serum ferritin and CRP levels, as confirmed in this study. Consequently, there was no linear association between serum ferritin and the novel reticulocyte parameters. The clinical usefulness of serum ferritin is, therefore, limited in dialysis patients and should be interpreted cautiously [3].

On the other hand, Ret-He and Delta-He exhibited a weak negative correlation with CRP. These findings align with the previous study by Zuther et al. [8], which reported that RET-He and Delta-He showed a moderate correlation with inflammatory biomarkers such as CRP and Procalcitonin among critically ill patients in intensive care units. Likewise, Weimann et al [27] concluded that Delta-He is a promising biomarker in discriminating anaemia due to chronic inflammation. Thus, RET-He and Delta-He are promising biomarkers of functional iron deficiency anaemia.

The clinical utility of RET-He and %Hypo-He as screening and diagnostic markers for iron-deficient erythropoiesis in dialysis patients has been extensively explored in previous studies. However, there is limited data regarding their diagnostic ability to detect IDA among dialysis patients. In our study, RET-He discriminated IDA with an AUC of 0.822 (95% CI: 0.739-0.888). This

result is consistent with previous studies by Dinh et al. [1] and Nalado et al. [4], which reported AUC values for reticulocyte haemoglobin content (CHr) of 0.748 (95% CI: 0.656–0.840) and 0.81 (95% CI: 0.76-0.87), respectively.

Although these earlier studies utilised the reticulocyte haemoglobin content (CHr) parameter provided by Siemens in their Advia haematology analyser, RET-He from the Sysmex analyser was employed in the current study. Both parameters assess the haemoglobin content of reticulocytes using different analytical methodologies. However, a previous study found a strong correlation between the two parameters, suggesting their clinical interchangeability [28].

The % Hypo-He is another valuable parameter for diagnosis of iron-deficient erythropoiesis. Although this parameter provides a snapshot of the quantity of iron available for erythropoiesis, its diagnostic performance may be hindered by the prolonged half-life of mature erythrocytes in circulation [29]. Therefore, it is unsuitable for monitoring intravenous iron therapy and for the early detection of iron-deficient erythropoiesis. Its clinical utility may also be affected by delays in sample processing, as its stability is < 6 hours [30]. Earlier studies by Dinh et al. [1] and Kee et al. [3] reported AUC values of 0.876 and 0.88, respectively, for % Hypo in the detection of IDA in dialysis patients.

However, in the current study, % Hypo-He demonstrated poor diagnostic capability (AUC=0.653). These discrepancies may arise from methodological differences. % Hypo-He, a parameter from the Sysmex analyser, was used in the current study, as opposed to % Hypo from the Siemens Advia analyser used in the earlier studies [1,3]. Additionally, a study by Urrechaga et al. [31] demonstrated that % Hypo and % Hypo-He cannot be used interchangeably due to differences in the analytical methodologies.

Delta-He is another promising biomarker explored in this study. A recent study by De La Cruz-Garcinuno et al. [32] demonstrated that Delta-He is an early predictor of IDA. They further concluded that the routine use of Delta-He in combination with RET-He would improve the early diagnosis and management of IDA [32]. Another study by Zuther et al. [8] demonstrated that Delta-

He has good diagnostic capability (AUC = 0.807) in detecting IDA. However, our study reported an AUC of 0.746 (95% CI: 0.655-0.823). These discrepancies might be associated with the study population, as the former study recruited critically ill patients in the intensive care unit. To the best of our knowledge, no works have been published on the clinical usefulness of this parameter in ESRD patients.

There has been a longstanding debate regarding the ideal cutoff point for these novel reticulocyte parameters in diagnosing IDA. The use of different cutoff values in various studies to discriminate IDA has led to variations in the sensitivity and specificity of these parameters. A previous study by Karunarathne et al. [13] reported a CHr cutoff value < 29 pg, with a sensitivity of 56% and specificity of 73% for detecting iron-deficient erythropoiesis in dialysis patients. Another study, Nalado et al. [4], demonstrated that the CHr cutoff point of < 28 pg was appropriate for discriminating IDA in pre-dialysis patients, with sensitivity, specificity, PPV, and NPV values of 62.6%, 80.2%, 63.3%, and 79.8%, respectively. In our study, the cutoff point of ≤ 31.2 pg was deemed appropriate for discriminating IDA with a sensitivity of 81.5%, specificity of 72.4%, PPV of 73.3%, and NPV of 80.8%. These discrepancies may be influenced by the study population and ethnic variation, as the initial study was conducted on pre-dialysis patients in South Africa.

Similarly, various cutoff points have been reported for Hypo-He. These discrepancies may arise from differences in analytical methodologies, as % Hypo-He identifies the proportion of RBC with MCH < 17 pg, whereas % Hypo measures RBC with Hb concentration < 280 g/l [31]. A study by Kee et al. [3] demonstrated that a % Hypo of > 4.3% can detect IDA with a sensitivity of 67.74% and a specificity of 97.50%. Additionally, NICE guidelines recommended a % Hypo cut off > 6%, in detecting ID. In the current study, a % Hypo-He of > 0.6% was appropriate for detecting IDA. Our results align with a previous study that reported an optimal cutoff point of > 0.6% for % Hypo-He in detecting ID among healthy blood donors [33].

In the current study, Delta-He at a cutoff point of $\leq 0.3\%$ was appropriate for detecting IDA. This cutoff point is lower than the previous study by

Zuther et al. [8], which reported that at a cutoff point of $\leq 0.4\%$, Delta-He demonstrated a sensitivity of 62.0% and a specificity of 86.5%. The discrepancy in the results may arise from differences of study populations as the previous study explored the clinical usefulness of this parameter among critically ill patients in the ICU [8].

The results of this study suggest that novel reticulocyte parameters demonstrate both high diagnostic specificity and sensitivity in diagnosing IDA in dialysis patients, with RET-He exhibiting superior diagnostic capability compared to Delta-He, Hypo-He, Hb, MCV, and MCH. This finding is consistent with the earlier research conducted by Urrechaga et al. [34], which reported the superiority of RET-He in the identification of IDA among patients with inflammatory bowel disease compared to %Hypo-He, MCH and MCV.

The current study also validated the suitability of the RET-He cutoff point of ≤ 31.2 pg for distinguishing IDA from non-IDA within our study cohort (Table 2). The IDA group demonstrated a significant decrease in MCH, RBC-HE, RET-He, Delta-He, iron, and TSAT, with a significant increase in Hypo-He. These findings suggest that RET-He ≤ 31.2 pg is a good discriminator of IDA in dialysis patients. However, during the sub-analysis of IDA patients, 11 out of 55 IDA patients were misdiagnosed using this cutoff point. This implies that RET-He should not be regarded as a stand-alone test; it should be used alongside traditional iron markers to make a diagnosis. Additionally, it should be interpreted in the context of the patient's clinical condition, as the diagnostic accuracy of RET-He is limited in the presence of certain confounding factors, which disrupt erythropoiesis and Hb synthesis. These include deficiency of vitamin B12 and folate, myelodysplastic syndrome and chemotherapy, all of which can reduce reticulocyte production and lower Ret-He levels [25].

The introduction of these novel reticulocyte parameters offers significant benefits for patient management. They are cost-effective compared to conventional biochemistry parameters, as they are measured in the reticulocyte channel of the Sysmex XN analyser [34]. Reticulocyte counts are routinely ordered for dialysis patients, meaning the laboratory may incur no additional cost in running

these novel parameters. Moreover, they provide a quick turnaround time because all the haematology parameters are assayed simultaneously in the same blood sample.

Limitations

The primary limitation of this study arises from its retrospective design, which may be prone to bias. Bone marrow aspiration is the gold standard method for assessing iron status. However, due to its invasive and traumatic nature, it is not routinely used to assess iron stores in our hospital. Therefore, iron deficiency was defined using ferritin and TSAT as a reference. In addition, most of the patients in this study were on intravenous iron supplements during the time of this study, which may have influenced the study’s outcome.

Conclusion

The present study demonstrates that novel reticulocyte parameters are valuable tools for diagnosing IDA among dialysis patients. Integrating these parameters into routine use would provide early, accurate, quick, and cost-effective assessments of iron-deficient erythropoiesis in the presence of confounding inflammatory conditions. This would aid in optimising the diagnosis and management of IDA among haemodialysis patients. However, the cutoff point of the current study may be subject to debate as it was from a single centre. A multi-centre study with a larger sample size would be beneficial in validating a cutoff point that could be widely adopted among dialysis centres.

Abbreviations

AUC	Area under the curve
CHr	Reticulocyte haemoglobin content (Siemens Advia)
CKD	Chronic Kidney Disease
CRP	C-reactive protein
Delta-He	Delta haemoglobin equivalent
eGFR	Estimated glomerular filtration rate
Fe	Serum iron
HB	Haemoglobin
% Hypo	Percentage hypochromic red cell (Siemens Advia)

% Hypo-He	% of hypo-haemoglobinised red cells (Sysmex XN)
IRF	Immature reticulocyte fractions
LID	Latent iron deficiency
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
NICE	National Institute for Health and Care Excellence
NIDA	Non-iron deficiency anaemia
NPV	Negative predictive value
PPV	Positive predictive value
PTH	Parathyroid hormone
RBC	Red blood cell count
RBC-He	Red blood cell haemoglobin measured in the reticulocyte channel
Ret-He	Reticulocyte haemoglobin equivalent
ROC	Receiver operator characteristics
TSAT	Transferrin saturation

Declarations

Ethics approval and consent to participate

The study protocol received approval from the Ethics and Medical Research Committee of Beaumont Hospital, Dublin, Ireland (approved September 16, 2024, Ref. 24/57); see Supplementary file. As this is a retrospective chart review study, informed consent was waived. All ethical principles for medical investigation in human beings outlined in the Helsinki Declaration of the World Medical Association were observed.
Consent for publication
Not applicable

Data availability

The datasets used and/ or analysed during the current study are attached to this manuscript as a supplementary file.

Competing interest

The authors declare that they have no competing interests

Funding

None

References

- Ghosh K, Ross C The teacher and the taught: medical education in India at the crossroads. *Natl Med J India*. 2009;22(3):147-9.
- Dinh NH, Cheanh Beaupha SM, Tran LTA. The validity of reticulocyte hemoglobin content and percentage of hypochromic red blood cells for screening iron-deficiency anemia among patients with end-stage renal disease: a retrospective analysis. *BMC Nephrol*. 2020; 21(1):142. Available at: doi: 10.1186/s12882-020-01796-8.
- Hain D, Bednarski D, Cahill M, Dix A, Foote B, Haras MS, et al. Iron-Deficiency Anaemia in CKD: A Narrative Review for the Kidney Care Team. *Kidney Med*. 2023; 5(8):100677. Available at: doi: 10.1016/j.xkme.2023.100677.
- Kee YK, Jeon HJ, Oh J, Shin DH. Hypochromic red cells as predictors of anemia in patients undergoing hemodialysis: an observational retrospective study. *Sci Rep*. 2021; 11(1):24215. Available at: doi: 10.1038/s41598-021-03746-2.
- Nalado AM, Mahlangu JN, Duarte R, Paget G, Olorunfemi G, Jacobson BF, Naicker S. Utility of reticulocyte haemoglobin content and percentage hypochromic red cells as markers of iron deficiency anaemia among black CKD patients in South Africa. *PLoS One*. 2018; 13(10):e0204899. Available at: doi: 10.1371/journal.pone.0204899.
- Pinto D, Paz M, Adragna M, López L. Clinical usefulness of the reticulocyte haemoglobin equivalent in children on hemodialysis. *Arch Argent Pediatr*. 2020; 118(6):411-417. Available at: doi: 10.5546/aap.2020.eng.411.
- Rohr M, Brandenburg V, Brunner-La Rocca HP. How to diagnose iron deficiency in chronic disease: A review of current methods and potential markers for the outcome. *Eur J Med Res*. 2023; 28(1):15. Available at: doi: 10.1186/s40001-022-00922-6.
- Rusch JA, van der Westhuizen DJ, Gill RS, Louw VJ. Diagnosing iron deficiency: Controversies and novel metrics. *Best Pract Res Clin Anaesthesiol*. 2023; 37(4):451-467. Available at: doi: 10.1016/j.bpa.2023.11.001.
- Zuther M, Rübsam ML, Zimmermann M, Zarbock A, Hönemann C. Improved Diagnosis of Iron Deficiency Anemia in the Critically Ill via Fluorescence Flowcytometric Hemoglobin Biomarkers. *Cells*. 2022; 12(1):140. Available at: doi: 10.3390/cells12010140.
- Ogawa C, Tsuchiya K, Maeda K. Reticulocyte haemoglobin content. *Clin Chim Acta*. 2020; 504:138-145. Available at: doi: 10.1016/j.cca.2020.01.032.
- Danielson K, Beshara S, Qureshi AR, Heimbürger O, Lindholm B, Hansson M, et al. Delta-He: a novel marker of inflammation predicting mortality and ESA response in peritoneal dialysis patients. *Clin Kidney J*. 2014; 7(3):275-81. Available at: doi.org/10.1093/ckj/sfu038.
- Hayes W. Measurement of iron status in chronic kidney disease. *Pediatr Nephrol*. 2019; 34(4):605-613. Available at: doi: 10.1007/s00467-018-3955-x.
- Aedh AI, Khalil MSM, Abd-Elkader AS, El-Khawanky MM, Alshehri HM, Hussein A, Alghamdi AAL, Hasan A. Reticulocyte Hemoglobin as a Screening Test for Iron Deficiency Anemia: A New Cut-Off. *Haematology Reports*. 2023; 15(1):201-211. <https://doi.org/10.3390/hematolrep15010021>
- Karunaratne P, Kulathilake C, Wijesiriwardena I, Hewageegana A, Marasinghe A. Evaluation of Iron Status by Reticulocyte Haemoglobin Content (Chr) in Chronic Kidney Disease Patients on Haemodialysis and Erythropoietin. *Indian J Hematol Blood Transfus*. 2022; 38(2):359-365. doi: 10.1007/s12288-021-01464-3.
- National Institute for Health and Care Excellence (NICE). Chronic kidney disease: assessment and management. NICE. 2021. Available at: <https://www.nice.org.uk/guidance/ng203/chapter/Recommendations#diagnosing-and-assessing-anaemia>. Accessed 20/02/2025.
- Kidney Disease Outcome Quality Initiative (KDOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease. KDOQI;2003. Available at: https://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bone/guide14.htm. Accessed 22/02/2025.
- Clancy CC, Browne LD, Gilligan R, Blake O, Stack AG. Prevalence of anaemia, iron, and vitamin deficiencies in the health system in the Republic of Ireland: a retrospective cohort study. *BJGP Open*. 2024;8(2):BJGPO.2023.0126. Available at: doi: 10.3399/BJGPO.2023.0126.
- Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF; STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527. Available at: doi: 10.1136/bmj.h5527. PMID: 26511519; PMCID: PMC4623764.
- Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I. Guideline for the laboratory diagnosis of functional iron deficiency. *Br J Haematol*. 2013 Jun 10;161(5):639-48. Available at: doi-org.tudublin.idm.oclc.org/10.1111/bjh.12311
- Kumar A, Sharma E, Marley A, Samaan MA, Brookes MJ. Iron deficiency anaemia: pathophysiology, assessment, practical management. *BMJ Open Gastroenterol*. 2022; 9(1): e000759. Available at: doi: 10.1136/bmjgast-2021-000759.
- Bujang MA, Adnan TH. Requirements for Minimum Sample Size for Sensitivity and Specificity Analysis. *J Clin Diagn Res*. 2016;v10(10): YE01-YE06. Available at: doi: 10.7860/JCDR/2016/18129.8744. Mishra P, Pandey CM, Singh U, Gupta A, Sahu C, Keshri A. Descriptive statistics and normality tests for statistical data. *Ann Card Anaesth*. 2019 Jan-Mar;22(1):67-72. Doi: 10.4103/aca.ACA_157_18. PMID: 30648682; PMCID: PMC6350423.
- Rusakov DA. A misadventure of the correlation coefficient. *Trends Neurosci*. 2023;46(2):94-96. Available at: doi: 10.1016/j.tins.2022.09.009.
- Çorbacıoğlu ŞK, Aksel G. Receiver operating characteristic curve analysis in diagnostic accuracy studies: A guide to interpreting the area under the curve value. *Turk J Emerg Med*. 2023; 23(4):195-198. Available at: doi: 10.4103/tjem.tjem_182_23.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing

- the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988; 44(3): 837–845.
24. Alageeli AA, Alqahtany FS, Algahtani FH. The Role of Reticulocyte Hemoglobin Content for the Diagnosis of Functional Iron Deficiency in Hemodialyzed Patients. *Saudi J Biol Sci*. 2021;28(1):50-54. Available at: doi: 10.1016/j.sjbs.2020.08.030.
 25. Choorapoikayil S, Kotlyar MJ, Kawohl L, Pratz PP, Mehic D, Kranke P, et al. Reticulocyte hemoglobin content: a new frontier in iron deficiency diagnostics for major surgical patients. *BMC Anesthesiol*. 2025; 25(1): 40. Available at: doi.org/10.1186/s12871-025-02905-6
 26. Weimann A, Cremer M, Hernáiz-Driever P, Zimmermann M. Delta-He, Ret-He, and a New Diagnostic Plot for Differential Diagnosis and Therapy Monitoring of Patients Suffering from Various Disease-Specific Types of Anaemia. *Clin Lab*. 2016;62(4):667-77. Available at: doi: 10.7754/clin.lab.2015.150830.
 27. Wirawan R, Tedja AT, Henrika F, Lydia A. Concordance between Reticulocyte Hemoglobin Equivalent and Reticulocyte Hemoglobin Content in CKD Patients Undergoing Hemodialysis. *Acta Med Indones*. 2017;49(1):34-40. Available at: PMID: 28450652.
 28. Sany D, El Shahawi Y, Taha J. Diagnosis of iron deficiency in hemodialysis patients: Usefulness of measuring reticulocyte hemoglobin equivalent. *Saudi J Kidney Dis Transpl*. 2020;31(6):1263-1272. Available at Doi: 10.4103/1319-2442.308335.
 29. Schapkaitz E. Stability of New Erythrocyte and Reticulocyte Parameters in Testing for Anemia on the Sysmex XN 9000. *Lab Med*. 2018 5;49(3):219-225. doi: Available at 10.1093/labmed/lmx095. PMID: 29365192.
 30. Urrechaga E, Merino M, De La Hera P, Javier AF. Markers of hypochromia in the study of erythropoiesis and iron availability in patients with inflammatory bowel disease. *Clinica Chimica Acta*. 2019; 493:S426–7. Available at: doi: 10.1080/00365513.2019.1700549.
 31. De la Cruz-Garcinuño M, Juárez-Vela R, Lasa-Berasain P, Ruiz de Viñaspre-Hernández R, Czaplá M, García-Muñoz L, Polo-Andrade E, Sarmiento C, Rodero-Martínez J, Alonso-Arias M, López-Tornero S, Quintana-Díaz M. Utility of reticulocyte haemoglobin as a new predictor of anaemia in intensive care unit patients. *Front Med (Lausanne)*. 2025; 12:1577047. Available at: doi: 10.3389/fmed.2025.1577047.
 32. Amir N, Md Noor S, Subbiah I, Osman M, Seman Z. Percentage of hypochromic red cells as a potential screening test to evaluate iron status in blood donors. *Int J Lab Hematol*. 2019 Jun;41(3):418-423. Available at doi: 10.1111/ijlh.13009.
 33. Urrechaga E, de la Hera P, Aguayo FJ. Reticulocyte haemoglobin and hypochromic erythrocytes in the study of erythropoiesis in patients with inflammatory bowel disease. *Scand J Clin Lab Invest*. 2020; 80(2):124-128. Available at: doi: 10.1080/00365513.2019.1700549.
 34. Neef V, Schmitt E, Bader P, Zierfuß F, Hintereder G, Steinbicker AU, Zacharowski K, Piekarski F. The Reticulocyte Hemoglobin Equivalent as a Screening Marker for Iron Deficiency and Iron Deficiency Anemia in Children. *J Clin Med*. 2021; 10(16):3506. Available at: doi: 10.3390/jcm10163506.

Clinical and Etiological Profile of Patients Presenting with dizziness to the Emergency department of a Tertiary Care Hospital in Eastern India

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Abstract

Background: Acute dizziness is an extremely common, diagnostically volatile presentation in the emergency department (ED). It ranges from benign disorders to life-threatening vascular crises. Indian studies evaluating clinical patterns using modern timing-and-trigger frameworks remain critically sparse. This study describes the clinical and etiological profile of patients presenting with dizziness to a tertiary care hospital in Eastern India.

Methods: A prospective observational study was conducted at a high-volume tertiary care emergency department in Eastern India over 18 months from December 2024 to May 2026. A total of 260 adult patients presenting with dizziness as a primary complaint were enrolled. Systematic evaluation relied on clinical history, structured bedside exams (such as HINTS plus and positional maneuvers), 12-lead electrocardiograms, random blood sugar measurements, and selective brain neuroimaging (NCCT/MRI). Patient condition was reassessed during follow-up.

Results: Of the 260 patients, 60.0% were female, and 65.8% were under 60 years of age. Dangerous causes were recorded in 161 cases (61.9%), while benign causes were noted in 99 cases (38.1%). Giddiness Not Otherwise Specified (NOS) was the most frequent benign diagnosis (15.0%), followed by Unstable Angina (7.3%), Benign Paroxysmal Positional Vertigo (BPPV; 7.3%), Arrhythmia (7.3%), and Subarachnoid Hemorrhage (SAH; 7.3%). Vertigo descriptions highly correlated with benign disorders (44.4% vs 9.9%, $p < 0.0001$), while disequilibrium (26.1%) and lightheadedness (61.5%) strongly favored dangerous central or medical mimics. Advanced age (≥ 60 years), ambulance transportation, history of diabetes, past history of ischemic heart disease, focal neuro-deficits, and papilledema were powerful indicators of life-threatening diagnoses ($p < 0.05$). Abnormal screening tools like ECG (86.3%) and NCCT head (90.7%) demonstrated strong predictive values for serious outcomes.

Conclusion: Serious, life-threatening pathologies comprise an unexpectedly large share of dizzy patients presenting to a major emergency hub in Eastern India. Implementing structured timing-and-trigger clinical protocols paired with restrictive, targeted testing path configurations is crucial to safe rule-out parameters and resource stewardship.

Keywords

Dizziness, HINTS plus, dangerous causes, BPPV, giddiness

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Introduction

Acute dizziness remains an incredibly frequent clinical complaint that prompts extensive utilization of acute care services, representing between 0.8% and 4.0% of total emergency department (ED) admissions globally [1, 2]. The diagnostic landscape confronting the emergency physician is uniquely complex, spanning a broad spectrum from safe, self-limiting inner ear conditions to rapid, life-threatening acute cerebrovascular or cardiovascular events [3, 4]. Because the description of dizziness is often highly variable, differentiating between a benign condition and a terminal emergency poses a significant clinical hurdle for frontline clinicians [5, 6].

For decades, clinical teaching and screening for the dizzy patient rested almost entirely upon the classic ‘symptom quality’ framework introduced in 1972 [7]. This traditional paradigm forced patients to choose a specific word to qualify their symptom into one of four rigid boxes: vertigo (spinning), presyncope (near-faint), disequilibrium (imbalance), or lightheadedness (vague/other) [7, 8]. However, modern neuro-otological data have completely undermined the validity of this model [9]. Clinical validation trials show that roughly half of ED patients select an entirely different description when asked the exact same question just minutes apart [10]. Furthermore, key cardiovascular and neurovascular conditions often present with true vertigo, while typical benign variants can present as vague imbalance or lightheadedness [11, 12].

To mitigate these shortcomings, expert consensus modern protocols favor a transition toward models emphasizing timing, triggers, and associated clinical scenarios, exemplified by the TiTrATE framework [13, 14]. This model maps acute clinical presentations into distinctive vestibular categories: Acute Vestibular Syndrome (AVS), Spontaneous Episodic Vestibular Syndrome (s-EVS), and Triggered Episodic Vestibular Syndrome (t-EVS) [15]. When properly utilized, targeted bedside clinical examinations—such as the three-part HINTS plus protocol (Head Impulse Test, Nystagmus characteristics, Test of Skew, plus hearing evaluation)—demonstrate superior accuracy to early magnetic resonance imaging (MRI) in identifying early brainstem or cerebellar stroke [16, 17].

Prospective observational data evaluating acute dizziness in the emergency network of Eastern India remain extremely scarce [3, 18]. Due to this local evidence gap, defensive medicine and unstratified screening workflows occur frequently, including the automatic ordering of non-contrast brain computed tomography (NCCT) and rapid screening electrocardiograms (ECGs) without clinical risk-scoring [19, 20]. This prospective study, tracking 260 patients over an 18-month period from December 2024 to May 2026, aims to outline the clinical profiles and etiological distributions of dizzy patients inside a high-volume tertiary care facility in Eastern India, providing data to optimize diagnostic pathways.

Methodology

Study Design and Context

A prospective, single-center observational study was carried out in the Department of Emergency Medicine at a high-volume tertiary care teaching facility in Eastern India. The trial ran for an 18-month timeline from December 2024 to May 2026. The research protocol was approved by the Institutional Ethics Committee, and formal written informed consent was secured from each patient or their proxy before enrollment.

Patient Selection Criteria

Adult patients aged 18 years and older presenting to the ED with a primary or major concurrent complaint of dizziness, giddiness, giddiness NOS, vertigo, or instability were screened. Exclusion criteria consisted of any history of traumatic brain injury within the preceding three months requiring hospitalization, or standard refusal of consent.

Clinical Assessments and Diagnostic Data Collection

A detailed clinical proforma was completed for each patient during the index ED evaluation. Key structured records included exact onset latency, episode duration, attack frequency (first vs. recurrent), specific triggering mechanisms (head turn, body posture changes), and effective alleviating factors. Associated symptoms were explicitly compiled,

specifically looking for chest pain, palpitations, headache, nausea/vomiting, visual disturbances, altered mental status, and focal neurological signs. Comprehensive past medical and long-term pharmacological treatment records were documented.

Results

Etiological Profile and Final Outcomes

A clear final diagnosis was confirmed for all 260

participants. Life-threatening, serious, or 'dangerous' diagnoses comprised 161 cases (61.9%), while 99 cases (38.1%) were confirmed as benign conditions. Diagnostic categorization showed that clinical neurological conditions (23.3%) and miscellaneous medical conditions (22.9%) were the most frequent primary classifications, followed by cardiovascular causes (22.0%), Giddiness Not Otherwise Specified (NOS; 15.0%), oto-vestibular disorders (11.9%), and metabolic errors (4.9%).

Table 1. Distribution of etiologies of dizziness

definitive diagnostic Categories	Frequency (n=260)	Percentage (%)
A. Benign Etiologies	99	38.1%
1. Giddiness Not Otherwise Specified (NOS)	39	15.0%
2. Benign Paroxysmal Positional Vertigo (BPPV)	19	7.3%
3. Vestibular Neuritis	13	5.0%
4. Hypertensive Urgency	9	3.5%
5. Hyperglycemia (Isolated / Controlled)	7	2.7%
6. Orthostatic Hypotension (Benign Variant)	5	1.9%
7. Vasovagal Syncope / Neurocardiogenic Faint	3	1.1%
8. Psychiatric Illness / Active Panic Disorder	2	0.8%
9. Cluster Headache / Acute Gastroenteritis / Anaphylaxis	2	0.8%
B. dangerous / Life-Threatening Etiologies	161	61.9%
1. Unstable Angina Pectoris	19	7.3%
2. Major Cardiac Arrhythmias (Blocks, Slow/Fast AF)	19	7.3%
3. Subarachnoid Hemorrhage (SAH)	19	7.3%
4. Acute ST-Elevation Myocardial Infarction (STEMI)	16	6.2%
5. Posterior Circulation Ischemic Stroke (PCS)	16	6.2%
6. Severe Anemia / Active Upper GI Bleed	15	5.8%
7. Medication Toxicity (Phenytoin, etc.) / Poisoning	17	6.5%
8. Intracranial Space Occupying Lesions (ICSOL)	9	3.5%
9. Central Nervous System Infections (Meningitis/Encephalitis)	5	1.9%
10. Acute Anterior Circulation Stroke (Hemiplegic CVA)	5	1.9%
11. Diabetic Ketosis / Diabetic Ketoacidosis (DKA)	6	2.3%
12. Complex Vascular Events (PE, CVT, Hypertensive Emergency, BIH)	15	5.8%

Distribution of Benign vs. Dangerous Causes (N=260)

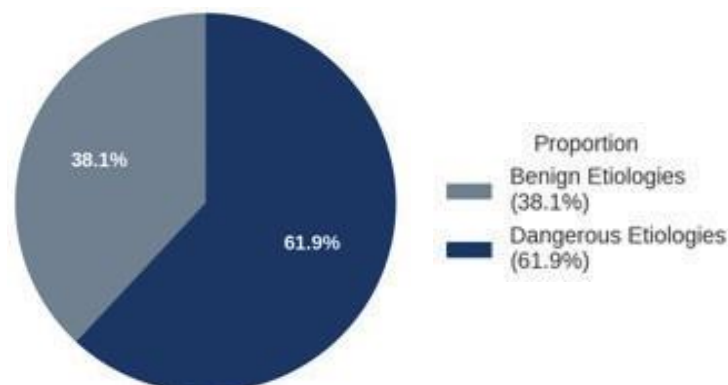


Fig. 1 Pie chart showing Benign and Dangerous etiologies (N=260).

Clinical Predictors Differentiating Benign from Dangerous Conditions

Clinical descriptor analyses revealed significant associations. While lightheadedness descriptions occurred across the sample, they were significantly more frequent among dangerous causes (61.5% vs

40.4%, $p < 0.0001$). Associated findings served as useful clinical indicators. Chest pain ($p = 0.002$), altered mental status ($p = 0.0003$), and objective gait instability ($p = 0.018$) were tightly linked to dangerous outcomes.

Table 2. Relative proportions of key demographic variables, high-acuity transports, symptoms, and medical history

Clinical Metric	Benign (n=99)	dangerous (n=161)	Total (N=260)	p-value
Age < 60 years	75 (75.8%)	96 (59.6%)	171 (65.8%)	0.024
Age ≥ 60 years	24 (24.2%)	65 (40.4%)	89 (34.2%)	
Ambulance Transportation	3 (3.0%)	28 (17.4%)	31 (11.9%)	0.002
Associated Chest Pain	10 (10.1%)	45 (28.0%)	55 (21.2%)	0.002
Associated Altered Mental Status	0 (0.0%)	19 (11.8%)	19 (7.3%)	0.0003
Associated Gait Disturbance	8 (8.1%)	32 (19.9%)	40 (15.4%)	0.018
Isolated Dizziness Presenting	15 (15.2%)	6 (3.7%)	21 (8.1%)	0.002
Comorbid Diabetes Mellitus	17 (17.2%)	55 (34.2%)	72 (27.7%)	0.007
Comorbid Ischemic Heart Disease	1 (1.0%)	24 (14.9%)	25 (9.6%)	0.0003

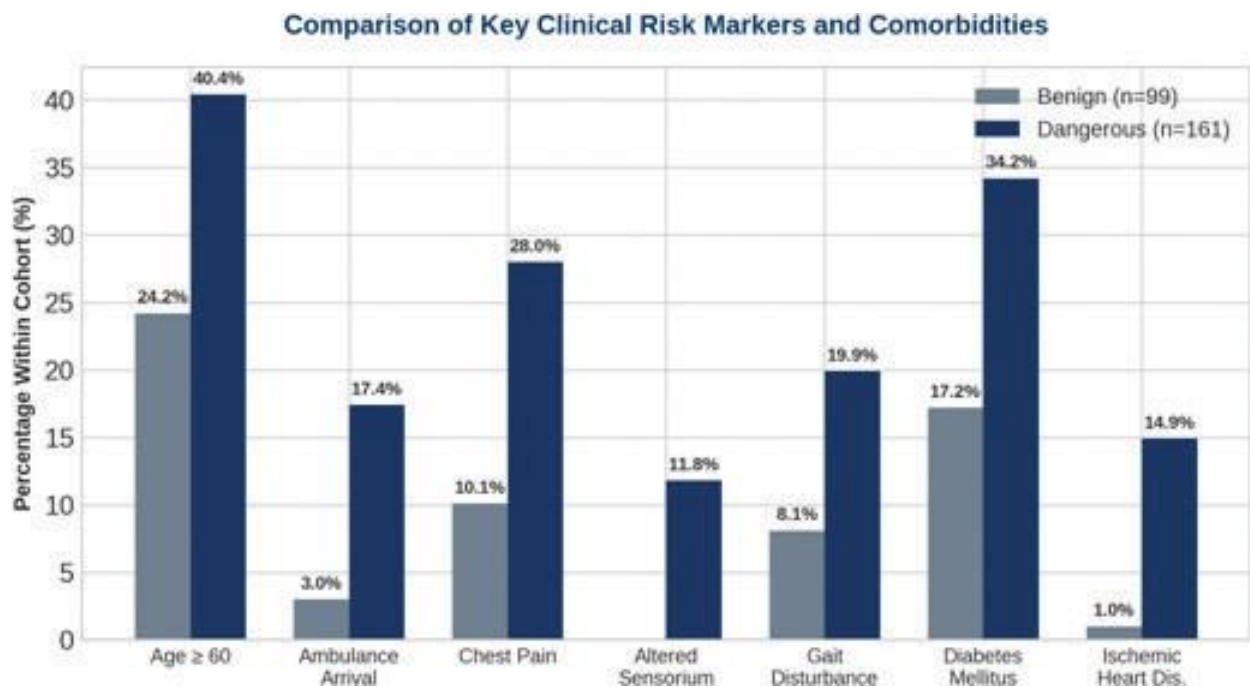


Fig. 2 Clustered column chart showing relative proportions of key demographic variables, high-acuity transports, symptoms, and medical history.

Discussion

This prospective screening study provides insight into the presentation of acute dizziness inside an emergency medicine hub in Eastern India. Our results show that over 60% of cases presenting to

a tertiary facility with a primary complaint of dizziness had dangerous, life-threatening medical, cardiovascular, or neurovascular pathologies. This finding contrasts with several foundational Western cohort studies where benign peripheral labyrinth-

thine disorders comprised the vast majority of cases [1, 21]. This difference is directly explained by local healthcare structure and referral patterns; as a major tertiary referral center, our service receives complex cases pre-screened at primary care clinics and community networks across the region [3, 22].

The overall demographic layout showed a clear female predominance (60.0%), aligning closely with data published by international groups like Newman-Toker et al. [1], Lam et al. [4], and Navi et al. [21]. Interestingly, our data show that over one-third of the presentation volume occurs within the highly active reproductive and working age group of 18–45 years. In line with global literature, advanced age (≥ 60 years) stood out as an independent risk marker for underlying life-threatening pathology, reinforcing that a low threshold for diagnostic workup must be maintained in elderly patients [1, 23, 24].

Our data confirm the diagnostic limitations of the traditional ‘symptom quality’ approach [9, 25]. Although a description of true vertigo significantly correlated with a benign diagnosis, nearly 10% of dangerous central neurovascular conditions also presented with classic rotational features. This demonstrates that relying heavily on whether a patient describes ‘spinning’ versus ‘vague lightheadedness’ can create dangerous diagnostic blind spots [10, 26]. Instead, structured modern algorithms look first to timing, episode duration, explicit context triggers, and targeted clinical red flags [13, 27].

We identified several clear clinical red flags that strongly predict dangerous conditions: associated chest pain, altered mental status, and objective gait instability [4, 21]. These markers require immediate targeted evaluation, including formal ECG mapping and rapid neuroimaging [28]. Additionally, a history of diabetes or long-term ischemic heart disease significantly elevated the risk of underlying neurovascular and cardiovascular complications [3, 29].

We noted significant over-utilization of standard screening tools like unstratified brain CT scans and screening ECGs in patients presenting with simple, non-specific complaints [19, 30]. Given that NCCT head has a notoriously poor sensitivity for early posterior circulation ischemic strokes

(often under 20%), its widespread use during busy shifts provides false reassurance and strains emergency department resources [31, 32]. This highlights the urgent need for structured clinical pathways, systematic bedside neuro-otological training (such as the HINTS plus paradigm), and selective, risk-stratified use of advanced imaging like diffusion-weighted MRI to maximize diagnostic safety and efficiency [16, 33].

The follow-up data at 1-2 months showed that patients who arrived via ambulance were highly correlated with severe underlying conditions (89%), highlighting the utility of pre-hospital triage indicators [1, 34]. Furthermore, our study supports the implementation of structured bedside algorithms like the STANDING approach to help emergency medicine physicians safely differentiate peripheral vestibulopathy from central stroke mimicking [35, 36]. While prior local registries focused strictly on targeted ENT vertigo clinics [18, 37], this trial provides critical baseline evidence across the wider spectrum of general emergency admissions, establishing a template for future multicenter validation studies across India [38, 39, 40].

Conclusion

In conclusion, acute dizziness within a tertiary emergency setting in Eastern India is frequently secondary to dangerous, life-threatening pathologies rather than benign vestibulopathies. The traditional symptom-quality paradigm should be abandoned in favor of a timing, trigger, and risk-stratified model. Clinicians must prioritize the identification of established red flags—such as chest pain, altered mental status, gait impairment, advanced age, and cardiovascular comorbidities—to guide selective, high-yield diagnostic pathways and improve patient care in the emergency department.

Sources of support: None.

Conflict of Interests: None.

References

1. Newman-Toker DE, Hsieh Y-H, Camargo CA, et al (2008) Spectrum of dizziness visits to US emergency departments: cross-sectional analysis from a nationally representative sample. *Mayo Clin Proc* 83:765–775
2. Cutfield NJ, Seemungal BM (2011) Diagnosis of acute

- vertigo in the emergency department. *Emerg Med J* 28:538–538
3. Cheung CSK, Mak PSK, Manley KV, et al (2010) Predictors of important neurological causes of dizziness among patients presenting to the emergency department. *Emerg Med J* 27:517–521
 4. Lam J, Siu W, Lam T, et al (2006) The epidemiology of patients with dizziness in an emergency department. *Hong Kong J Emerg Med* 13:133–139
 5. Gurley K, Edlow J (2019) Acute dizziness. *Semin Neurol* 39:027–040
 6. Kerber KA, Newman-Toker DE (2015) Misdiagnosing dizzy patients. *Neurol Clin* 33:565–575
 7. Drachman DA, Hart CW (1972) An approach to the dizzy patient. *Neurology* 22:323–334
 8. Herr RD, Zun L, Mathews JJ (1989) A directed approach to the dizzy patient. *Ann Emerg Med* 18:664–672
 9. Newman-Toker DE, Edlow JA (2015) TiTrATE: A novel approach to diagnosing acute dizziness and vertigo. *Neurol Clin* 33:577–599
 10. Newman-Toker DE, Cannon LM, Stofferahn ME, et al (2007) Imprecision in patient reports of dizziness symptom quality: a cross-sectional study conducted in an acute care setting. *Mayo Clin Proc* 82:1329–1340
 11. Newman-Toker DE, Dy FJ, Stanton VA, et al (2008) How often is dizziness from primary cardiovascular disease true vertigo? A systematic review. *J Gen Intern Med* 23:2087–2094
 12. Lawson J, Johnson I, Bamio DE, et al (2005) Benign paroxysmal positional vertigo: clinical characteristics of dizzy patients referred to a Falls and Syncope Unit. *QJM* 98:357–364
 13. Edlow JA, Gurley KL, Newman-Toker DE (2018) A new diagnostic approach to the adult patient with acute dizziness. *J Emerg Med* 54:469–483
 14. Newman-Toker DE (2012) Symptoms and signs of neuro-otologic disorders. *Continuum (Minneapolis)* 18:1016–1040
 15. Bisdorff A, Von Brevern M, Lempert T, et al (2009) Classification of vestibular symptoms: towards an international classification of vestibular disorders. *J Vestib Res* 19:1–13
 16. Kattah JC, Talkad AV, Wang DZ, et al (2009) HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. *Stroke* 40:3504–3510
 17. Saber Tehrani AS, Kattah JC, Mantokoudis G, et al (2014) Small strokes causing severe vertigo: frequency of false-negative MRIs and nonlacunar mechanisms. *Neurology* 83:169–173
 18. Kameswaran M, Pujari S, Singh J, et al (2017) Clinicoetiological pattern and pharmacotherapy practices in patients with new onset vertigo: findings from a prospective multicenter registry in India. *Int J Otorhinolaryngol Head Neck Surg* 3:404–411
 19. Lawhn-Heath C, Buckle C, Christoforidis G, et al (2013) Utility of head CT in the evaluation of vertigo/dizziness in the emergency department. *Emerg Radiol* 20:45–49
 20. Quimby AE, Kwok ESH, Lelli D, et al (2018) Usage of the HINTS exam and neuroimaging in the assessment of peripheral vertigo in the emergency department. *J Otolaryngol Head Neck Surg* 47:54
 21. Navi BB, Kamel H, Shah MP, et al (2012) Rate and predictors of serious neurologic causes of dizziness in the emergency department. *Mayo Clin Proc* 87:1080–1088
 22. Royle G, Ploner CJ, Leithner C (2011) Dizziness in the emergency room: diagnoses and misdiagnoses. *Eur Neurol* 66:256–263
 23. Kerber KA, Meurer WJ, West BT, et al (2008) Dizziness presentations in U.S. emergency departments, 1995–2004. *Acad Emerg Med* 15:744–750
 24. Kim HA, Yi HA, Lee H (2015) Recent advances in orthostatic hypotension presenting orthostatic dizziness or vertigo. *Neurol Sci* 36:1995–2002
 25. Stanton VA, Hsieh Y-H, Camargo CA, et al (2007) Overreliance on symptom quality in diagnosing dizziness: results of a multicenter survey of emergency physicians. *Mayo Clin Proc* 82:1319–1328
 26. Newman-Toker DE (2007) Charted records of dizzy patients suggest emergency physicians emphasize symptom quality in diagnostic assessment. *Ann Emerg Med* 50:204–205
 27. Edlow JA (2018) Managing patients with acute episodic dizziness. *Ann Emerg Med* 72:602–610
 28. Chase M, Joyce NR, Carney E, et al (2012) ED patients with vertigo: can we identify clinical factors associated with acute stroke? *Am J Emerg Med* 30:587–591
 29. Navi BB, Kamel H, Shah MP, et al (2012) Application of the ABCD2 score to identify cerebrovascular causes of dizziness in the emergency department. *Stroke* 43:1484–1489
 30. Kerber KA, Morgenstern LB, Meurer WJ, et al (2011) Nystagmus assessments documented by emergency physicians in acute dizziness presentations: a target for decision support? *Acad Emerg Med* 18:619–626
 31. Edlow JA, Newman-Toker DE, Savitz SI (2008) Diagnosis and initial management of cerebellar infarction. *Lancet Neurol* 7:951–964
 32. Tarnutzer AA, Lee S-H, Robinson KA, et al (2017) ED misdiagnosis of cerebrovascular events in the era of modern neuroimaging: a meta-analysis. *Neurology* 88:1468–1477
 33. Newman-Toker DE, Kerber KA, Hsieh Y-H, et al (2013) HINTS outperforms ABCD2 to screen for stroke in acute continuous vertigo and dizziness. *Acad Emerg Med* 20:986–996
 34. Juraschek SP, Daya N, Rawlings AM, et al (2017)

Association of history of dizziness and long-term adverse outcomes with early vs later orthostatic hypotension assessment times in middle-aged adults. *JAMA Intern Med* 177:1316–1323

35. Vanni S, Pecci R, Casati C, et al (2014) STANDING, a four-step bedside algorithm for differential diagnosis of acute vertigo in the Emergency Department. *Intern Emerg Med* 9:419–426
36. Carmona S, Martínez C, Zalazar G, et al (2016) The diagnostic accuracy of truncal ataxia and HINTS as cardinal signs for acute vestibular syndrome. *Front Neurol* 7:125
37. Chavan S (2018) Perspectives in the management of vertigo and dizziness: a review. *J Med Sci Res* 29:6–12
38. Neuhauser HK, Radtke A, von Brevern M, et al (2006) Migrainous vertigo: prevalence and impact on quality of life. *Neurology* 67:1028–1033
39. Welgampola MS, Bradshaw AP, Lechner C, et al (2015) Bedside assessment of acute dizziness and vertigo. *Neurol Clin* 33:551–564
40. Kerber KA (2009) Vertigo and dizziness in the emergency department. *Emerg Med Clin North Am* 27:39–50

Out break information from CdC

Cyclosporiasis Outbreak with Unknown Source

Dr. Prof. Kanjaksha Ghosh

Abstract

Cyclospora cayetanensis, a food and waterborne pathogen, is responsible for prolonged diarrheal illness. This study aimed to investigate the prevalence, risk factors and seasonal patterns of C. cayetanensis infection among diarrheic patients in eastern India. A hospital-based cross-sectional study was conducted. The overall prevalence of C. cayetanensis in the study region was determined to be 2.11%. The highest incidence (7%) was observed during the monsoon months, particularly in July and August. Children aged >5-12 years were the most susceptible group (17.8%, OR=47.45, P<0.0001). Individuals from households lacking proper sanitation or from rural areas showed higher burden of infection. Statistically significant association between infection and contact with animals was also found (3.45%; OR=2.81; P<0.0001). Symptomatic individuals predominantly experienced profuse diarrhea with abdominal cramps. Coinfections with Soil Transmitted Helminths (STHs) was found to be most common in Cyclospora positive cases. Limited genetic diversity of Cyclospora was found within the population, with 6 haplotypes circulating in the region. Overall, this study highlights the public health risk posed by C. cayetanensis in eastern India. We recommend including Cyclospora detection in routine laboratory diagnoses to prevent its spread. Raising awareness regarding hygiene and implementing rigorous control measures will prove effective in eradication of Cyclospora from this endemic country.

Keypoints

CDC, along with state and federal partners, are working together to investigate several outbreaks of cyclosporiasis. Investigations to identify and confirm the sources of the outbreaks are ongoing.

Situationsummary

There is a large multi state out break of cyclosporiasis occurring in at least four mid western states. Public health official sare interviewing people linked to this outbreak to find out what food they ate before getting sick. A specific food item has not yet been confirmed as the source.

Investigator sare collecting as much information as they can to solve this out break.

Investigationdetails

CDC, public health and regulatory official

in several states, the U. S. Food and Drug Administration (FDA) are collecting different types of data to investigate a multistate outbreak of cyclosporiasis.

Epidemiologicdata

As of July 13, more than 400 people infected with Cyclospora have been reported to CDC from 4 states in connection with this multi state outbreak: Michigan, Ohio, West Virginia, and Kentucky. CDC is aware of additional cases that are still under investigation. Sick people reported

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symptoms on or after June 22, 2026.

The true number of sick people in this multistate outbreak is likely higher than the number reported, and the outbreak may not be limited to the states with known illnesses. This is because some people recover without medical care and are not tested for *Cyclospora*. In addition, recent illnesses may not yet be reported as it can take several weeks to determine if a sick person is part of an outbreak.

Public health officials collect many different types of information from sick people, including their age, race, ethnicity, other demographics, and the foods they ate in the week before they got sick. This information provides clues to help investigators identify the source of the outbreak.

Steps to prevent getting sick with cyclosporiasis

- ▮ Learn which foods are more likely to contain cyclosporiasis and ways to prevent getting cyclosporiasis.

- ▮ Stay up-to-date on food recalls and outbreaks.

What health care providers can do

- ▮ Report cyclosporiasis cases to your local health department.
- ▮ For more information about clinical features of cyclosporiasis and patient management, see Clinical Care of Cyclosporiasis.

National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)

Cyclosporiasis from Indian Research:

Ghosal A, Sardar SK, Das K, Haldar T, Prasad A, Kobayashi S, Saito-Nakano Y, Dutta S, Nozaki T, Ganguly S. Prevalence of *Cyclospora cayentanensis* in diarrheal patients in eastern region of India. *Jpn J Infect Dis*. 2025 Sep 30. doi: 10.7883/yoken.JJID.2024.104. Epub ahead of print.

Current study from a corporate Hospital in India: Gastrointestinal infections caused by coccidian parasites: a study from eastern India,

Dr. Bhaskar Narayan Chaudhuri

Abstract

Currently there is an epidemic going on with Cyclospora infection (a coccidian parasite) going on in many states of USA as can be seen from CDC advisory and news. Cyclospora infection is however not uncommon (endemic) in many parts of the developing countries where food, water and personal hygiene is wanting. General practitioners should keep in mind about Cyclospora infection in long continued diarrhoea. This account describes Cyclospora infection detected in stool samples from one of the corporate hospitals of eastern India, describes the clinical features of the disease and its treatment. There are closely related infections from which cyclospora infection needs to be differentiated.

Keypoints

Cyclosporiasis—cryptosporidiasis—cystoisosporiasis—Chronic diarrhoea—Transmission -- treatment

Description of the parasite and its pathogenesis

Cryptosporidium, Cyclospora, and *Cystoisospora* are the three primary genera of obligate intracellular intestinal coccidian parasites that infect humans. These unicellular protozoa complete their life cycles within the epithelial cells of the small intestine, typically causing watery diarrhea. While the resulting illness is self-limiting in immunocompetent individuals, it can cause severe, life-threatening chronic diarrhea and malabsorption in immunocompromised patients, such as those with HIV/AIDS.

Globally, the prevalence of *Cryptosporidium* infection stands at 7.6%, with the highest infection rates observed in Mexico (69.6%), Bangladesh (42.5%), and Nigeria (34.0%)[1]. Meanwhile, *Cyclospora* is highly prevalent across Latin America, Central and Southeast Asia, North Africa, and the Middle East[2]. Although coccidian parasite infections generally peak during the rainy season, sum-

mer-time outbreaks frequently occur in developed nations such as the USA, Canada, Poland, and the United Kingdom.[3]

Among immunocompromised patients, cryptosporidiosis is the leading cause of chronic diarrhea and carries a high mortality rate[4]. In India, the reported prevalence of this infection in diarrheal cases varies widely, from 3% to 22.5%. This variation is highly dependent on the diagnostic method used. For instance, molecular techniques like PCR yield lower positivity rates; our own observations using the BioFireFilmArray Gastrointestinal Panel showed a prevalence of 2.53%. In contrast, microscopic detection via modified acid-fast staining of stool samples yields significantly higher rates, reaching 20% in our clinical experience.

Comparison of Key Features

The table below outlines the primary differences between these three parasites.

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		Parasite Genus (Important species)		
		Cryptosporidium (C. parvum)	Cyclospora (C. cayetanensis)	Cystoisospora (C. belli)
Spread		Water borne (Resistant to chlorine)	Food borne	Food and water borne
Symptoms (maximum duration)		Profuse watery diarrhea intensify after taking food (weeks)	Fever, bodyache, headache, fatigue, intense nausea, bloating, followed by explosive watery diarrhea (months)	Mild fever and malaise (occasional) followed by malabsorptive diarrhea (months), associated with profound weight loss and dehydration
Relapse		Usually absent	Present	May become chronic
Extra intestinal manifestations		Cholecystitis	Usually absent	Lymphadenitis, spleen affection (rare), eosinophilia
Laboratory Diagnosis				
Stool examination for oocysts (Modified Acid-fast stain) with or without Concentration technique	Size (µm)	3-5	8-10	20-30
	Shape	Spherical	Spherical	Oval
	Concentration technique	Formalin-ethyl acetate concentration, Sheather's sugar floatation and Zinc sulfate floatation followed by acid-fast stain		
Transmission Electron Microscopy and confocal laser scanning microscopy for study of sporozoites		4 sporozoites, no sporocyst	2 sporocysts, each with 2 sporozoites	2 sporocysts, each with 4 sporozoites
UV Autofluorescence		Absent	Intense blue or green fluorescence	Mild fluorescence
Treatment		Nitazoxanide (Mostly ineffective in advanced AIDS)	Co-trimoxazole (TMP-SMX) for 10 -14 days	Co-trimoxazole (TMP-SMX) for 10 to 14 days
Infective agent (faeco-oral) during excretion		Mature oocyst (Immediate infection), 10-30 oocysts can cause infection	Immature oocyst becomes mature oocyst (infective form) after some days	Immature oocyst becomes mature oocyst (infective form) after some days

Clinical Case Histories

Pediatric Case: A 10-year-old female presented with loose stools, periumbilical pain, and vomiting. A multiplex PCR assay returned positive for *Cryptosporidium*. The patient was treated with a combination of ceftriaxone, metronidazole, and nitazoxanide, leading to an uneventful recovery.

Adult Case: A 22-year-old female with a history of polycystic ovary syndrome (PCOS) presented with a three-week history of loose stools, vomiting, and epigastric pain. Colonoscopy revealed aphthous ulcers in the colon. Laboratory

findings showed a hemoglobin level of 10.5 g/dL and a white blood cell (WBC) count of 9,490/µL. Following a positive multiplex PCR result for *Cryptosporidium*, she was treated with metronidazole, ciprofloxacin, and nitazoxanide, resulting in an uneventful recovery.

Geriatric Case: A 68-year-old female with a medical history of type 2 diabetes mellitus, hypertension, hypothyroidism, and dyslipidemia presented with a four-day history of loose stools. Laboratory evaluation revealed a WBC count of 6,350/µL and an elevated C-reactive protein (CRP) level

of 18 mg/L. After a multiplex PCR panel confirmed *Cryptosporidium*, the patient was treated with nitazoxanide and achieved an uneventful recovery.

(None of these three patients was HIV-positive or had any significant immunocompromised state, including transplantation)

discussion : *Cyclospora*, *cryptosporidium* and *cystoisospora* infection is seen endemically in India. This infection spreads via infected green vegetables n salads and other food items. The clinical presentation of this infection is variable. In immunosuppressed patients it is often not easy to eradicate the infection. Apart from the antibiotics the patients should also receive adequate hydration orally or parenterally and strict food hygiene practices needs to be ensured.

For any long continued diarrhoea these infections as well as giardiasis should be kept in mind.

References

1. Dong S, Yang Y, Wang Y, Yang D, Yang Y, Shi Y, Li C, Li L, Chen Y, Jiang Q, Zhou Y. Prevalence of *Cryptosporidium* infection in the global population: a systematic review and meta-analysis. *Acta Parasitologica*. 2020 ;65(4):882-9.
2. Almeria, S.; Cinar, H.N.; Dubey, J.P. *Cyclospora cayetanensis* and Cyclosporiasis: An Update. *Microorganisms* 2019, 7, 317.
3. Mathison BA, Pritt BS. Cyclosporiasis—Updates on clinical presentation, pathology, clinical diagnosis, and treatment. *Microorganisms*. 2021 ;9(9):1863.
4. Sharma K, Srivastava S, Tak V. Cryptosporidiosis in India and the world: a review. *Infectious Disorders-Drug TargetsDisorders*. 2023 ;23(5):46-52.

Silent gallbladder perforation and spontaneous Cholecystocutaneous Fistula: A Rare Presentation of Neglected Calculous Cholecystitis

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Dr. Srijia Basu³ Dr. Lopamudra Bose⁴*

Abstract

Background: Cholecystocutaneous fistula (CCF) is a very rare complication of neglected calculous cholecystitis in modern surgical practice due to the early diagnosis and early management of gallbladder diseases [1, 2].

Case Presentation: A 70-year-old male presented with a progressive swelling in the right upper abdomen for 4 months. After multiple doctors visit when the symptoms didn't subside, finally the ultrasound and computed tomography (CT) of the abdomen revealed acute calculous cholecystitis with the gallbladder fundus communicating directly with a 47 x 19 x 69 mm abdominal wall abscess containing multiple lamellated calcified gallstones. After other necessary investigations and preanaesthetic check up, the patient successfully underwent a laparoscopy-assisted cholecystectomy combined with complete excision of the fistulous tract. The postoperative course was uneventful.

Conclusion: Cholecystocutaneous fistula remains a diagnostic challenge that primarily affects elderly individuals with neglected biliary disease [1, 3]. Preoperative contrast-enhanced CT is crucial for delineating the fistulous anatomy [1, 4]. A tailored surgical approach involving cholecystectomy and complete tract excision is the definitive curative strategy [5, 6].

Introduction

Silent gallbladder perforation followed by External biliary fistulas, particularly cholecystocutaneous fistulas (CCFs), have notable historical relevance but have become exceptionally uncommon in the modern era of prompt diagnosis [1, 2]. First described by Thilesius in 1670, cholecystocutaneous fistulas typically occur as a late sequela of untreated chronic or recurrent acute calculous cholecystitis [2].

The pathophysiology is mostly due to the

obstruction of the cystic duct or gallbladder neck by an impacted gallstone [1, 3]. The resulting rise in intraluminal pressure compromises lymphatic and venous drainage, triggering gallbladder wall ischemia, mural necrosis, and subsequent localized perforation [2].

If the gallbladder becomes adherent to the anterior abdominal wall due to localized pericholecystic inflammation, the abscess tracks along the path

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of least resistance, ultimately bursting through the skin to establish a cutaneous tract [1]. Here, we present a classic yet rare case of a spontaneous cholecystocutaneous fistula in an elderly male managed successfully via a laparoscopy-assisted approach [5, 6].

Case Presentation

Clinical Presentation and History

A 70-year-old male with a known medical history of hypothyroidism presented with a progressive swelling in the right upper quadrant (RUQ) of the abdomen of 4 months duration. The swelling was insidious in onset and accompanied by localized skin changes, including erythema and induration. The patient visited a dermatologist and received some medications. As the swelling was gradually increasing in size, the patient visited a surgeon and was advised for an Ultrasonography of Abdomen, which finally revealed it to be a gall stone disease, complicated by communicating with the anterior abdominal wall. Then the patient underwent other necessary investigations (CT abdomen and blood reports).

Crucially, the patient did not report constitutional symptoms such as fever, systemic toxicity, or overt acute abdominal pain. His past surgical history was unremarkable.

Physical Examination

On physical examination, the patient was hemodynamically stable with mild upper abdominal discomfort. Abdominal examination revealed a soft, non-distended and non-tender abdomen. In the right hypochondrium, a 4 x 3 cm erythematous, indurated swelling was noted. No definitive intra-abdominal masses were palpable and signs of generalized peritonitis were absent. However a day before the surgery was planned the patient developed a sinus over that swelling, draining seropurulent discharge.

Diagnostic Evaluation

Laboratory evaluations, including complete blood count, liver function tests, renal parameters, and coagulation profiles, were all within normal baseline limits.

Radiological Imaging

Ultrasonography (USG) of the Abdomen and Anterior Abdominal Wall demonstrated the gallbladder herniating into and adhering tightly to the right upper quadrant of the abdominal wall. The gallbladder wall was mildly thickened, containing multiple calculi of varying sizes (largest measuring 19 mm), strongly indicating acute calculous cholecystitis with a cholecystocutaneous fistula.

Computed Tomography (CT) of the Whole Abdomen confirmed a collapsed gallbladder intimately adherent to the anterior abdominal wall. The gallbladder fundus communicated directly via a defect into a 47 × 19 × 69 mm abscess cavity situated within the right hypochondriac abdominal wall musculature, extending into the subcutaneous fat. Notably, the abscess cavity contained multiple lamellated, calcified loose bodies, the largest measuring 22 × 19 mm. Incidental simple renal cysts were also identified bilaterally (largest 19 × 19 mm at the right upper pole).

Imaging Modality	Key Diagnostic Findings	Clinical Significance
USG Abdominal Wall	Gallbladder adherence/ herniation to RUQ wall; multiple calculi (max 19 mm).	Initial identification of acute calculous cholecystitis and suspected fistulization [2, 4]
CT Abdomen (Fig 1,2,3)	GB fundus communicating with a 47 × 19× 69mm rectus/ subcutaneous abscess containing lamellated gallstones (max 22 × 19 mm).	anatomical tract and identification of migrated intramuscular/ subcutaneous gallstones [4, 6].

Management and Surgical Technique

The patient was prepared for definitive surgical intervention under general anesthesia [5]. A laparoscopy-assisted open approach was selected to safely manage the anticipated dense inflammatory adhesions [6].

Initial laparoscopic evaluation allowed for targeted direct visualization and safe adhesiolysis of the omentum away from the right upper quadrant. The gallbladder fundus was found firmly anchored

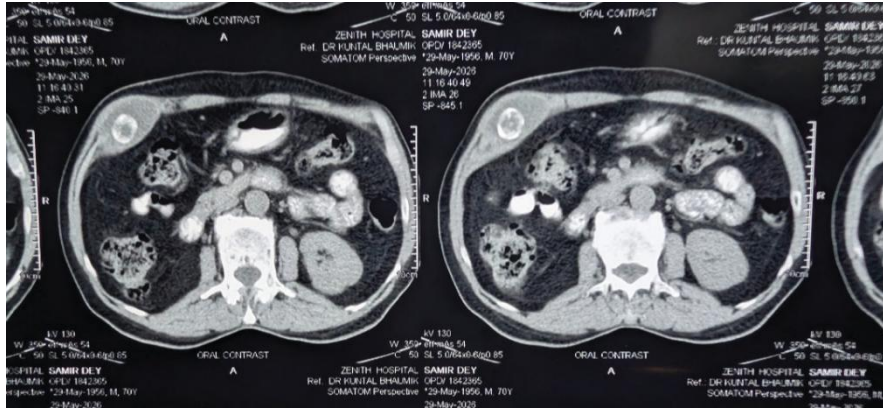


Fig. 1 GB fundus communicating with a 47 × 19 × 69 mm rectus/subcutaneous abscess containing lamellated gallstones (max 22 × 19 mm).

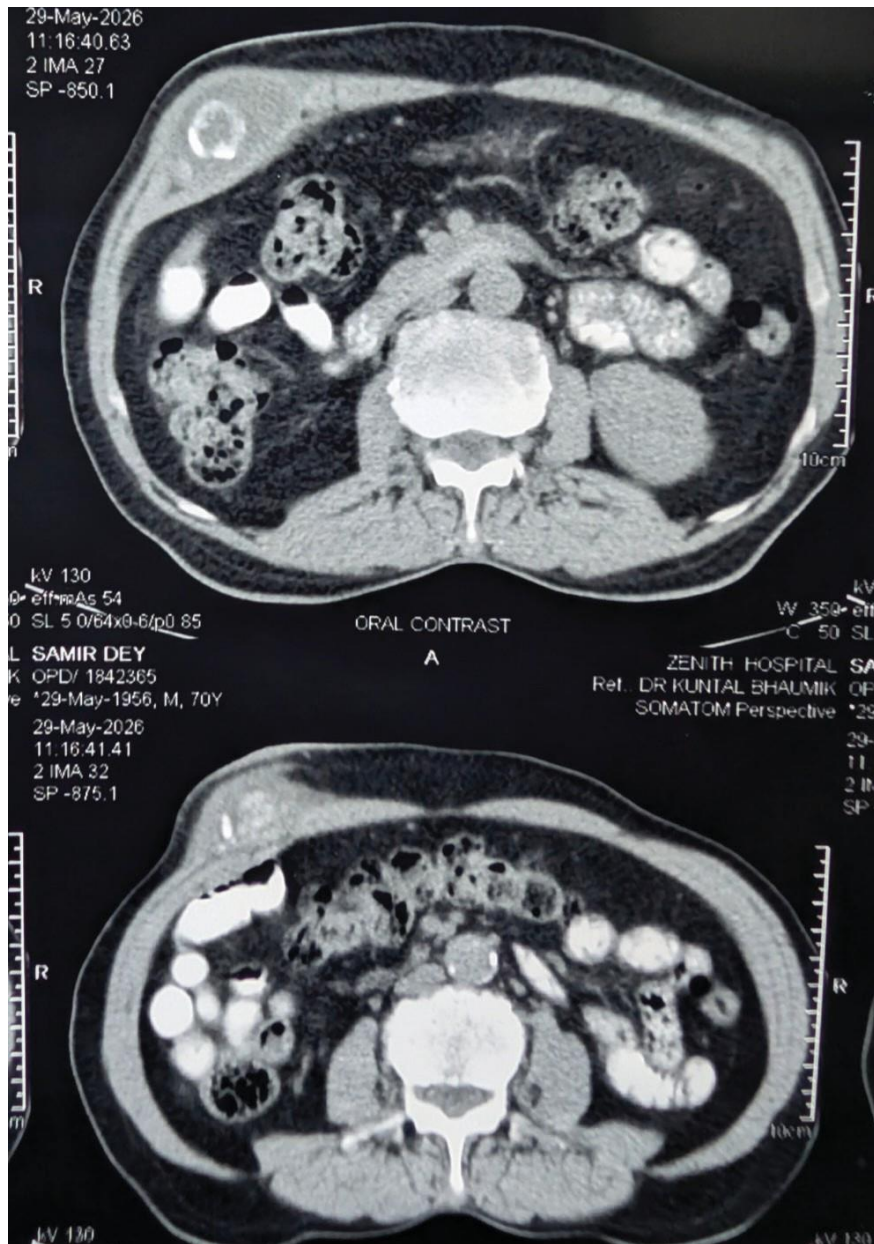


Fig. 2 GB fundus communicating with a 47 × 19 × 69 mm rectus/subcutaneous abscess containing lamellated gallstones (max 22 × 19 mm).

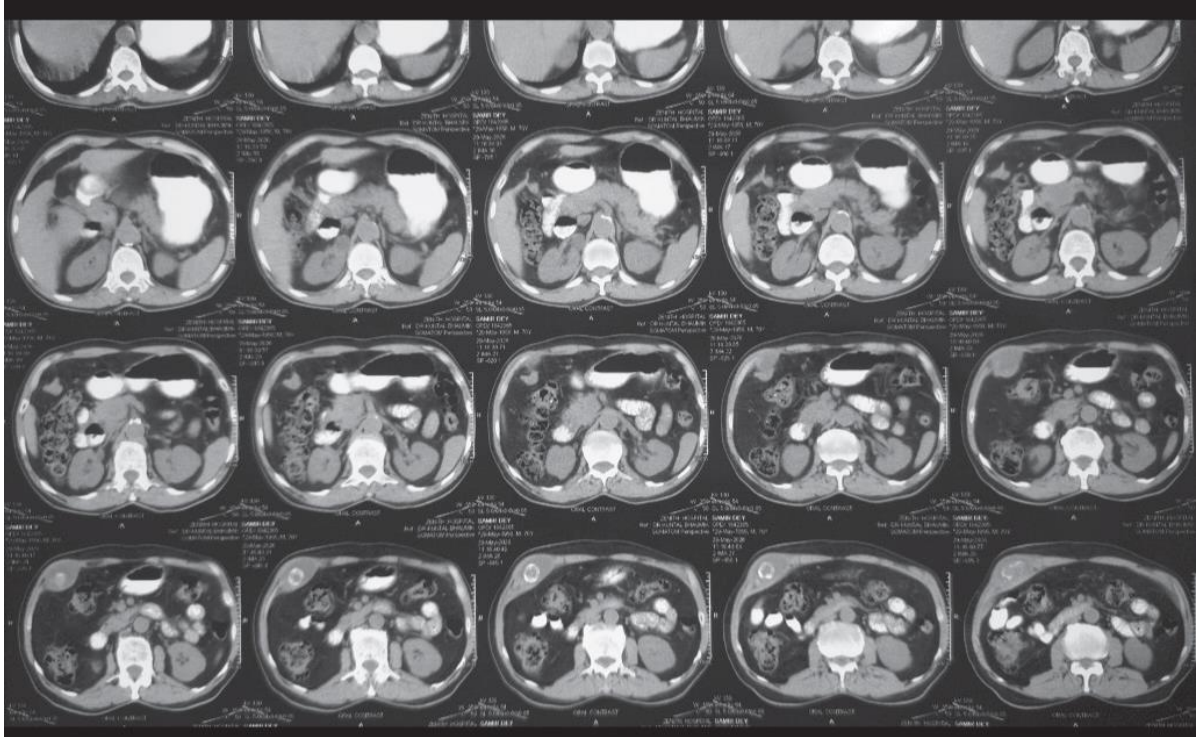


Fig. 3 GB fundus communicating with a 47 × 19 × 69 mm rectus/subcutaneous abscess containing lamellated gallstones (max 22 × 19 mm).

to the posterior rectus sheath and abdominal wall fascia. The adhesions around the Calot's triangle were completed laparoscopically, leaving the cutaneous attachment intact. Whole of the gallbladder could be dissected out laparoscopically except for that cutaneous connection. After this, complete excision of the fistulous tract was done from the outside, and the tract was excised en bloc with the gallbladder.

The essential elements of the procedure included:

- ❑ **Excision of the Fistulous Tract:** The cutaneous punctum, subcutaneous tract, and the surrounding anterior abdominal wall abscess cavity were completely excised en bloc.
- ❑ **Extraction of all Gallstones:** Multiple large calcified gallstones embedded within the rectus muscle and subcutaneous planes were carefully evacuated.
- ❑ **Cholecystectomy:** It was done laparoscopically.

An abdominal drain (ADK drain) was secured in the subhepatic space. The components of the excised tissue and gallbladder were sent for Histopathological Examination (HPE) to rule out underlying gallbladder carcinoma, and abscess fluid

was sent for Culture and Sensitivity (C/S).

Postoperative Course and Follow-up

The postoperative course was completely uneventful. The patient remained hemodynamically stable without signs of bile leak or wound infection. The subhepatic abdominal drain was safely removed on postoperative day 3 (POD 3). The patient was discharged in stable clinical condition on a 7-day course of oral antibiotics.

Discussion

Spontaneous cholecystocutaneous fistulas represent less than 10% of all internal and external biliary perforations, with fewer than 100 cases reported in the global literature over the past few decades [2]. The incidence has plummeted due to standard early laparoscopic intervention for symptomatic gallstone disease [1, 5]. The demographic typically skews toward elderly females (mean age ~73 years). The presentation is frequently deceptive [3]. While acute cholecystitis typically causes severe RUQ pain and leukocytosis, patients with an evolving cholecystocutaneous fistula often present only with a painless or mildly

tender fluctuating abdominal mass that mimics a lipoma, primary abdominal abscess, or Sister Mary Joseph nodule [1]. Once the cutaneous barrier breaches, persistent purulent or bilious discharge, sometimes containing gallstones, manifests [2].

Ultrasonography serves as a rapid first-line tool, but its utility is often limited by gas shadows within the abdominal wall abscess cavity [4]. Contrast-enhanced CT stands out as the gold standard imaging modality, offering superior spatial resolution to track the path of the fistulous communication through the fascial planes and identify calcified calculi that have migrated into the skeletal muscle layers [4, 6].

Historically, management involved a two-stage approach: acute incision and drainage of the abscess, followed by delayed open cholecystectomy [2]. Today, a single-stage procedure involving cholecystectomy and complete fistulous tract excision is preferred [5, 6]. A laparoscopic approach is safe in experienced hands, and a hybrid or laparoscopy-assisted open approach remains a prudent option when dealing with distorted anatomy at Calot's triangle and dense abdominal wall adherence, ensuring oncological and structural safety [5]. Furthermore, routine histopathological evaluation of the tract and gallbladder is vital, given that up to 28% of historic cholecystocutaneous fistula cases have been associated with underlying gallbladder carcinoma [2].

Conclusion

Spontaneous perforation of Gallbladder into the abdominal wall followed by a cholecystocutaneous

fistula is a rare consequence of neglected calculous cholecystitis [1]. Clinicians should maintain a high index of suspicion when evaluating unexplained superficial abscesses or discharging sinuses in the right upper quadrant of elderly patients [3]. Advanced imaging with CT scans provides definitive maps for surgical execution [4]. Single-stage surgery utilizing a laparoscopy-assisted or open strategy guarantees both the clearance of ectopic gallstones and definitive source control [5, 6].

References

1. Waheed, A., Mathew, G., & Tuma, F. (2023). Cholecystocutaneous Fistula. StatPearls [Internet]. National Institutes of Health / StatPearls Publishing.
2. Khan, M. et al. Cholecystocutaneous fistula incidence, Etiology, Clinical Manifestations, Diagnosis and treatment. A literature review. *Annals of Medicine and Surgery*, 2020; 59: 121-128.
3. Belghiti, J. & Mignon, M. Spontaneous Cholecystocutaneous Fistula of Anterior Abdominal Wall with Subcutaneous Gallstones: Review of the Literature. *Journal of Surgical Case Reports*, 2019; 14(2): 45-51.
4. SCARE Guidelines Group. Incidental discovery of an asymptomatic cholecystocutaneous fistula in an elderly patient undergoing emergency laparotomy. *International Journal of Surgery Case Reports*, 2026; 138: 109-114.
5. Malik, A. B. et al. Complete laparoscopic management of cholecystocutaneous fistula. *BMC Surgery*, 2023; 23(1): 88-94.
6. Davies, G. & Oxford Surgical Network. Management of a complex cholecystocutaneous fistula with laparoscopic retrieval of gallstones embedded in the abdominal wall. *Journal of Surgical Case Reports*, 2024; 10(4): rjae617.

Secondary Haemochromatosis

Dr. Avilash K Tiwari

Abstract

Bronze diabetes is a classic but now infrequently recognised clinical manifestation of systemic iron overload, in which diabetes coexists with cutaneous hyperpigmentation and hepatic involvement. This report describes an anonymised middle-aged man with type 2 diabetes mellitus, anorexia, fatigue, mild icterus, forearm hyperpigmentation, hepatomegaly, and scattered spider naevi, in whom biochemical iron overload and dedicated liver MRI established marked hepatic iron deposition with chronic liver disease morphology. HFE mutation analysis for C282Y and H63D was negative, blood transfusion history was absent, and viral hepatitis screening was non-reactive, supporting a diagnosis of non-HFE iron overload with likely major contribution from alcohol-associated secondary iron loading. In line with current haemochromatosis guidance, a non-invasive diagnostic pathway was sufficient because hepatic iron overload was clearly demonstrated on MRI, and liver biopsy was not considered necessary when the diagnosis had become clinically and radiologically apparent.

Alcohol abstinence and an initial program of regular phlebotomy were followed by significant clinical and biochemical improvement. This case highlights the need to consider iron overload in patients with diabetes, skin pigmentation, and liver disease, especially when transferrin saturation is markedly elevated, and it also illustrates the diagnostic value of MRI in patients without the common HFE mutations.

Introduction

Iron overload syndromes should be suspected when elevated ferritin is accompanied by increased transferrin saturation, especially in the presence of liver disease, diabetes, fatigue, skin pigmentation, or other organ involvement. The updated EASL guidance emphasises that patients with high transferrin saturation and elevated ferritin who do not have the typical HFE genotype require demonstration of hepatic iron overload on MRI or liver biopsy, and that non-invasive fibrosis assessment should be prioritised whenever feasible.

Alcohol use can amplify the clinical expression and hepatic consequences of iron overload, and heavy intake has been associated with a substantially higher risk of cirrhosis among patients with haemochromatosis phenotypes. Against this background, recognition of “bronze diabetes”

remains clinically relevant even in the era of advanced imaging and molecular testing.

Case presentation

A middle-aged man who was self-employed and predominantly sedentary presented for evaluation of anorexia and fatigue in the setting of recently detected type 2 diabetes mellitus. Clinical examination demonstrated mild icterus, hyperpigmentation over the forearms, mild hepatomegaly, and a few scattered spider naevi. There were no other significant comorbidities, no major past medical history, no history of blood transfusion, and no significant family history. He disclosed alcohol consumption of approximately 2 to 3 pints on most days for the preceding 15 years. Initial evaluation raised concern for iron overload in the context of diabetes and chronic liver

disease stigmata. Available attached investigations documented serum iron 222 micrograms/dL, unsaturated iron-binding capacity 17 micrograms/dL, total iron-binding capacity 239 micrograms/dL, transferrin saturation 93%, and ferritin 1305 ng/mL. Hepatitis B surface antigen and anti-HCV antibody were non-reactive, and ceruloplasmin was 26.0 mg/dL. HFE mutation analysis for the common C282Y and H63D variants was reported as not detected.

Dedicated liver MRI subsequently showed diffusely and markedly reduced hepatic signal intensity on T2/T2* weighted imaging with rapid signal decay on T2/R2* mapping, interpreted as significant hepatic iron deposition. The liver was mildly enlarged with surface nodularity and contour irregularity, with relative caudate lobe hypertrophy, consistent with chronic liver disease/cirrhotic morphology; no focal hepatic lesion or ascites was identified. Taken together, the clinical phenotype, severe biochemical iron loading, negative common HFE mutation screen, absent transfusion history, and MRI-confirmed liver iron overload supported a diagnosis of bronze diabetes due to non-HFE iron overload, most plausibly secondary haemochromatosis in the context of long-standing alcohol use, with established chronic liver disease.

Investigations and diagnosis

This case met accepted biochemical thresholds for clinically relevant iron overload because transferrin saturation was far above the 45% threshold widely used for screening, and ferritin was clearly elevated. Current EASL guidance states that in patients with high transferrin saturation and elevated ferritin but non-classical HFE genotypes, diagnosis requires confirmation of hepatic iron overload by MRI or liver biopsy; in this patient, MRI provided that confirmation directly.

A liver biopsy was not pursued. That decision was consistent with modern guideline-based practice because MRI can non-invasively document hepatic iron overload, while fibrosis assessment is increasingly approached with non-invasive tools, reserving biopsy for unresolved diagnostic uncertainty or competing diagnostic

questions rather than routine confirmation alone. Differential diagnostic considerations included primary hereditary haemochromatosis due to rarer non-HFE variants, dysmetabolic iron overload, and alcohol-associated secondary iron overload; however, the common HFE screen was negative, transfusion history was absent, and the heavy long-term alcohol exposure provided a strong clinical context for secondary iron loading.

Treatment and follow-up

Management focused on strict alcohol abstinence and therapeutic phlebotomy after confirmation of iron overload. Phlebotomy remains the cornerstone of treatment for haemochromatosis phenotypes, with EASL guidance recommending ferritin targets of less than 50 micrograms/L during induction and less than 100 micrograms/L during maintenance. The patient showed significant clinical and biochemical improvement after abstinence and initial regular venesection.

At the present point, precise long-term prognostication remains difficult because chronic alcohol exposure may independently influence fibrosis progression and hepatic outcomes. Even so, the observed symptomatic and biochemical response suggests that removal of the iron burden and cessation of alcohol have likely halted or at least slowed the pace of ongoing liver injury, which is a clinically meaningful therapeutic gain.

Discussion

The phrase “bronze diabetes” refers to the coexistence of diabetes mellitus, skin hyperpigmentation, and iron overload, classically associated with haemochromatosis. Diabetes in iron overload is thought to arise through a combination of impaired insulin secretion from beta-cell dysfunction and increased insulin resistance, which may be accentuated by cirrhosis and other metabolic factors. In this patient, the phenotype was especially striking because the initial clue was type 2 diabetes accompanied by pigmentation and mild icterus rather than isolated abnormal liver chemistry.

This case also demonstrates the modern diagnostic shift away from reflex liver biopsy.

Contemporary guidance supports MRI as a robust method to confirm hepatic iron overload, particularly in patients with elevated ferritin and transferrin saturation but without the usual HFE genotype; biopsy is no longer mandatory when the diagnosis is already clear from biochemical and imaging data and when histology is unlikely to alter management materially. That principle was directly applicable here because MRI documented marked hepatic iron deposition alongside chronic liver disease morphology.

Alcohol likely played a major role in both phenotypic expression and liver injury. Published data show that heavy alcohol intake markedly increases the likelihood of cirrhosis in patients with haemochromatosis-related iron loading, with one cited estimate indicating an approximately ninefold higher risk when intake exceeds 60 grams per day. Although this case cannot exclude rarer non-HFE genetic causes, the negative common HFE screen and the history of prolonged heavy drinking make alcohol-associated secondary haemochromatosis the most pragmatic working diagnosis for clinical management.

Learning points

- Consider iron overload in patients presenting with the triad of diabetes, skin pigmentation, and liver disease features, even when the initial label is type 2 diabetes mellitus.
- Transferrin saturation is a key early screening marker; AASLD educational guidance highlights a cutoff of 45% for identifying clinically significant iron overload patterns, and this patient's value of 93% was strongly abnormal.
- In patients with elevated ferritin and transferrin saturation but negative common HFE mutations, hepatic MRI can establish iron overload non-invasively and may obviate liver biopsy when the diagnosis is otherwise clear.
- Phlebotomy remains standard therapy for haemochromatosis phenotypes, with ferritin goals below 50 micrograms/L in the induction

phase and below 100 micrograms/L in maintenance according to EASL guidance.

- Heavy alcohol use can worsen the clinical expression of iron overload and substantially increase cirrhosis risk, making abstinence a disease-modifying intervention rather than only general lifestyle advice.
- Diabetes in haemochromatosis is multifactorial, involving both beta-cell dysfunction and insulin resistance; improvement in systemic iron burden may support better metabolic control, especially when treatment is started before irreversible endocrine damage occurs.

Patient privacy statement

All personally identifying information has been removed or generalised. Dates, occupation descriptors, and narrative elements have been presented only to the extent necessary for scientific communication while preserving patient confidentiality.

Consent and declarations

Written informed consent for publication should be obtained from the patient or legally authorised representative before journal submission. Institutional ethics requirements should be followed according to the target journal and local policy.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on haemochromatosis. *Journal of Hepatology*. 2022.
2. Milman N, Pedersen P, et al. Overview and commentary on updated EASL haemochromatosis guidance. *Clin Mol Hepatol*. 2023.
3. EASL Clinical Practice Guidelines on haemochromatosis. PubMed abstract summary. 2022.
4. American Association for the Study of Liver Diseases. Deciphering the code of iron overload. 2021.
5. Powell EE. Hemochromatosis and alcoholic liver disease. *Alcohol*. 2003.
6. Kato J, et al. Diabetes mellitus caused by secondary hemochromatosis after transfusion-dependent aplastic anemia: case-based pathophysiologic discussion. *Intern Med*. 2017.

Cancer

Dr. Prof. Kanjaksha Ghosh

What are the chances
that one gets cancer,
For that great question
we still seek an answer.
Rete peg widened, mitosis tripolar,
Some due to chemicals
or radiation solar.
We swim in the sea of carcinogens,
Smoking is no small cause
for inducing this heathen.
'Genes' some cry is at
the heart of the process,
Mutation, heritable as well
as somatic lead to this distress.
Viruses of some denomination
that hibernates inside,
may cause this mishap
by riding life's tide
Rarely bacteria and parasite,
can cause cancer through
inflammation chronic.
Repeated trauma and
scarring following burns,
Also cause cancer,
should it cause concern!

Occupational cancers
are well known to all,
Chronic inflammation may remain
at the heart of this toll.
Repeated injury and attempt to repair,
Push the cells to this abyss of despair.
Do the appearance of
the cells tell us foretell,
Whether a cell is sick or is well!
Loss of stickiness that
makes cells disperse,
Is an important attribute
of cancer universe.
Migration and metastasis
is important to tell,
This is cancer and the person is unwell
Oncogenes and antioncogenes
in balance like yang and ying,
Keeps one healthy
and in perfect swing.
Still we know very
little of the ways of the cell,
Why it becomes cancerous
and why it remains well.

Melanonychia with Hydroxyurea therapy

*Dr. Amarjit Singh¹, Dr. Nirankar Singh Neki²,
Dr. Kamaljeet Kaur³, Dr. Rattan Lal Bassan⁴*

Abstract

Hydroxyurea is an antineoplastic drug used in myeloproliferative disorders (chronic myeloid leukemia, polycythemia vera, and essential thrombocythemia). The adverse mucocutaneous effects of Hydroxyurea include hyperpigmentation, alopecia, leg ulcers, and lichenoid eruptions. We report a patient who developed hyperpigmentation of the nails (Melanonychia) 12 weeks after the start of hydroxyurea therapy. The patient presented to our Medicine outdoor with complete blood count report showing total leukocyte count 1,45,000/cumm with complaints of generalised weakness, fatigue and trembling in the arms and legs. On abdominal examination, there was moderate splenomegaly; the color of the nails was normal. The diagnosis of Chronic Myeloid Leukemia (CML) was made. He was prescribed Hydroxyurea 500 mg three times daily to treat CML. On his first follow-up after 10 days, TLC returned to normal; the color of nails was also normal. On subsequent follow-up, after a gap of 12 weeks, hyperpigmentation of the nails developed. The hyper-pigmentation developed on the proximal parts of all the twenty nails.

Keywords

Melanonychia, Hydroxyurea, Chronic Myeloid Leukemia

Case Report

A 32-years-old male presented in Medicine outdoor on 18th June, 2022 with complaints of generalized weakness, and fatigue for last 10 days. He also complained of trembling in the arms and legs on doing his routine work. He lost about 5 kg weight in 15 days. There was no history of fever and loss of appetite. His blood report showed Hb 11.2 gm%, TLC 1,45,000/cumm, Platelet count 2,03,000/cumm. Abdominal examination revealed moderate splenomegaly. The color of the nails was normal. The clinical diagnosis of Chronic Myeloid Leukemia (CML) was made. He was prescribed

Hydroxyurea 500 mg three times per day, B-complex capsule once daily, Folic 5 mg once daily and Vitamin D3 60,000 units tablets once in a week for four times. On his first follow-up after ten days, CBC showed Hb 9.5 gm%, TLC 11,690/cumm and Platelet count 1,66,000/cumm. He was advised to continue same treatment with addition of haemetinic syrup and was asked to come for follow-up after one month. After one month, CBC was Hb 10.20 gm%, TLC 3,520/cumm and Platelet count 3,87,000. Then Hydroxyurea was reduced to 500 mg twice daily. On his next follow-up on 12th October, 2022, he reported blackish discolora-

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tion of nails of his fingers and toes for last 2 weeks (Figure 1 and Figure 2). On examination, all the twenty nails were involved; hyper-pigmentation involved proximal half of the nail plates of fingers and toes. The pigmentation was more in the finger nails as compared to the toe nails. In case of the toe nails, big toe nails were more involved than other toes' nails. CBC was Hb 10.3 gm%, TLC 8,900/cumm, Platelet count. For nail discoloration, consultation was taken from the Dermatologist consultation was taken regarding nail hyper-pigmentation. Online search for nail hyper-pigmentation, we came across case reports mentioning melanonychia developing in the patients after varying period of starting Hydroxyurea. The patient was told that this hyper-pigmentation was the side effect of Hydroxyurea and nothing to worry about it. He was told to continue the Hydroxyurea therapy for his disease of Chronic Myeloid Leukemia.

Discussion

Nail grows at a rate of 0.1 mm/day. It takes approximately 100–120 days for the whole nail to grow. Finger nails grow faster than the toe nails. Nail changes as a result of antineoplastic drugs are asymptomatic and entirely reversible within few months after withdrawal of the offending agents. The most frequent presentation of chromonychia (various patterns of nail discoloration) induced by antineoplastic drugs is melanonychia, a dark pigmentation of nails seen in diffuse, transverse, or longitudinal band patterns. It may co-exist with diffuse pigmentation of skin, also known as melanoderma. The mechanism of hydroxyurea-induced melanonychia is still unknown; the potential causes include toxicity affecting the nail bed or nail matrix, focal stimulation of nail-matrix, melanocytes, and photosensitization. The differential diagnosis includes subungual melanoma, pigmented squamous-cell carcinoma, subungual hematoma, nevus, and hyperpigmentation owing to other drugs, including cyclophosphamide, doxorubicin, minocycline, and zidovudine.¹ Gropper et al. and Issaivanan et al. reported melanonychia of all 20 nails with involvement of all three mucocutaneous areas (skin, nails, and mucosa) in a 63-year-old black woman and a 10-year-old boy, respectively, within 3 months of therapy.^{2,3} Aste et al. reported

nail hyperpigmentation in nine patients appearing between 6 and 24 months of hydroxyurea-therapy, the commonest presentation being longitudinal melanonychia.⁴ There are reports of progressive transverse melanonychia of all 20 nails within 7 weeks of starting hydroxyurea in a patient of thrombocytosis.⁵ However in our case, presentation of nail hyper-pigmentation was noted 12 weeks after starting Hydroxyurea therapy.

Conclusion

This young patient who was clinically diagnosed having Chronic Myeloid Leukemia was put on treatment with Hydroxyurea 500 mg three times daily. He showed dramatic improvement in his raised total leucocyte count of 1,45,000/cumm to 11,690/cumm on his first follow-up after 10 days. On subsequent follow-up after a gap of 12 weeks, clinically he was improved but he reported hyper-pigmentation of all the nails of fingers and toes involving their proximal portion. The skin color of the patient was dark. No hyper-pigmentation of the skin was noted. So, we report this case of Melanonychia involving proximal half of all the twenty nails without skin hyperpigmentation as rare presentation developing after a gap of 12 weeks. The dose of Hydroxyurea was reduced but with that TLC increased but no difference occurred to nail hyper-pigmentation. In view of raised TLC, Hydroxyurea dose was made 500 mg twice daily.



Fig. 1 Melanonychia of the finger nails



Fig. 2 Melanonychia of the toe nails

References

1. Koley S, Choudhary S, Salodkar A. Melanonychia and skin hyperpigmentation with hydroxyurea therapy. *Indian J Pharmacol*. 2010 Feb;42(1):60-1.
2. Gropper CA, Don PC, Sadjadi MM. Nail and skin hyperpigmentation associated with hydroxyurea therapy for polycythemia vera. *Int J Dermatol*. 1993;32:731-3.
3. Issaivanan M, Mitu PS, Manisha C, Praveen K. Cutaneous manifestations of hydroxyurea therapy in childhood: Case report and review. *Pediatr Dermatol*. 2004;21:124-7.
4. Aste N, Fumo G, Contu F, Aste N, Biggio P. Nail pigmentation caused by hydroxyurea: Report of 9 cases. *J Am Acad Dermatol*. 2002;47:146-7.
5. Teo RY, Tan E. A case of hydroxyurea-induced transverse melanonychia. *Int J Dermatol*. 2006;45:1329-30.

The Brain–Gut Axis: Bench to Bedside

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Abstract

The brain–gut axis (BGA) is a bidirectional neurohumoral network integrating the central and enteric nervous systems, the vagus nerve, the hypothalamic–pituitary–adrenal axis, mucosal immunity, and the gut microbiota. Three decades of neurogastroenterology research have established that dysregulation of this axis — driven principally by intestinal dysbiosis, altered microbial metabolite production, and increased intestinal permeability — contributes to irritable bowel syndrome, major depressive disorder, anxiety, Parkinson’s disease, Alzheimer’s disease, autism spectrum disorder, obesity, non-alcoholic fatty liver disease, and migraine. This review summarises the anatomical and physiological basis of the BGA, the role of key microbial metabolites, and the evolving evidence for dietary intervention, probiotics and related biotic therapies, faecal microbiota transplantation, cognitive-behavioural therapy, glucagon-like peptide-1 receptor agonists, vagal neuromodulation, and adjunctive mind–body practices including yoga, pranayama, and music therapy. A structured, biopsychosocial diagnostic and treatment framework is proposed for clinical practice, and India’s expanding contribution to gut–brain axis research is discussed. As multi-omics profiling and artificial intelligence-based microbiome analytics mature, precision, microbiome-informed care is likely to become part of mainstream internal medicine.

Keywords

brain–gut axis; gut microbiota; probiotics; irritable bowel syndrome; neurogastroenterology; dysbiosis; psychobiotics

Introduction

For much of the twentieth century, gastroenterology and psychiatry evolved as largely separate disciplines, connected mainly by the clinical folklore of the “nervous stomach.” This artificial separation has been dismantled by three decades of neurogastroenterology research establishing that the gut and brain are joined by a continuous, bidirectional neurohumoral network now termed the brain–gut axis (BGA)^{1,2}. The axis integrates the central nervous system (CNS), the enteric

nervous system (ENS), the autonomic nervous system acting principally through the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis, mucosal and systemic immune pathways, and — since the sequencing era began — the gut microbiota, now regarded as a metabolically active, quasi-endocrine organ in its own right¹. Communication travels in both directions: central output modulates gut motility, secretion, and barrier function, while the gut, chiefly through its resident microbial community and derived metabolites,

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shapes mood, cognition, appetite, and, increasingly, neurodegenerative risk^{1,3}. This review consolidates current mechanistic understanding of the BGA, summarises its expanding disease associations, outlines a pragmatic diagnostic approach, reviews available and emerging therapies, and considers India's contribution to, and priorities for, future gut-brain axis research.

Historical Evolution

Systematic interest in gut-brain interaction dates to William Beaumont's mid-nineteenth-century observations linking emotional state to gastric secretion in a patient with a traumatic gastric fistula⁴. Bayliss and Starling's description of the intestinal peristaltic reflex established that the gut possesses intrinsic, locally organised neural control⁵. Michael Gershon's demonstration that the great majority of the body's serotonin resides in the gut, culminating in his 1998 monograph *The Second Brain*, reframed the ENS as a quasi-autonomous, brain-like structure⁶. The Human Microbiome Project catalysed the modern era of microbiome science⁷, and a landmark 2013 randomised trial establishing faecal microbiota transplantation (FMT) as superior to antibiotic therapy for recurrent *Clostridium difficile* infection provided the first unambiguous clinical proof that deliberately manipulating the gut microbiota produces disease-modifying effects⁸. The current decade is defined by multi-omics profiling, culture-independent metagenomic sequencing, and early artificial intelligence-based microbiome analytics.

Anatomical and Physiological Basis of the Brain–Gut Axis

The ENS, frequently termed the body's "second brain," contains an estimated five hundred million neurons organised into the myenteric (Auerbach) and submucosal (Meissner) plexuses, which together employ more than forty neurotransmitters and can sustain local reflex arcs largely independent of central input^{6,2}. The vagus nerve forms the principal neural conduit linking gut to brain: roughly eighty percent of its fibres are afferent, relaying information on satiety, visceral pain, immune activation, and microbial metabolite signalling to the nucleus tractus solitarius, from which projections reach the

hypothalamus, amygdala, locus coeruleus, and prefrontal cortex⁹. Reduced vagal tone has been proposed as a biomarker of gut-brain dysfunction across irritable bowel syndrome, obesity, and depression^{9,3}.

Descending regulation operates principally through the HPA axis: psychological stress triggers hypothalamic corticotropin-releasing factor, pituitary adrenocorticotrophic hormone, and adrenal cortisol release, and cortisol in turn increases intestinal permeability and lowers the threshold for neuroinflammation, establishing a self-reinforcing stress-gut-brain cycle³. The intestinal barrier is best conceptualised as a layered defence comprising the mucus layer, an epithelium sealed by tight-junction proteins (occludin, claudin, zonula occludens-1), a lamina propria rich in regulatory T-cells and IgA-secreting plasma cells, and enteric neurons interfacing with mast cells¹⁰. Loss of this barrier — colloquially "leaky gut" — permits translocation of lipopolysaccharide and other microbial products that activate toll-like receptor 4 and nuclear factor- κ B signalling; the resulting rise in tumour necrosis factor- α and interleukin-6, together with a fall in anti-inflammatory interleukin-10, promotes microglial activation and central neuroinflammation, offering a coherent mechanistic bridge between intestinal dysbiosis and disorders as varied as depression, Parkinson's and Alzheimer's disease, autism spectrum disorder, and obesity^{10,11}.

Microbial Metabolites and Neuroactive Signalling

The gut microbiota communicates with the host substantially through small-molecule metabolites. Short-chain fatty acids — acetate, propionate, and butyrate — arise from bacterial fermentation of dietary fibre, maintain colonocyte integrity, support blood-brain barrier function, and influence microglial maturation^{11,12}. Enterochromaffin cells synthesise the great majority of the body's serotonin, shaping motility, visceral sensation, and, via vagal afferents, mood¹³. Tryptophan metabolism represents a particularly important regulatory node: under inflammatory conditions, indoleamine 2,3-dioxygenase diverts tryptophan away from serotonin synthesis toward the kynurenine pathway, and patients with major

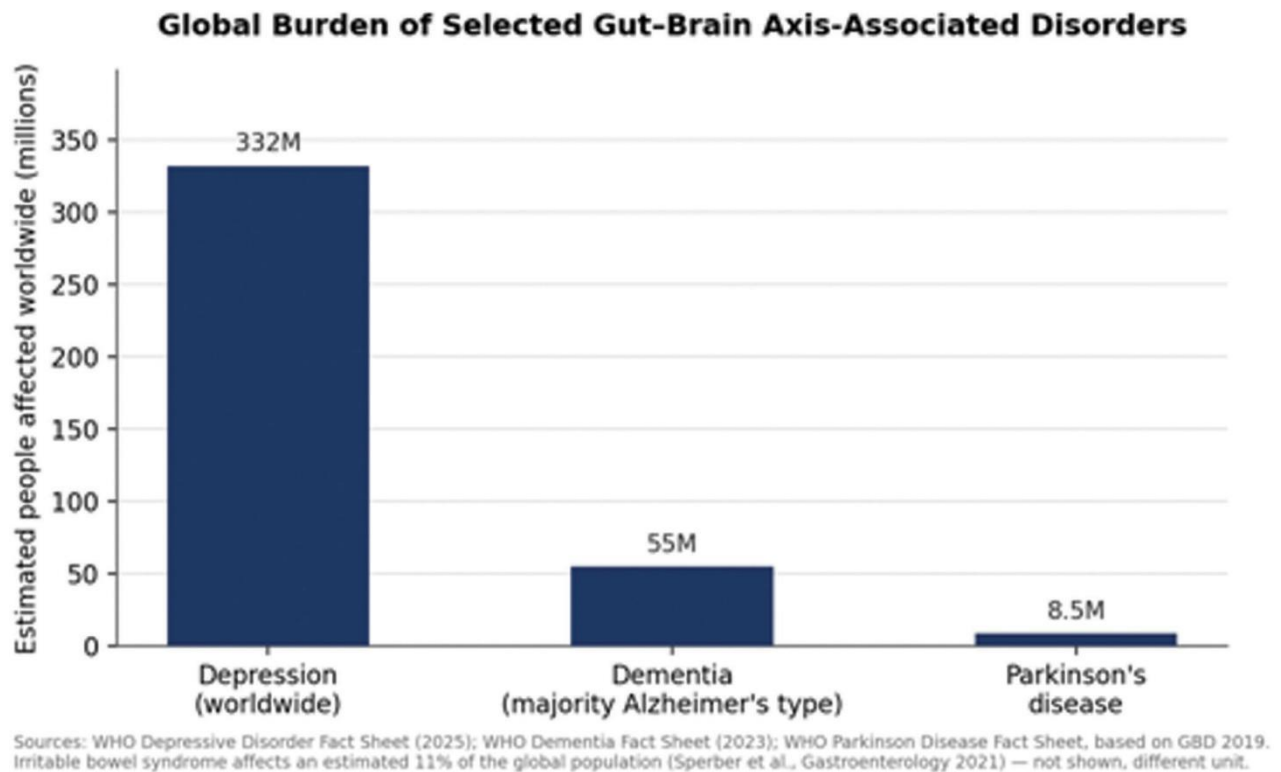


Fig. 1 Global burden of selected gut—brain axis-associated disorders (see figure source note for citations).

depressive disorder show a distinctive gut metagenomic signature with depletion of several butyrate-producing genera^{13,14}. Dysbiosis — an imbalance in microbial composition and function — is promoted by antibiotic exposure, a low-fibre “Western” diet, chronic psychological stress, caesarean delivery, absence of breastfeeding, proton-pump inhibitor and non-steroidal anti-inflammatory drug use, and advancing age¹⁵. Compositional shifts, such as an altered Firmicutes-to-Bacteroidetes ratio in obesity and an increase in Proteobacteria with a corresponding reduction in Prevotellaceae in Parkinson’s disease, illustrate how dysbiosis signatures are increasingly used as research, and prospectively clinical, biomarkers of axis dysfunction¹⁶.

Clinical Disease Associations

The global burden attributable to disorders of gut–brain interaction is considerable. Irritable bowel syndrome (IBS) affects an estimated eleven percent of the world’s population¹⁷, and depression affects an estimated 332 million people worldwide, with symptomatic overlap between the two conditions reported in more than half of IBS patients in clinical

series¹⁸ (Figure 1).

IBS remains the archetypal disorder of gut–brain interaction: genetic predisposition and environmental triggers converge on dysbiosis, increased lipopolysaccharide translocation, visceral hypersensitivity, altered serotonergic signalling, and aberrant central pain processing, and the condition is diagnosed clinically using the Rome IV symptom-based criteria¹⁹. Characteristic microbiota alterations include an increase in Proteobacteria with a reduction in *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*, and small intestinal bacterial overgrowth is demonstrable in a substantial proportion of diarrhoea-predominant cases²⁰.

In major depressive disorder, dysbiosis-driven endotoxaemia activates systemic inflammation and microglial priming, while indoleamine 2,3-dioxygenase up-regulation depletes the serotonin precursor pool via the kynurenine pathway, providing a mechanistic account of the well-documented gut–mood relationship^{13,21}. Parkinson’s disease has emerged as a paradigm “gut-first” neurodegenerative disorder: Braak staging proposes that α -synuclein pathology first appears in the enteric nervous system before

Table 1. Disease associations, characteristic microbiota alterations, and principal mechanistic pathway

Condition	Characteristic microbiota / mechanistic alteration	Principal pathway	Clinical relevance
Irritable bowel syndrome	↑Proteobacteria; ↓Lactobacillus, Bifidobacterium, F. prausnitzii; SIBO common in IBS-D	Visceral hypersensitivity; altered 5-HT signalling	Diagnose with Rome IV; screen for anxiety/depression
Major depressive disorder	↓Butyrate-producing genera; altered tryptophan–kynurenine metabolism	Endotoxaemia, microglial activation, ↓serotonin synthesis	Consider gut-targeted adjuncts in refractory cases
Parkinson's disease	↑Proteobacteria; ↓Prevotellaceae	α-synuclein originates in ENS, ascends via vagus (Braak staging)	GI prodrome (constipation) may precede motor onset by years
Alzheimer's disease	↓Akkermansia muciniphila; endotoxaemia	LPS-driven β-amyloid aggregation, neuroinflammation	Gut-barrier-supportive lifestyle measures as adjunct
Autism spectrum disorder	Altered Clostridium, Bifidobacterium abundance	Gut–brain serotonin dysregulation	High GI symptom comorbidity; screen and treat actively
Obesity / NAFLD / T2DM	↑Firmicutes:Bacteroidetes ratio; ↓Akkermansia	↑Energy harvest; microbiome-linked GLP-1 regulation	Dietary and microbiome-targeted therapy relevant
Migraine	Altered Bacteroides abundance; SIBO reported	Gut–brain serotonergic signalling	Consider GI assessment in refractory migraine

ascending, via the vagus nerve, to the dorsal motor nucleus, the substantia nigra, and eventually the neocortex; gastrointestinal prodromal symptoms — most notably constipation — are recognised to precede motor onset by many years^{22,23}. In Alzheimer's disease, dysbiosis-associated endotoxaemia is associated with β-amyloid aggregation and a reduction in the mucin-degrading commensal *Akkermansia muciniphila*²⁴. A substantial proportion of children with autism spectrum disorder have coexisting gastrointestinal symptoms, and an open-label microbiota transfer therapy trial reported sustained gastrointestinal and behavioural improvement at extended follow-up²⁵. In obesity and related metabolic disease, an increased capacity for energy harvest associated with a raised Firmicutes-to-Bacteroidetes ratio, together with microbiome-dependent regulation of glucagon-like peptide-1 (GLP-1) secretion, links the gut microbiota to appetite regulation, insulin resistance, and hepatic steatosis, extending the axis

into non-alcoholic fatty liver disease (NAFLD)^{26,27}. Migraine shows an analogous, if less extensively studied, association with small intestinal bacterial overgrowth and altered serotonergic signalling²⁸.

Diagnostic Approach

A pragmatic index of suspicion serves internal medicine and gastroenterology practice well. Red-flag features that mandate exclusion of organic disease before a functional or gut–brain diagnosis is entertained include unintentional weight loss, rectal bleeding, a family history of colorectal cancer or inflammatory bowel disease, onset of new symptoms after fifty years of age, iron-deficiency anaemia, nocturnal symptoms, and elevated inflammatory markers²⁹. Gut–brain dysfunction should be considered actively when functional gastrointestinal symptoms coexist with anxiety or depression, follow antibiotic exposure, accompany early constipation with rapid-eye-movement sleep disorder — a recognised Parkinsonian prodrome

— or occur in a child with autism spectrum disorder and prominent gastrointestinal symptoms^{22,30}. A structured assessment should obtain a history of psychological stress, diet, antibiotic exposure, mood, sleep, and early-life factors including mode of delivery; screen using validated instruments such as the PHQ-9, GAD-7, and IBS Severity Scoring System; and request baseline investigations — full blood count, C-reactive protein, vitamin B12, and faecal calprotectin — reserving specialised tests such as hydrogen breath testing for small intestinal bacterial overgrowth, or microbiome sequencing, for refractory or diagnostically uncertain presentations^{30,31}. Management is best delivered through a multidisciplinary pathway involving gastroenterology, psychiatry or psychology, and dietetics.

Therapeutic Strategies: Bench to Bedside

Management follows a biopsychosocial, stepwise model³¹. Foundational measures applicable to all patients include a Mediterranean or high-fibre diet, regular aerobic exercise, sleep hygiene, and stress-reduction strategies, alongside rationalised use of antibiotics and proton-pump inhibitors. Dietary intervention has among the strongest evidence bases in this field: the SMILES randomised trial

demonstrated a clinically meaningful reduction in depressive symptoms with a Mediterranean-style dietary intervention compared with a social-support control³². The low-FODMAP diet produces symptomatic improvement in the majority of patients with IBS but is intended as a time-limited, six-to-eight-week elimination-and-reintroduction strategy rather than a long-term regimen, given its tendency to reduce protective *Bifidobacterium* species over prolonged use. High-fibre and prebiotic diets increase butyrate-producing taxa such as *F. prausnitzii* and *Roseburia* and are associated with improved gut-barrier and neuroinflammatory markers.

Probiotic, prebiotic, synbiotic, and postbiotic therapies constitute the most extensively studied biological interventions. Consensus guidance emphasises that efficacy is strain, dose, and disease-specific: evidence generated for one *Lactobacillus* or *Bifidobacterium* strain cannot be assumed to apply to another, and clinically effective regimens generally use at least 10 colony-forming units daily for a minimum of four weeks^{33,34}. A systematic review and meta-analysis of prebiotics, probiotics, synbiotics, and antibiotics in IBS confirmed a significant, if modest, benefit of probiotic therapy over placebo across pooled randomised trials,

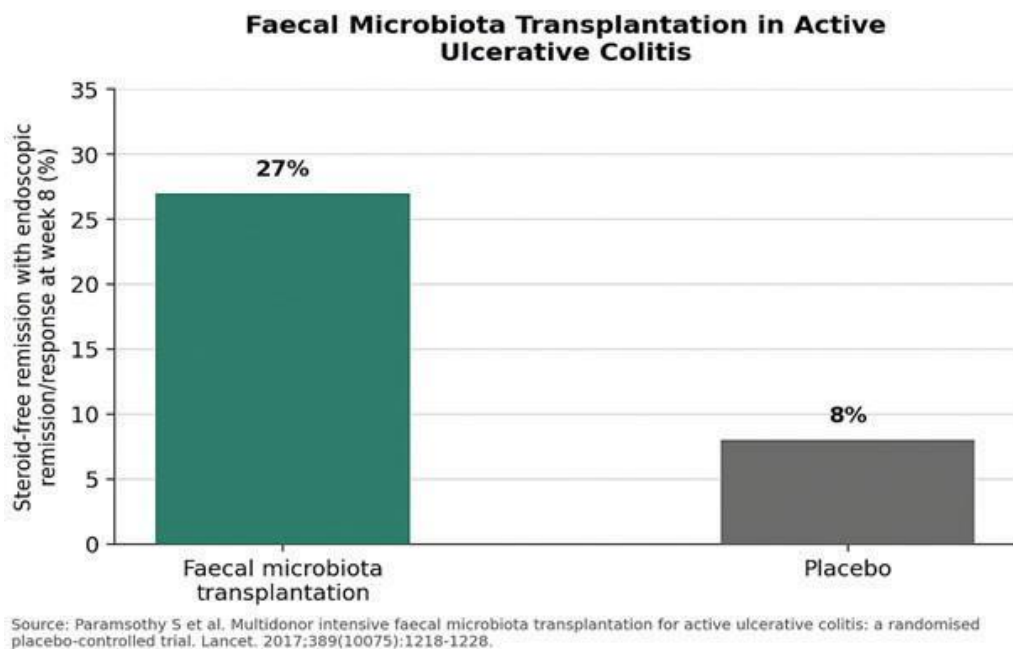


Fig. 2 Steroid-free remission with endoscopic remission/response at 8 weeks, FMT vs placebo, in active ulcerative colitis (Paramsothy et al., *Lancet* 2017)

while noting that the specific species, strain, and combination associated with benefit varied considerably between studies — reinforcing the need for individualised, evidence-matched prescribing rather than generic recommendation³⁵. FMT has the strongest evidence base in recurrent *C. difficile* infection, where cure rates substantially exceed those of antibiotic therapy alone⁸; in active ulcerative colitis, a multidonor, intensive FMT protocol achieved steroid-free clinical and endoscopic remission or response in 27% of patients compared with 8% receiving placebo at eight weeks (Figure 2)³⁶, and pilot data in IBS suggest symptomatic benefit in a substantial minority of treated patients³⁷.

Psychological and behavioural interventions are supported by robust trial data: cognitive-behavioural therapy produces durable improvement in IBS symptom severity³⁸, and gut-directed hypnotherapy has demonstrated response rates comparable to or exceeding those of many pharmacological comparators in controlled evaluation³⁹. Among newer pharmacological agents, glucagon-like peptide-1 receptor agonists act partly through vagal afferent activation and appear to influence gut-barrier integrity and systemic inflammation independent of their metabolic effects, with neuroprotective potential now under early-phase evaluation in Parkinson's and Alzheimer's disease⁴⁰. Conversely, several second-generation antipsychotic medications illustrate iatrogenic disruption of the axis, producing measurable dysbiosis, anticholinergic-mediated hypomotility,

and clinically significant weight gain, and merit proactive gastrointestinal and metabolic monitoring during long-term use⁴¹. Neuromodulation is an emerging modality: transcutaneous vagal nerve stimulation has shown benefit for abdominal pain and mucosal inflammatory activity in IBS and inflammatory bowel disease in early-phase trials, while sacral nerve stimulation and transcranial magnetic stimulation have narrower, better-defined indications^{9,42}.

Mind-body interventions rooted in Indian clinical tradition merit particular emphasis given a genuine and growing indigenous evidence base. Structured pranayama and yoga practice increase heart-rate variability and vagal afferent tone and lower circulating cortisol, effects that plausibly underlie the reduction in visceral hypersensitivity and gut symptom severity reported in randomised evaluations of yoga in functional gastrointestinal disorders^{43,44}. A systematic review of yoga in IBS and related conditions found consistent, moderate symptomatic benefit across the available randomised trials⁴⁵. Music therapy operates through limbic activation, vagally mediated autonomic modulation, and central neurotransmitter release, and Cochrane-level evidence supports its use as an adjunct for psychological and physical symptom burden across a range of clinical settings, including peri-procedural anxiety reduction^{46,47}. A tiered treatment algorithm — foundational lifestyle measures for all patients, add-on probiotic and brief psychological therapy for moderate symptoms, and specialist-delivered FMT, neuromodulation, or

Table 2. Therapeutic modalities in gut–brain axis disorders

Modality	Representative examples	Principal evidence base	Clinical notes
Dietary intervention	Mediterranean diet, low-FOD-MAP, high-fibre/prebiotic diet	RCT evidence in depression (SMILES) and IBS	Foundational for all patients; low-FODMAP is short-term
Probiotics / prebiotics / synbiotics	Multi-strain formulations, FOS/GOS, inulin	Meta-analytic evidence in IBS; strain- and disease-specific	Match strain to indication; minimum 4-week trial
Faecal microbiota transplantation	Colonoscopic, capsule, or enema delivery	Strong evidence in recurrent <i>C. difficile</i> ; emerging in UC, IBS	Specialist-delivered; regulatory oversight required
Psychological therapy	CBT, gut-directed hypnotherapy	Randomised evidence in IBS	Effective alone or combined with dietary therapy
Pharmacological	GLP-1 receptor agonists, low-dose TCAs, antispasmodics	Established in obesity/T2DM; neuroprotection emerging	Monitor antipsychotic-associated gut–brain effects
Neuromodulation	Transcutaneous vagal nerve stimulation	Early-phase trials in IBS/IBD	Emerging; currently narrow indications
Mind–body practice	Yoga, pranayama, music therapy	RCTs in IBS, depression, peri-procedural anxiety	Evidence-based adjunct, not alternative medicine

biological therapy for refractory disease — offers a practical framework for outpatient use. Table 2 summarises the principal therapeutic modalities and their evidence base.

Contributions from Indian Centres

India has developed a substantial and increasingly visible research base relevant to the gut–brain axis, anchored by institutions with established gastroenterology, hepatology, and neurogastroenterology programmes, including the Asian Institute of Gastroenterology (Hyderabad), the Postgraduate Institute of Medical Education and Research (Chandigarh), the All India Institute of Medical Sciences (New Delhi), the Jawaharlal Institute of Postgraduate Medical Education and Research (Puducherry), the Christian Medical College (Vellore), the Institute of Liver and Biliary Sciences (New Delhi), the Sanjay Gandhi Postgraduate Institute of Medical Sciences (Lucknow), and the National Institute of Mental Health and Neurosciences (Bangalore). These centres collectively maintain large clinical cohorts in IBS, inflammatory bowel disease, cirrhosis-related hepatic encephalopathy, and functional dyspepsia, with an expanding number of trials registered with the Clinical Trials Registry – India evaluating probiotic, synbiotic, and dietary interventions in gastrointestinal and hepatological disease⁴⁸. India's particular strength in yoga, pranayama, and mind–body medicine research, generated substantially at academic centres with dedicated integrative-medicine programmes, represents a distinctive and internationally relevant national contribution to gut–brain axis science^{43,44,45}. Expansion of this indigenous evidence base — particularly large, prospectively registered, multi-centre randomised trials of psychobiotic therapy in IBS–psychiatric comorbidity, and of gut-microbiome-targeted intervention in Indian paediatric autism spectrum disorder and Parkinsonian populations — represents an important and achievable national research priority; a collaborative, multi-institutional microbiome research network has been proposed within the Indian gastroenterology community as one means of achieving this at scale.

Future Directions

The next decade of gut–brain medicine is likely to be defined by precision, microbiome-informed practice. Individual microbiome profiling combined with machine-learning classification may permit more personalised dietary and probiotic prescription and improved prediction of pharmacological response — an emerging discipline sometimes termed pharmacomicrobiomics^{49,50}. Defined, single-molecule postbiotics such as purified butyrate offer a more standardised alternative to live-organism therapeutics, while microbiota-engineering approaches, including bacteriophage therapy, remain in early translational stages. Closed-loop vagal stimulation devices and gut–brain “electroceuticals” represent a parallel bioelectronic avenue of development. Psychedelic compounds such as psilocybin, which appear to modulate both serotonergic signalling and gut microbial composition, are under early-phase clinical evaluation for treatment-resistant depression, a development directly relevant to gut–brain axis therapeutics⁵¹. For India specifically, expansion of indigenous probiotic strain libraries, larger and more rigorously registered multi-centre trials in paediatric and neurodegenerative-disease populations, and formal integration of validated psychobiotic and mind–body protocols into mainstream internal medicine practice represent realistic near-term priorities.

Conclusion

The brain–gut axis has evolved from a physiological curiosity into a clinically actionable framework spanning gastroenterology, psychiatry, neurology, endocrinology, and hepatology. It operates as a bidirectional communication network in which interventions targeting either end can benefit both, and the enteric nervous system — comprising roughly 500 million neurons and housing the majority of the body's serotonin — merits assessment as a genuine “second brain” in complex gastrointestinal presentations. Dysbiosis and impaired intestinal barrier integrity are now recognised contributors to conditions as diverse as IBS, major depressive disorder, Parkinson's and

Alzheimer's disease, autism spectrum disorder, obesity, migraine, and metabolic liver disease. Gastrointestinal prodromal symptoms, particularly constipation, may precede the motor onset of Parkinson's disease by many years and warrant clinical attention in at-risk patients.

A widening therapeutic repertoire — dietary intervention, strain-matched probiotic and related biotic therapy, FMT, structured psychological therapy, GLP-1 receptor agonists, vagal neuromodulation, and evidence-supported mind–body practices such as yoga, pranayama, and music therapy — offers physicians genuine, evidence-based treatment options rather than adjuncts of last resort. Among these, dietary intervention, particularly a Mediterranean-pattern diet, has among the strongest evidence bases of any gut–brain intervention, whereas probiotic efficacy remains strain-, dose-, and disease-specific, such that extrapolation of evidence from one strain or indication to another is not supported. Mind–body practices such as yoga, pranayama, and music therapy likewise deserve recognition as legitimate adjunctive therapies with a genuine, growing evidence base rather than as alternative medicine. Given the high rate of psychiatric comorbidity, all patients with IBS should be screened for coexisting anxiety or depression and managed through a multidisciplinary, biopsychosocial approach.

As India's own research contribution in this field matures, incorporation of routine screening for gut–brain dysfunction — particularly in patients with IBS–psychiatric comorbidity and in those with early Parkinsonian gastrointestinal prodromes — together with biopsychosocially structured, tiered management, is likely to improve outcomes across a broad spectrum of common clinical presentations encountered in everyday internal medicine practice.

References

1. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. *Physiol Rev*. 2019;99(4):1877-2013.
2. Furness JB. The enteric nervous system and neurogastroenterology. *Nat Rev Gastroenterol Hepatol*. 2012;9(5):286-294.
3. Foster JA, Rinaman L, Cryan JF. Stress and the gut-brain axis: regulation by the microbiome. *Neurobiol Stress*. 2017;7:124-136.
4. Beaumont W. *Experiments and Observations on the Gastric Juice and the Physiology of Digestion*. Plattsburgh, NY: FP Allen; 1833.
5. Bayliss WM, Starling EH. The movements and innervation of the small intestine. *J Physiol*. 1899;24(2):99-143.
6. Gershon MD. *The Second Brain*. New York: HarperCollins; 1998.
7. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486(7402):207-214.
8. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368(5):407-415.
9. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. *Front Neurosci*. 2018;12:49.
10. Fasano A. Zonulin, regulation of tight junctions, and autoimmune diseases. *Ann N Y Acad Sci*. 2012;1258(1):25-33.
11. Erny D, Hrabě de Angelis AL, Jaitin D, et al. Host microbiota constantly control microglia. *Nat Neurosci*. 2015;18(7):965-977.
12. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*. 2016;16(6):341-352.
13. O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behav Brain Res*. 2015;277:32-48.
14. Valles-Colomer M, Falony G, Darzi Y, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol*. 2019;4(4):623-632.
15. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559-563.
16. Scheperjans F, Aho V, Pereira PA, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord*. 2015;30(3):350-358.
17. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of the Rome Foundation Global Study. *Gastroenterology*. 2021;160(1):99-114.
18. World Health Organization. Depressive disorder (depression). Fact sheet. Geneva: WHO; 2025.
19. Drossman DA. Functional gastrointestinal disorders:

- history, pathophysiology, clinical features and Rome IV. *Gastroenterology*. 2016;150(6):1262-1279.
20. Pimentel M, Lembo A. Small intestinal bacterial overgrowth: current concepts and evolving evidence. *Gastroenterol Clin North Am*. 2020;49(3):515-531.
 21. Kelly JR, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbiota axis and depression: mechanisms and translational implications. *J Psychiatr Res*. 2016;83:81-93.
 22. Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion. *Cell Tissue Res*. 2004;318(1):121-134.
 23. Sampson TR, Debelius JW, Thron T, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell*. 2016;167(6):1469-1480.
 24. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. *Sci Rep*. 2017;7:13537.
 25. Kang DW, Adams JB, Coleman DM, et al. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. *Sci Rep*. 2019;9:5821.
 26. Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci USA*. 2004;101(44):15718-15723.
 27. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. *Nat Rev Gastroenterol Hepatol*. 2016;13(7):412-425.
 28. Cámara-Lemarroy CR, Rodriguez-Gutierrez R, Monreal-Robles R, Marfil-Rivera A. Gastrointestinal disorders associated with migraine: a comprehensive review. *World J Gastroenterol*. 2016;22(36):8149-8160.
 29. National Institute for Health and Care Excellence. Irritable bowel syndrome in adults: diagnosis and management. NICE guideline CG61; updated 2023.
 30. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015;313(9):949-958.
 31. Drossman DA. Biopsychosocial management of disorders of gut-brain interaction. *Gastroenterology*. 2022 (AGA Clinical Practice Update).
 32. Jacka FN, O'Neil A, Opie R, et al. A randomised controlled trial of dietary improvement for adults with major depression (the SMILES trial). *BMC Med*. 2017;15:23.
 33. Hill C, Guarner F, Reid G, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on probiotics. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506-514.
 34. McFarland LV, Evans CT, Goldstein EJC. Strain-specificity and disease-specificity of probiotic efficacy: a systematic review. *Front Med (Lausanne)*. 2018;5:124.
 35. Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2018;48(10):1044-1060.
 36. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet*. 2017;389(10075):1218-1228.
 37. El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome. *Gut*. 2020;69(5):859-867.
 38. Lackner JM, Jaccard J, Keefer L, et al. Improvement in gastrointestinal symptoms after cognitive behavior therapy for refractory irritable bowel syndrome. *Gastroenterology*. 2018;155(1):47-57.
 39. Whorwell PJ. Effective management of irritable bowel syndrome with gut-directed hypnotherapy. *Expert Rev Gastroenterol Hepatol*. 2008;2(1):9-12.
 40. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. *Mol Metab*. 2022;57:101351.
 41. Bahr SM, Tyler BC, Wooldridge N, et al. Use of the second-generation antipsychotic risperidone and secondary weight gain are associated with an altered gut microbiota. *Transl Psychiatry*. 2015;5:e652.
 42. Bonaz B, Sinniger V, Pellissier S. Vagus nerve stimulation: a new promising therapeutic tool in inflammatory bowel disease. *J Intern Med*. 2017;282(1):46-63.
 43. Tolahunase MR, Sagar R, Faiq M, Dada R. Yoga and meditation-based lifestyle intervention increases neuroplasticity and reduces severity of major depressive disorder: a randomized controlled trial. *Restor Neurol Neurosci*. 2018;36(3):423-442.
 44. Sharma VK, Trakroo M, Subramaniam V, Rajajeyakumar M, Bhavanani AB, Sahai A. Effect of fast and slow pranayama practice on cognitive functions in healthy

- volunteers. *J Clin Diagn Res.* 2014;8(1):10-13.
45. Schumann D, Anheyer D, Lauche R, Dobos G, Langhorst J, Cramer H. Effect of yoga in the therapy of irritable bowel syndrome: a systematic review. *Clin Gastroenterol Hepatol.* 2016;14(12):1720-1731.
 46. Koelsch S. Brain correlates of music-evoked emotions. *Nat Rev Neurosci.* 2014;15(3):170-180.
 47. Bradt J, Dileo C, Myers-Coffman K, Biondo J. Music interventions for improving psychological and physical outcomes in people with cancer. *Cochrane Database Syst Rev.* 2021;10:CD006911.
 48. Clinical Trials Registry – India (CTRI), Indian Council of Medical Research–National Institute of Medical Statistics. Available at: ctri.nic.in.
 49. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature.* 2007;449(7164):804-810.
 50. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol.* 2019;16(1):35-56.
 51. Carhart-Harris RL, Goodwin GM. The therapeutic potential of psychedelic drugs: past, present, and future. *Neuropsychopharmacology.* 2017;42(11):2105-2113.

Multiple Wasp Stings Causing Systemic Envenomation: A Case Report

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Abstract

Multiple wasp stings can result in severe systemic toxicity far beyond immediate IgE-mediated allergic reactions. Massive envenomation delivers a high load of direct toxins that can cause intravascular hemolysis, rhabdomyolysis, acute kidney injury (AKI), hepatic dysfunction, and multi-organ dysfunction syndrome (MODS).

A 56-year-old previously healthy male farmer presented with generalized anasarca, facial puffiness, deep jaundice, and anuria 72 hours after sustaining approximately 40 wasp stings across his upper body. Physical examination revealed extensive necrotic skin lesions at the sting sites. Laboratory evaluation demonstrated Stage 3 acute kidney injury (serum creatinine 6.4 mg/dL), severe rhabdomyolysis (creatinine phosphokinase 24,500 U/L), intravascular hemolysis (LDH 1,850 U/L, indirect hyperbilirubinemia), and transaminitis. The patient was admitted to the Intensive Care Unit (ICU) and managed with intensive supportive therapy, broad-spectrum antibiotics, and 5 sessions of intermittent hemodialysis. Over a 14-day hospital stay, his renal function and metabolic parameters progressively normalized. At a 4-week follow-up, his renal function had completely recovered to baseline.

Massive wasp envenomation is a medical emergency capable of causing pigment-induced nephropathy and MODS via direct venom toxicity. Early recognition, aggressive supportive care, and timely initiation of renal replacement therapy are critical to ensuring survival and complete reversal of organ dysfunction.

Keywords

Wasp sting, Acute kidney injury, Hemolysis, Rhabdomyolysis, Multi-organ dysfunction syndrome, Hemodialysis.

Introduction

Wasp stings are a common environmental hazard worldwide. While most incidents result in self-limiting localized inflammatory responses or, occasionally, IgE-mediated anaphylaxis, massive envenomation

from multiple stings represents an entirely distinct clinical entity [1]. In these cases, pathology is driven by direct, dose-dependent venom toxicity rather than an allergic mechanism [2].

Venom from the family Vespidae contains a potent cocktail of biologically active

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macromolecules, including enzymes (phospholipase A₂ and hyaluronidase), polypeptides (mastoparan and melittin-like peptides), and vasoactive amines (histamine, serotonin, kinins, and acetylcholine) [3]. When injected in large quantities, these substances exert direct cytotoxic effects, causing widespread damage such as rhabdomyolysis, intravascular hemolysis, and direct acute tubular necrosis (ATN) [4]. Acute kidney injury (AKI) is the most critical systemic complication of massive envenomation, frequently demanding renal replacement therapy (RRT) [5]. This report outlines a case of severe multi-organ dysfunction syndrome (MODS) following massive wasp envenomation, highlighting the successful deployment of early intermittent hemodialysis and intensive supportive care.

Case Presentation

A 56-year-old previously healthy male farmer presented to the emergency department with a 24-hour history of complete anuria, progressive generalized body swelling, facial puffiness, and yellow discoloration of the eyes.

Three days prior to admission, while clearing brush outdoors, the patient was attacked by a swarm of wasps, sustaining approximately 40 stings concentrated on his left shoulder, upper back, neck, scalp, and left upper limb. He experienced immediate, severe localized burning pain and rapid swelling of the left arm. Over the subsequent 48 to 72 hours, his local symptoms expanded into systemic dysfunction: he developed gross dark-brown urine that rapidly progressed to absolute anuria, alongside generalized fluid retention and deep jaundice. He had no relevant medical history, including no prior diagnoses of diabetes, hypertension, chronic kidney disease, liver disease, or recent exposure to nephrotoxic medications.

On arrival, the patient appeared acutely ill, distressed, and severely volume-overloaded. Vital signs were Blood Pressure: 160/95 mmHg, Pulse Rate: 108 beats/minute (sinus tachycardia), Respiratory Rate: 24 breaths/minute, Temperature: 36.8°C (Afebrile) and Oxygen Saturation: 96% on room air. Physical Examination revealed mild pallor, deep scleral icterus; marked periorbital and facial edema; **(Figure 1)** generalized pitting edema (anasarca); severe non-pitting edema of the

entire left upper limb. Numerous clustered punctate sting marks were present, showing central blackish necrosis (ranging from 3 to 7 mm) surrounded by irregular zones of erythema and induration across the left shoulder, posterior neck, upper back, and left arm. **(Figure 2)** Cardiovascular, respiratory, and neurological examinations were otherwise within normal limits, with no signs of active anaphylaxis (e.g., wheezing, stridor, or urticaria).



Fig. 1 Marked facial and periorbital edema and scleral icterus



Fig. 2 Multiple punctate sting marks

Investigations

Initial laboratory evaluation confirmed multi-organ involvement characterized by severe Stage 3 AKI, severe rhabdomyolysis, acute hepatocellular injury, and intravascular hemolysis. Urinalysis performed on a tiny volume of dark-brown urine obtained via

catheterization just prior to true anuria revealed a 4+ dipstick positive for blood, but microscopic examination showed only 1–2 red blood cells per high-power field. This striking discrepancy confirmed massive pigmenturia (hemoglobinuria and myoglobinuria).

Table 1: Laboratory Parameters During Admission and Follow-up

Parameter (Normal Range)	day 1	Day 3	Day 5	Day 8	day 14	Day 30
Hemoglobin (13.5–17.5 g/dL)	11.2	9.8	9.1	10.0	11.8	13.6
White Blood Cells (4.0–11.0 x 10 ⁹ /L)	17.4	14.2	11.5	9.2	7.4	6.5
Blood Urea Nitrogen (7–20 mg/dL)	66	84	55	32	16	14
Serum Creatinine (0.7–1.3 mg/dL)	6.4	8.1	5.2	2.8	1.1	0.8
Serum Potassium (3.5–5.1 mEq/L)	6.3	5.4	4.6	4.2	4.0	4.3
Total Bilirubin (0.2–1.2 mg/dL)	8.4	9.2	5.1	2.3	1.0	0.6
Indirect Bilirubin (<0.8 mg/dL)	6.1	6.8	3.5	1.4	0.5	0.2
AST (10–40 U/L)	450	520	210	74	32	22
ALT (7–56 U/L)	380	410	195	68	35	24
Creatine Kinase (55–170 U/L)	24500	18200	6400	1150	140	95
LDH (140–280 U/L)	1850	2100	1120	540	240	190

Management and Hospital Course

The patient was immediately admitted to the Medical Intensive Care Unit (MICU) under a multidisciplinary team. Due to clinical fluid overload (anasarca, hypertension, and elevated jugular venous pressure) secondary to anuria, aggressive fluid resuscitation was avoided. Central venous access was secured, and strict fluid restriction was enforced. Severe hyperkalemia (Potassium 6.3 mEq/L) accompanied by metabolic acidosis (bicarbonate 12 mEq/L) was treated urgently with intravenous calcium gluconate, insulin-dextrose infusion, and sodium bicarbonate nebulization. Intravenous hydrocortisone (100 mg every 8 hours) and chlorpheniramine were initiated to counter systemic inflammatory capillary leak syndrome. Due to the extensive skin necrosis and high risk of secondary bacterial infection from environmental exposure, broad-spectrum antibiotic therapy (Intravenous Piperacillin/Tazobactam 4.5g every 8 hours, dose-adjusted for renal failure) was started alongside meticulous local debridement and aseptic dressings. Given the refractory anuria, severe volume overload, and metabolic imbalances, intermittent hemodialysis (IHD) was initiated on Day 1 via a temporary

right internal jugular dialysis catheter. The patient underwent a total of 5 sessions of intermittent hemodialysis over the first 7 days of admission. By Day 5, the patient entered the diuretic phase of ATN, with urine output rising from 0 mL/day to 1,800 mL/day, eventually peaking at 3,500 mL/day on Day 8. Following the resolution of the anuria, the generalized anasarca and upper limb swelling dramatically improved. Liver transaminases and hyperbilirubinemia steadily trended down, reflecting the cessation of active hemolysis and the resolution of direct hepatic toxicity. The necrotic skin lesions demarcated cleanly and began granulating well without requiring surgical grafting. The patient was safely stepped down to the medical ward on Day 9 and discharged on Day 14 in stable clinical condition with completely normalized serum creatinine (1.1 mg/dL). At his 4-week outpatient nephrology follow-up (Day 30), he remained asymptomatic, his skin lesions had completely epithelialized, and his renal function remained excellent (creatinine 0.8 mg/dL).

Discussion

Massive hymenoptera envenomation from multiple stings triggers a toxemic syndrome distinct

from classical anaphylactic shock [1, 2]. While a single sting can kill an individual highly allergic to wasp venom, a non-allergic individual can tolerate multiple stings, but a threshold of approximately 20 to 30 massive stings delivers a lethal dose of venom components capable of causing multi-organ dysfunction [4, 5].

The etiology of AKI in our patient was clearly multifactorial [6]. First, pigment nephropathy played a major role: massive rhabdomyolysis (evidenced by CPK >24,000 U/L) and intravascular hemolysis (evidenced by marked indirect hyperbilirubinemia, low hemoglobin, and elevated LDH) released massive amounts of free myoglobin and hemoglobin into the circulation. In the acidic microenvironment of the renal tubules, these pigments precipitate with Tamm-Horsfall protein, forming obstructive casts and inducing severe lipid peroxidation. Second, direct renal tubular toxicity occurs because wasp venom components like phospholipase A₂ and mastoparan cause direct damage to the proximal tubular epithelial cells, accelerating acute tubular necrosis [3, 7]. Third, direct venom-mediated release of potent vasoconstrictors (endothelin) coupled with systemic capillary leak leads to profound intrarenal vasoconstriction, compounding ischemic ATN [6].

Hepatic involvement, manifested here by transient transaminitis and deep jaundice, occurs due to direct toxic damage inflicted on hepatocytes by the venom components absorbed into the portal circulation [5, 7]. Severe localized limb swelling and generalized anasarca were driven by a combination of venom-induced endothelial pore widening (capillary leak syndrome) and profound salt and water retention from anuric renal failure [1]. Literature indicates that mortality from massive envenomation remains high if RRT is unavailable or delayed [5, 8]. Hemodialysis serves a multi-pronged purpose: it corrects life-threatening hyperkalemia, manages volume overload, corrects severe metabolic acidosis, and aids in the clearance of smaller uremic toxins while the renal tubules regenerate [2, 8]. In this case, the rapid initiation

of RRT on Day 1 successfully bridged the patient through the peak of toxemia and ATN, resulting in a full, complication-free recovery of renal function.

Conclusion

Massive wasp envenomation is a critical toxicological emergency that causes severe, multi-system damage via direct venom actions. Clinicians must recognize that pigment-induced AKI, rhabdomyolysis, and hepatic dysfunction can evolve rapidly over 48 to 72 hours, even without an initial allergic reaction. Early, aggressive supportive management, proactive wound monitoring, and the timely initiation of hemodialysis are vital to preventing permanent renal damage and reducing mortality.

References

1. Vikrant S, Parashar A. Wasp sting-induced acute kidney injury: a serious complication of hymenoptera envenomation. *Clin Kidney J.* 2017;10(5):671-676.
2. Zhang L, Yang Y, Tang X, et al. Acute kidney injury following multiple wasp stings: a case series and literature review. *Kidney Int.* 2021;99(4):942-951.
3. Grisotto LS, Mendes GE, Castro I, et al. Mechanisms of wasp venom-induced acute kidney injury. *Toxicon.* 2006;48(8):962-970.
4. Chao-Wei L, Sheng-Wen H, Chin-Liang M, et al. Multiple wasp stings associated with rhabdomyolysis, intravascular hemolysis, and acute kidney injury. *Am J Kidney Dis.* 2019;74(3):412-416.
5. Sakhuja V, Bhalla A, Pereira BJ, et al. Acute renal failure following multiple wasp stings. *Nephrol Dial Transplant.* 1999;14(4):1012-1014.
6. Radhakrishnan J, Al-Awqati Q. Pigment nephropathy from rhabdomyolysis and hemolysis: pathogenetic insights. *J Am Soc Nephrol.* 2018;29(12):2761-2763.
7. Dhanapriya J, Dineshkumar T, Gopalakrishnan N, et al. Acute kidney injury following wasp stings: a report of 12 cases from a tertiary care center. *Indian J Nephrol.* 2016;26(4):254-258.
8. Fitzgerald JC, Topjian AA, Mclean CA, et al. Multi-organ dysfunction syndrome following massive hymenoptera envenomation in pediatric patients: the role of extracorporeal therapies. *Intensive Care Med.* 2015;41(7):1310-1315.

A rare finding in a case of Carcinoma Cervix detected with MRI performed with vaginal jelly – A case report

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Abstract

Background: Imaging plays a pivotal role in cervical cancer management which was recently incorporated in the FIGO 2021 staging. MRI with vaginal opacification has increased accuracy of staging. **Our case:** 58 years postmenopausal lady presented with vaginal discharge and bleeding for 7 months. Biopsy from infiltrative growth in cervix showed squamous cell carcinoma. Radiological staging was performed incorporating CEMRI Pelvis with vaginal opacification. It showed 2.6 cm heterogeneously contrast enhancing lesion at cervix with vaginal involvement and focal perforation in the posterior wall with extravasation of hypodense fluid in the extra peritoneal rectovaginal pouch. **discussion and conclusion:** Ultrasound gel with its advantage of viscosity and high signal intensity on T2 weighted images has been used in most studies. The detection of unusual very small defect in posterior vaginal wall that may be missed by conventional MRI protocol signifies the importance of vaginal opacification method for radiological staging of cervical cancer.

Keywords

ACervical cancer, MRI with ultrasound jelly, Vaginal opacification

Introduction

India is contributing about 20% of new cases and 25% of deaths due to cervical cancer globally.¹ The updated FIGO staging (2018) gives added importance to MRI for pre operative staging to improve treatment selection and uniform comparison of outcomes.² For decades, MRI examination with vaginal opacification are being performed in cervical cancers for pre operative staging and RT planning in many centers worldwide. MRI has an accuracy of 85 % for staging cervical cancer which could be further improved with use of vaginal jelly.³ Our case report suggests the rare but important findings that could be missed by conventional MRI protocol.

Case report

A 58 years' postmenopausal lady with four living issues presented to outpatient department with history of discharge per vagina for 7 months and intermittent bleeding per vagina for 3 months. There was no significant family history. On examination her performance status was good. Neck nodes and inguinal nodes were not palpable. Per speculum examination showed infiltrative growth of cervix involving anterior and posterior vaginal wall. Per vaginal and rectal examination corroborates with per speculum findings with no involvement of parametria or rectal mucosa. Systemic examination revealed no specific abnormalities. Cervical tissue biopsy showed poorly differentiated squamous carcinoma (p16 positive). CEMRI pelvis with

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vaginal jelly and CECT Thorax and abdomen was performed for radiological staging.

Radiological procedure and findings: MRI pelvis was performed with 1.5 Tesla MRI system Simens Avantofit. 30 ml of ultrasound jelly was instilled into the vagina using a 50 cc syringe prior to the scan while the patient is lying on the couch. 48 Channel flex Body Coil (HD) was used for MRI acquisition.

Pre contrast T2, T1, STIR, T1FS axial, coronal, saggital and post contrast T1FS axial, coronal, saggital with delayed axial was performed. It showed 2.6 cm heterogeneously contrast enhancing soft tissue lesion at cervix with involvement of upper anterior and posterior vagina with focal perforation of 5 mm in the posterior wall with extravasation of hypodense fluid in the extra peritoneal rectovaginal

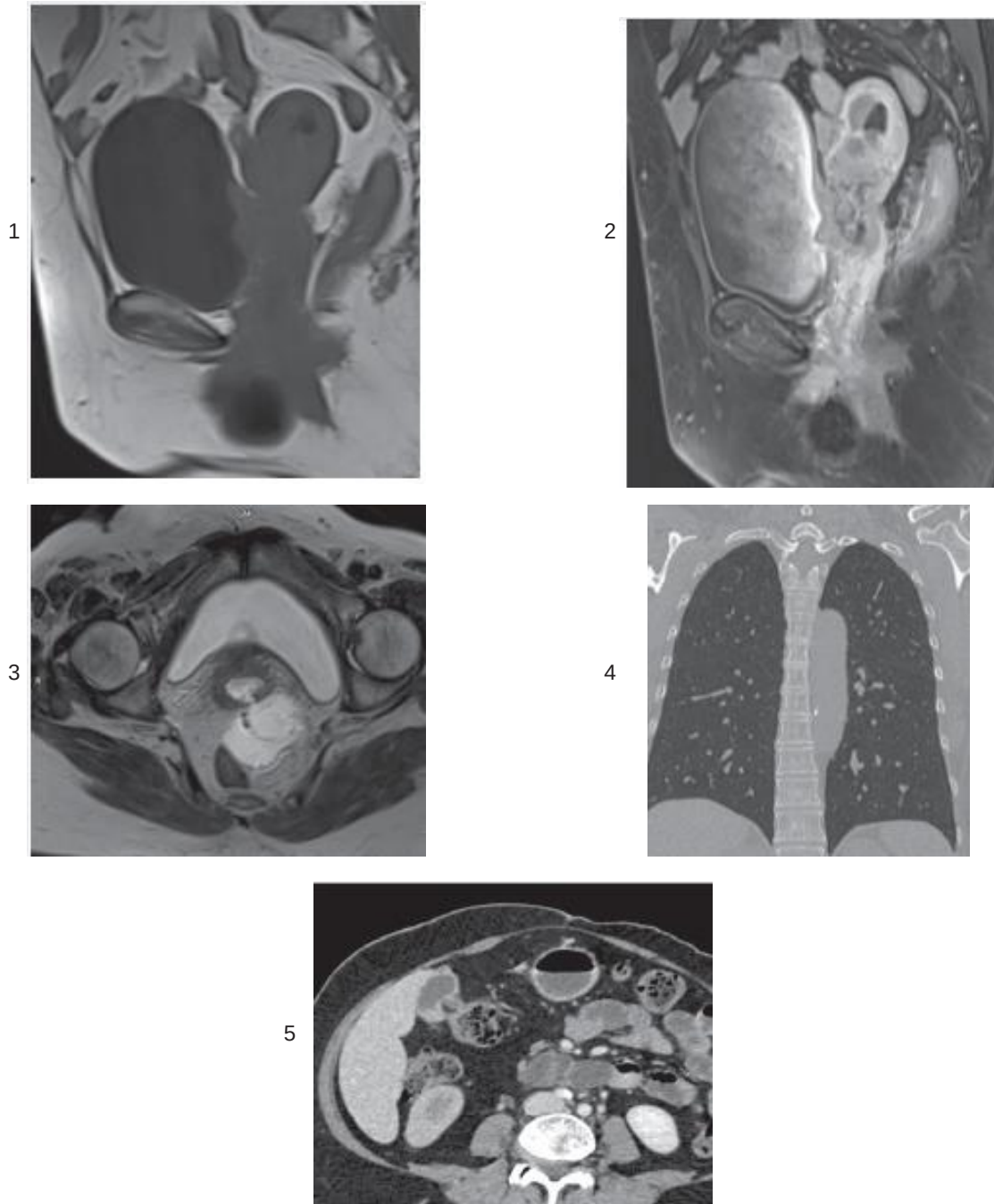


Fig. 1 & 2. Pre and postcontrast T1W saggital images show heterogeneously enhancing soft tissue in cervix. **Fig. 3.** T2W axial image shows focal perforation in posterior fornix having extravasation of fluid content. **Fig 4 & 5** CT images show no evidence of metastasis in thorax and retroperitoneum..

pouch. The lesion is inseparable from the posterior wall of urinary bladder and not invading bilateral parametrium. CECT Thorax and abdomen showed no metastasis. Post imaging: She presented with inflammatory response to ultrasound gel which was managed conservatively.

Discussion

In our study we detected very small defect (5 mm) over posterior vaginal wall that was missed by clinical examination. Ultrasound gel with its advantage of viscosity and high signal intensity on T2 weighted images has been used for better delineation of vaginal cavity.⁴ Instillation of 50 to 100 cc of aqueous gel provides adequate distension of vaginal canal with more accurate evaluation of tumour morphology and vaginal involvement.⁵ Some studies showed 30 ml is enough to distend the vagina beyond its natural form.⁶ Radiological staging with MRI before and after opacification revealed that opacification correctly lowered staging in 7 patients, compared to pre-opacification MRI and that it accurately increased it in 3, changing treatment planning in 14% of cases, with appropriate treatment chosen in 90% of cases versus 79% without use of vaginal opacification.^(7,8) The detection of this vaginal wall defect helps the radiotherapist for proper radiotherapy planning as in our case. As the ultrasound jelly is slowly absorbable, it hardly stays in the rectovaginal area and causes abscess

Conclusion

The use of vaginal jelly during performing MRI in the preoperative workup of patients with cervical cancer provides better anatomical involvement. However the subcentimetric vaginal wall defect that can be missed by clinical and conventional radiological examination was accurately picked up by vaginal opacification. Hence this method must be included in radiological staging of cervical cancers.

References

- Ramamoorthy, T., Kulothungan, V., Sathishkumar, K. et al. Burden of cervical cancer in India: estimates of years of life lost, years lived with disability and disability adjusted life years at national and subnational levels using

the National Cancer Registry Programme data. *Reprod Health* 21.2024; 111. doi:10.1186/s12978-024-01837-7.

- Miriam Y. Salib, James H. B. Russell, Victoria R. Stewart, Siham A. Sudderuddin, Tara D. Barwick, Andrea G. Rockall, Nishat Bharwani. 2018 FOGO Staging Classification for Cervical Cancer: Added Benefits of Imaging. 2020. 40; 1823-1824. *RadioGraphics*.
- Ozsarlak O, Tjalma W, Schepens E, et al. The correlation of preoperative CT, MR imaging, and clinical staging (FIGO) with histopathology findings in primary cervical carcinoma. *Eur Radiol*. 2003; 13:2338–2345.
- Kikuchi I, Kuwatsuru R, Yamazaki K, Kumakiri J, Aoki Y, Takeda S. Evaluation of the usefulness of the MRI jelly method for diagnosing complete cul-de-sac obliteration. *Biomed Res Int*. 2014;2014:437962. doi: 10.1155/2014/437962.
- Dimopoulos JCA, Schard G, Berger D, et al. Systematic evaluation of MRI findings in different stages of treatment of cervical cancer: potential of MRI on delineation of target, pathoanatomic structures, and organs at risk. *Int J Radiat Oncol Biol Phys*. 2006; 64: 1380–8.
- Skehan K, Richardson M, O'Connor LM, Dickson S, Martin K, Govindarajulu G, Sridharan S. Viscous Aqueous Gel Illustrating Natural Anatomy: The VAGINA method in gynaecological MRI simulation. *J Med Radiat Sci*. 2024;71(1):150-155. doi: 10.1002/jmrs.716.
- Akata D, Kerimoglu U, Hazirolan T, Karcaaltincaba M, Köse F, Ozmen MN, et al. Efficacy of transvaginal contrast-enhanced MRI in the early staging of cervical carcinoma. *Eur Radiol*. 2005;15:1727-1733.
- Balleyguier C, Sala E, da Cunha T, et al. Staging of uterine cervical cancer with MRI: guidelines of the European Society of Urogenital Radiology. *Eur Radiol*. 2011; 21: 1102–10.

MRI – Magnetic resonance imaging

FIGO - International Federation of Gynecology and Obstetrics

CEMRI - Contrast-Enhanced Magnetic Resonance Imaging

CECT - Contrast-Enhanced Computed Tomography

Conflict of Interest – No conflict of interest to disclose

Funding – None

Ethics – Not applicable

Acknowledgement.- my original article (case report) 'A rare finding in a case of Carcinoma Cervix detected with MRI performed with vaginal jelly' in your Journal. It is a technique of Imaging which can help the clinician to tailor cervical cancer treatment depending on its finding. Hence this technique should be included in every case of cervical cancer.

Beyond Hyperglycemia: A Case of Euglycemic Diabetic Ketoacidosis

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Abstract

Euglycemic diabetic ketoacidosis (EDKA) is an increasingly recognised complication of sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy, characterised by high anion gap metabolic acidosis and ketonaemia in the absence of the marked hyperglycaemia that typically prompts clinicians to consider diabetic ketoacidosis. We report the case of a 46-year-old woman with type 2 diabetes mellitus, recently started on dapagliflozin, who presented with a four-day history of dyspnoea, nausea, vomiting and abdominal pain following a week of inadequate oral intake and diminished appetite due to religious fasting. She was severely dehydrated and drowsy at presentation, with tachycardia, tachypnoea and Kussmaul breathing, and arterial blood gas analysis revealed profound acidaemia (pH 6.9, a markedly low bicarbonate 2.0 mmol/L (and a raised anion gap, (29) despite a capillary blood glucose of only 244 mg/dL. She was managed in the intensive care unit with aggressive fluid resuscitation, intravenous insulin infusion, sodium bicarbonate and potassium replacement, with discontinuation of the offending drug, and made a complete recovery, being discharged on day eight. This case underscores the need for a high index of suspicion for EDKA in SGLT2 inhibitor-treated patients presenting with unexplained metabolic acidosis and gastrointestinal symptoms, even when glucose values appear reassuring.

Keywords

Euglycemic diabetic ketoacidosis ; SGLT2 inhibitor ; dapagliflozin ; high anion gap metabolic acidosis ; type 2 diabetes mellitus

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors — canagliflozin, dapagliflozin and empagliflozin among others — have become a cornerstone of modern type 2 diabetes management, valued for their glycaemic efficacy as well as their demonstrated cardiovascular and renal protective effects. Their mechanism of action, inhibition of proximal tubular glucose reabsorption, produces controlled glucosuria and a consequent reduction in plasma glucose independent of insulin secretion. This same mechanism, however, predisposes to an important and under-recognised adverse effect:

euglycemic diabetic ketoacidosis (EDKA).

EDKA was first described by Munro and colleagues in 1973, well before the advent of SGLT2 inhibitors, in a series of patients with diabetic ketoacidosis whose glucose values were unexpectedly near-normal [3]. Interest in the entity was renewed after the United States Food and Drug Administration issued a safety communication in May 2015 warning that SGLT2 inhibitors could precipitate ketoacidosis with only mild to moderate glucose elevation [6]. Unlike classical diabetic ketoacidosis, which is defined in most guidelines by a blood glucose exceeding 250 mg/dL, EDKA

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presents with glucose values typically below 200–250 mg/dL alongside a high anion gap metabolic acidosis and significant ketonaemia [1,2]. This atypical biochemical picture removes the single most familiar diagnostic cue clinicians rely on, and as a result EDKA is frequently missed or diagnosed late, particularly in busy emergency settings where a normal or only mildly elevated capillary glucose can falsely reassure the treating team.

Case Presentation

History

A 46-year-old woman with a known history of type 2 diabetes mellitus presented with dyspnoea, nausea, vomiting and abdominal pain for four days. These symptoms were preceded by inadequate oral intake due to religious fasting and a diminished appetite over the preceding week. Her drug history was notable for the recent addition of dapagliflozin, an SGLT2 inhibitor, to her existing antidiabetic regimen.

Examination

On presentation, she was severely dehydrated and drowsy. Vital signs revealed a blood pressure of 130/86 mmHg, pulse rate of 126/min, respiratory rate of 28/min with Kussmaul breathing, oxygen saturation of 96% on 2 litres of supplemental oxygen, temperature of 97.8°F, and a capillary blood glucose of 244 mg/dL. Systemic examination was otherwise unremarkable. Given the severity of her clinical state, she was admitted directly to the intensive care unit, where her airway was secured to ensure adequate protection.

Investigations

Arterial blood gas analysis demonstrated severe metabolic acidosis, with a pH of 6.9, serum bicarbonate of 2.0 mmol/L, serum lactate of 2.15 mmol/L, and a markedly elevated anion gap of 29. Blood and urine studies showed elevated ketone levels. Notably, her capillary blood glucose was only 244 mg/dL — not the marked hyperglycaemia typically expected in diabetic ketoacidosis. Haematological and inflammatory workup revealed neutrophilic leucocytosis with an elevated C-reactive

protein, and renal parameters showed a marginally raised urea of 54 mg/dL and creatinine of 1.5 mg/dL, consistent with dehydration-related prerenal impairment. The constellation of severe acidosis, elevated anion gap and significant ketosis with near-normal glucose, in a patient recently started on an SGLT2 inhibitor and with a clear precipitating history of prolonged fasting, established the diagnosis of severe EDKA secondary to SGLT2 inhibitor use.

Table 1: Summary of key admission investigations.

Parameter	Patient value on admission	Reference Range
pH Arterial	6.9	7.45 – 7.35
bicarbon- Serum (-HCO ₃) ate	L/mmol 2.0	L/mmol 26 – 22
lactate Serum	L/mmol 2.15	L/mmol 2.2 – 0.5
gap Anion	29	L/mEq 12 – 8
blood Capillary glucose	dL/mg 244	dL/mg 140 – 70 (random)
urine/Blood ketones	Elevated	Negative
leucocyte Total count	Neutrophilic leucocytosis	11,000 – 4,000 μ L/
pro- reactive-C (CRP) tein	Elevated	L/mg 5 >
urea Blood	dL/mg 54	dL/mg 43 – 17
creatinine Serum	dL/mg 1.5	dL/mg 1.2 – 0.6

Treatment and Outcome

The offending agent, dapagliflozin, was discontinued immediately. The patient was treated with aggressive intravenous fluid resuscitation, comprising an initial 3-litre bolus followed by a continuous infusion at 300 mL/hour, in conjunction with 200 mEq of sodium bicarbonate, an intravenous insulin infusion, and potassium replacement therapy titrated to serial electrolyte monitoring. Serial arterial blood gas analyses demonstrated a progressive resolution of the metabolic acidosis, with normalisation of the anion gap and clearance of ketonaemia over five days. The patient showed steady clinical improvement throughout her admission and was discharged without complications on day eight, with normalised blood pH and resolution of ketonaemia. She was counselled against restarting an SGLT2 inhibitor

and was transitioned to an alternative antidiabetic regimen with clear guidance on sick-day rules and adequate oral intake.

Discussion

This case illustrates several teaching points that are directly relevant to clinical practice in an era of expanding SGLT2 inhibitor use. First, EDKA is defined by the co-occurrence of high anion gap metabolic acidosis and ketonaemia with blood glucose typically below 200–250 mg/dL, in contrast to classical diabetic ketoacidosis where glucose usually exceeds 250 mg/dL [1,2]. Applying pH, bicarbonate and anion gap-based criteria for diagnosis and severity — rather than glucose thresholds — is essential to avoid missing EDKA [2].

Second, the pathophysiology of SGLT2 inhibitor-associated EDKA is multifactorial. Glucosuria induced by SGLT2 blockade lowers plasma glucose and insulin requirement, while a relative or absolute reduction in insulin, combined with a paradoxical rise in glucagon, shifts metabolism from carbohydrate to lipid oxidation. Enhanced lipolysis increases free fatty acid delivery to the liver, and upregulated hepatic ketogenesis follows, compounded by increased renal reabsorption of ketone bodies [4]. Volume depletion from osmotic diuresis further impairs renal clearance of the resulting acid load. In our patient, this cascade was set in motion against a background of markedly reduced carbohydrate and fluid intake due to religious fasting — a well-recognised precipitant, alongside infection, surgery, alcohol use and very-low-carbohydrate diets [4,5]. The elevated CRP and neutrophilic leucocytosis in this patient also raised the possibility of a superimposed infective trigger, illustrating that precipitants often coexist rather than acting in isolation.

Third, the diagnostic delay inherent to EDKA carries real clinical consequences. Because glucose values do not trigger the usual clinical suspicion for ketoacidosis, patients may present late, as this patient did, with several days of gastrointestinal and respiratory symptoms culminating in severe acidaemia and reduced responsiveness. A high index of suspicion is warranted in any patient on an SGLT2 inhibitor presenting with unexplained nausea, vomiting, abdominal pain or dyspnoea, regardless

of the glucose reading, and serum or urine ketones together with a venous or arterial blood gas should be checked liberally in this population [2,6].

Management follows the same principles as conventional DKA: prompt discontinuation of the SGLT2 inhibitor, aggressive isotonic fluid resuscitation, intravenous insulin infusion with concurrent dextrose supplementation once glucose falls below approximately 200 mg/dL to avoid hypoglycaemia while ketosis is cleared, careful potassium replacement, and judicious use of bicarbonate reserved for severe acidaemia. Identification and treatment of the precipitating cause is equally important. Following resolution, SGLT2 inhibitors are generally not restarted, and patients require education on sick-day medication rules, adequate hydration and early presentation with warning symptoms [1,5]. Regulatory bodies, including the FDA and European Medicines Agency, have highlighted this risk since 2015, and post-marketing surveillance continues to refine understanding of incidence and risk factors, though absolute risk in unselected type 2 diabetes populations remains low [6,7].

Conclusion

This case highlights the importance of maintaining a high index of suspicion for euglycemic diabetic ketoacidosis in diabetic patients receiving SGLT2 inhibitors, especially in the presence of precipitating factors such as prolonged fasting. Because the hallmark hyperglycaemia of classical DKA may be absent, diagnosis relies on recognising the clinical picture and confirming high anion gap metabolic acidosis with ketonaemia irrespective of glucose values. Early recognition, prompt discontinuation of the offending agent, and timely institution of standard DKA management are essential to reduce morbidity and mortality associated with this increasingly encountered complication.

Declarations

Informed consent was obtained from the patient for publication of this case report.

Conflict of interest: The authors declare no conflict of interest.

Funding: None declared.

References

1. Chow E, Clement S, Garg R. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. *BMJ Open Diabetes Res Care*. 2023;11:e003666.
2. Rawla P, Vellipuram AR, Bandaru SS, Pradeep Raj J. Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. *Endocrinol Diabetes Metab Case Rep*. 2017 Sep 4;2017:17-0081.
3. Munro JF, Campbell IW, McCuish AC, Duncan LJ. Euglycaemic diabetic ketoacidosis. *Br Med J*. 1973;2(5866):578–580.
4. Somagutta MR, Agadi K, Hange N, Jain MS, Batti E, Emuze BO, Amos-Arowoshegbe EO, Popescu S, Hanan S, Kumar VR, Pormento K. Euglycemic diabetic ketoacidosis and sodium-glucose cotransporter-2 inhibitors: a focused review of pathophysiology, risk factors, and triggers. *Cureus*. 2021;13(3):e13665.
5. Dutta S, Kumar T, Singh S, Ambwani S, Charan J, Varthya SB. Euglycemic diabetic ketoacidosis associated with SGLT2 inhibitors: a systematic review and quantitative analysis. *J Family Med Prim Care*. 2022;11(3):927–940.
6. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Silver Spring, MD: FDA; 15 May 2015.
7. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*. 2015;38(9):1638–1642.

Post Exposure Prophylaxis. Following accidental exposure to blood

Dr. B. B. Rewari

Introduction

Accidental exposure to blood and other body fluids or tissues is common among health care providers despite following universal work precautions. Such exposure can lead to lot of anxiety and must be dealt as an emergency. Hence adequate knowledge about the management of such exposures is essential to allay the fear of acquiring various blood borne infections, especially HIV and hepatitis.

The term "Health Care Personnel (HCP)" does not mean only doctors or nurses but includes any persons working in healthcare settings who are potentially exposed to infectious materials (e.g. blood, tissue, and specific body fluids and medical supplies, equipment, or environmental surfaces contaminated with these substances).

The term "Exposure" is not only a percutaneous injury (e.g. needle-stick or cut with a sharp instrument) but also includes contact with the mucous membranes of the eye or mouth, with non-intact skin (when the exposed skin is chapped skin or afflicted with dermatitis) or even with intact skin when the duration of contact is prolonged with blood or other potentially infectious body fluids.

Post exposure prophylaxis (PEP) refers to the comprehensive management instituted to minimize the risk of infection following potential exposure to blood-borne pathogens (HIV, HBV, HCV). This includes first aid, counselling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person and depending on the risk assessment, the provision of short term (4 weeks) of antiretroviral

drugs, with follow up and support including maintaining confidentiality.

In addition to HCP following occupational exposure, PEP can also be provided to sexual assault victims, even though they are categorized under non-occupational category.

Average Risk of Acquiring HIV, Hepatitis B, Hepatitis C after Occupational Exposure

The average risk of acquiring HIV infection after different types of occupational exposure is low compared to risk of acquiring infection with HBV or HCV.

In terms of occupational exposure, the important routes are needle stick exposure (0.3% risk for HIV, 9-30% for HBV, and 1-1.8% for HCV) and mucous membrane exposure (0.09% for HIV).

The risk of acquiring infection varies with type of body fluid (Table 1)

Table 1: Risk of Exposure from different body fluids

Exposure to body fluids considered 'at risk'	Exposure to body fluids considered 'not at risk,' unless these fluids contain visible blood
Blood Semen Vaginal secretions Cerebrospinal fluid Synovial, pleural, peritoneal, pericardial fluid Amniotic fluid Other body fluids contaminated with visible blood	Tears Sweat Urine & faeces Saliva Sputum Vomit

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The common type of needle stick injuries is shown in Figure 1.

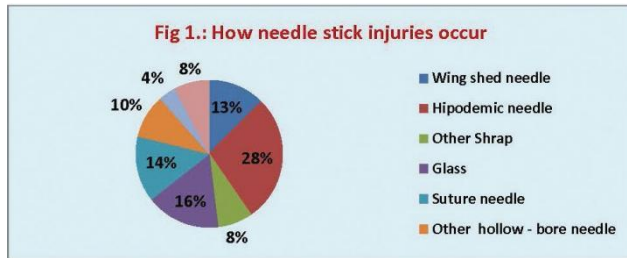


Fig. 1. Common type of needle stick injuries

The common activities that can lead to exposure are shown in Figure 2

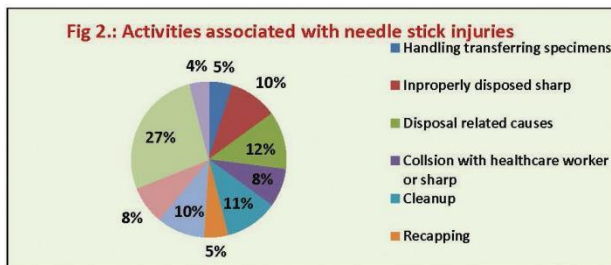


Fig. 2. Common activities associated with exposure

How to protect oneself from needle stick/ sharps injuries:

- Strict compliance to universal work precautions
- Avoid the use of injections where safe and effective alternatives are available e.g. oral, drugs
- Avoid recapping needles (Figure 3)
- Plan for safe handling and disposal of needles after use
- Promptly dispose of used needles in appropriate sharps disposal containers
- Report all needle stick and sharps-related injuries promptly to ensure that you
 - Receive appropriate follow-up care
 - Participate in training related to infection prevention
 - Use devices with safety features provided by the institute (wherever possible)

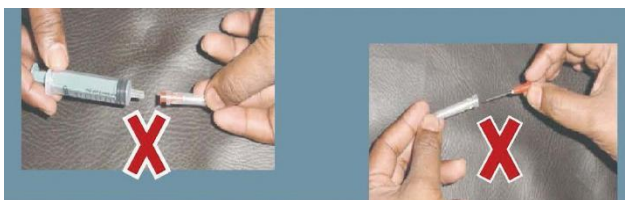


Fig. 3. "Do Not Recap Needle"

Minimise the use of sharps/injections: Try to minimize the use of invasive interventions for example — to use oral drugs in place of injections wherever possible. Wherever the use of sharps is indicated, try to use safer alternatives where practical and possible within the limitations of the system.

Protection against hepatitis B: All Health Care Providers (HCP) should be vaccinated against the hepatitis B virus. The vaccination for Hepatitis B consists of 3 doses: baseline, 1 month, and 6 months. Most (99%) seroconvert after completing the full course. There is no vaccine or prophylaxis against hepatitis C.

Table 2: Universal Precautions.

Universal precautions are intended to prevent the exposure of health-care workers and patients to blood borne pathogens. These must be practiced in regard to the blood and body fluids of all patients, regardless of their infection status.

Universal precautions include:

- Hand-washing before and after all medical procedures
- Safe handling and immediate safe disposal of sharps: not recapping needles; using special containers for sharp disposals; using needle cutter/destroyers; using forceps instead of fingers for guiding sutures; using vacutainers where possible
- Safe decontamination of instruments
- Use of protective barriers whenever indicated to prevent direct contact with blood and body fluid such as gloves, masks, goggles, aprons, and boots. A HCP who has a cut or abrasion should cover the wound before providing care
- Safe disposal of contaminated waste



Fig. 4. "Precautions during common procedures"

Always use protective gear/Consider all blood samples as potentially

Follow universal precautions practice-Safe handling of sharp instruments-Use

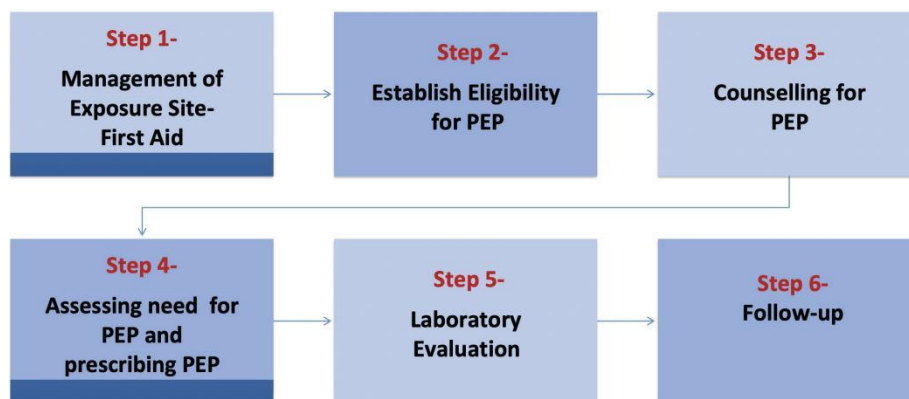


Fig. 5. "Directional Flow for management of an exposed person"

Management of the Exposed Person

The key steps involved in management of an exposure to blood and other body fluids is depicted in Figure 5 below:

Step 1: Management of Exposure Site-First Aid

For skin—if the skin is pierced by a needle-stick or sharp instrument:

- Immediately wash the wound and surrounding skin with water and soap and rinse
- Do not scrub
- Do not use antiseptics or skin washes
- Don't use Bleach, chlorine, alcohol, betadine
- **After a splash of blood or body fluids:**
- **To unbroken skin:**
 - Wash the area immediately
 - Do not use antiseptics

• For the eye:

- Irrigate exposed eye immediately with water or normal saline
- Sit in a chair, tilt head back and ask a colleague to gently pour water or normal saline over the eye
- If wearing contact lens, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean them in the normal manner. This will make them safe to wear again
- Do not use soap or disinfectant on the eye

• For Mouth:

- Spit fluid out immediately
- Rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times

- Do not use soap or disinfectant in the mouth
- Consult the designated physician of the institution for management of the exposure immediately

Step 2: Establish eligibility for PEP

A designated person/trained doctor must assess the risk of HIV and HBV transmission following an AEB. This evaluation must be made rapidly, so as to start any treatment as soon as possible after the accident. This assessment must be made thoroughly (because not every AEB requires prophylactic treatment).

The first dose of PEP should be administered ideally within 2 hours (but certainly within the first 72 hours) of exposure and the risk evaluated as soon as possible.

Two main factors determine the risk of infection:

1. the nature of exposure and
2. the status of the source patient.

The exposures that warrant PEP include exposure to:

- Body fluids: blood, blood-stained saliva, breast milk, genital secretions, cerebrospinal, amniotic, peritoneal, synovial, pericardial/pleural fluids
- Mucous membrane: sexual activity; splashes to eye, nose, or oral cavity
- Parenteral exposures :
 - An accident with a high-calibre needle (>18 G) visibly contaminated with blood
 - a deep wound (hemorrhagic wound and/or

very painful); transmission of a significant volume of blood

- an accident with material that has previously been used intravenously or intra-arterially

The exposures that do not warrant PEP include:

- The exposed individual is already HIV positive
- The source is established to be HIV negative
- Exposures to bodily fluids that do not pose a significant risk, i.e. tears, non-blood-stained saliva, urine, and sweat
- Exposure to intact skin (unless abraded or inflicted with dermatitis)
- If source HIV status is unknown: PEP is advised on case-to-case basis, based on:
 - Severity of exposure and
 - If wearing contact lens, leave them in place Epidemiologic likelihood of HIV transmission (prevalence in the area)

Step 3: Counselling for PEP

1. Provide information on risks and benefits of PEP
2. Counsel on window period, baseline tests, safety/efficacy of PEP drugs and need for safe sexual practices (till baseline and 3- month HIV test are negative)
3. Provide Psychosocial support to address anxiety/depression & refer, if specialized support required
4. Counsel women on use of PEP during pregnancy & Breastfeeding

Step 4: Assessing Need for PEP and Prescribing PEP

- PEP should be started as soon as possible (ideally within 2 hours), preferably within

72 hours of exposure (based on eligibility assessment)

- If HCP presents after 72 hours of exposure, PEP can still be used after counselling about its effectiveness.
- Prophylaxis to be continued for 4 weeks (28 days)
- The preferred and alternative regimen for PEP are listed in Table 4 below
- Do not delay PEP initiation in cases of :
 - Known or suspected pregnancy:
 - Breastfeeding exposed women
 - Source patient is on ART or possibly has HIV drug resistance: Refer/consult an expert as soon as possible.
- Refer to an expert in case of drug intolerance, any major toxicity, non-adherence/complicated cases (e.g. major psychological problem)

PEP for Hepatitis B

All health staff should be vaccinated against hepatitis B. The vaccination for Hepatitis B consists of 3 doses: initial, 1 month, and 6 months. Sero-conversion after completing the full course is 99%. If the exposed person is unvaccinated or unclear vaccination status give complete hepatitis B vaccine series.

PEP for Hepatitis C:

There is presently no prophylaxis available against hepatitis C. There is no evidence that interferon, pegalated or not, with or without Ribavirin or DAAs are more effective when given at this time than when given at the time of disease. Post-exposure management for HCV is based on early identification of chronic HCV disease and referral to a specialist for management.

Table 5: "HBV vaccination after an AEB

HBV vaccination after an AEB	
HBV vaccination status of exposed persons	Action after AEB
Never vaccinated	Give complete hepatitis B vaccine series
Vaccinated, anti-HB-S not known	Give Hep B Vaccine Booster
Vaccinated more than 5 years ago	Give Hep B Vaccine Booster
Note: If available, testing for the antibody level (anti-HbS) is not necessary. Hep B vaccine should be given as soon as possible after exposure. Do not wait for anti-HbS results, if test is done. Adequate levels of serum Ab to HbSAg (i.e. anti-HbS) is >10 IU/L	

Step 5: Laboratory Evaluation

The reason for HIV testing soon after an occupational exposure is to establish a "baseline" against which to compare future test results. If the HCP is HIV-negative at the baseline test, it is in principle possible to prove that subsequent infection identified by follow-up testing is related to the occupational exposure (depending on the timing of infection and consideration of other risks or exposures).

Do not delay PEP if HIV testing is not available.

Step 6: Follow-up of an Exposed Person:

Whether or not PEP prophylaxis has been started, follow up is indicated to monitor for possible infections and provide psychological support.

Clinical follow-up: In addition, in the weeks following an AEB, the exposed person must be monitored for the eventual appearance of signs indicating an HIV seroconversion: acute fever, generalised lymphadenopathy, cutaneous eruption, pharyngitis, non-specific flu symptoms and ulcers of the mouth or genital area. These symptoms appear in 50-70% of individuals with an HIV primary (acute) infection and almost always within 3 to

6 weeks after exposure. When a primary (acute) infection is suspected, referral to an ART centre or for expert opinion should be arranged immediately.

Adherence and side effect counselling should be provided and reinforced at every follow-up visit.

Laboratory follow-up: The exposed persons should have post-PEP follow up HIV tests. Testing at the completion of PEP may give an initial indication of seroconversion outcome if the available antibody test is very sensitive. However, testing at 4-6 weeks may not be enough as use of PEP may prolong the time to seroconversion; and there is not enough time to diagnose all persons who seroconvert. Therefore, testing at 3 months and again at 6 months is recommended. T

Common side effects of PEP drugs

Common side effects of Tenofovir include nausea, vomiting in some persons but need to monitor the blood urea and creatinine. The DTG may cause insomnia, dizziness, headache, and tiredness. It has got drug-drug interactions with polyvalent cation products containing Al, Ca, Fe, Mg and Zn (eg: antacids, multivitamins & supplements), Metformin and Rifamycin group of drugs

Table 6: Recommended baseline laboratory investigations

Baseline laboratory investigations		
Timing	In person taking PEP (standard regimen)	In persons not taking PEP
Baseline	HIV, HCV, anti-HBs*, Complete blood count, Transaminases	HIV, HCV, anti-HBs *
* HIV, HBV and HCV testing of exposed staff within 6 days of an AEB is recommended (baseline sero-status). Offer an HIV test in case of an AEB, as a positive HIV status may indicate the need to discontinue PEP. The decision on whether to test for HIV or not should be based on informed consent of the exposed person.		

Table 7: Recommended Follow-up laboratory monitoring (during and after PEP)

Timing	In person taking PEP
Weeks 2 and 4	• Complete blood count • Serum Creatinine • Fasting blood sugar/Random blood sugar (for patients on Dolutegravir)
Week 6	HIV test
Week 12 (Month 3)	HIV test
Week 24 (Month 6)	HIV test

Conclusion

It is most important to implement a universal work precaution plan in the facility. All patients/samples need to be considered as potentially infectious. In case of needle stick injury evolution of risk of acquiring infection needs to be done immediately. If eligible, PEP must be initiated within 2 hours, preferably within 72 hours. A single fixed dose combination of TDF + FTC/3TC +DTG is standard PEP regimen to be taken for 28 days. Counselling remains an important pillar to allay fears, understand, start and complete the PEP. Long-acting injectable agents (e.g., cabotegravir) are emerging as future PEP options. However major gaps are underutilization and low awareness, despite proven effectiveness

References

1. National AIDS Control Organization. (2021). National guidelines for HIV care and treatment 2021. Ministry of Health and Family Welfare, Government of India. https://naco.gov.in/sites/default/files/National_Guidelines_for_HIV_Care_and_Treatment_2021.pdf
2. World Health Organization. (2024). Guidelines for HIV post-exposure prophylaxis. World Health Organization. Available at <https://www.who.int/publications/i/item/9789240095137>
3. Tanner MR, O'Shea JG, Byrd KM, et al. Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV — CDC Recommendations, United States, 2025. *MMWR Recomm Rep* 2025;74(No. RR-1):1–56. DOI: <http://dx.doi.org/10.15585/mmwr.rr7401a1>
4. Cresswell, F., Ascoe, J., & British Association for Sexual Health and HIV (BASHH) / British HIV Association (BHIVA) Clinical Effectiveness Group. (2021). UK guideline for the use of HIV post-exposure prophylaxis 2021. *HIV Medicine*, 23(5), 494–545. <https://doi.org/10.1111/hiv.13271>
5. Gandhi, R. T., Landovitz, R. J., Sax, P. E., Bedimo, R. J., Benson, C. A., Buchbinder, S. P., del Rio, C., Eron, J. J., Jr., Günthard, H. F., Hoy, J. F., Kuritzkes, D. R., Thompson, M. A., Volberding, P. A., & Smith, D. M. (2025). Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2024 recommendations of the International Antiviral Society–USA Panel. *JAMA*, 333(7), 609–628. <https://doi.org/10.1001/jama.2024.24543>
6. Fox, J., & International AIDS Society. (2025). HIV Post Exposure Prophylaxis: prospects, opportunities and challenges. *Journal of the International AIDS Society*, 28(1), e26390. <https://doi.org/10.1002/jia2.26390>

Echocardiography in Heart Failure-The Checklist For Physicians

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Abstract

Heart failure is a clinical syndrome in which echocardiography remains central to diagnosis, phenotyping, prognostication, and longitudinal management. Contemporary guidelines continue to recommend transthoracic echocardiography as the first-line imaging modality in patients with suspected or established heart failure, because it provides a comprehensive assessment of ventricular size and function, valvular disease, pulmonary pressures, right heart involvement, and hemodynamic surrogates. Recent updates have also strengthened the role of echocardiography in evaluating left ventricular diastolic function and in supporting diagnosis of heart failure with preserved ejection fraction (HFpEF), with the ASE publishing an updated framework in 2025.

A practical physician-facing checklist can standardize interpretation, improve diagnostic yield, and reduce missed opportunities in heart failure care. This review summarizes the key echocardiographic domains that should be assessed in every heart failure patient: chamber dimensions, biventricular systolic function, wall motion, diastolic function, valvular lesions, pulmonary pressure estimation, right-sided function, pericardial disease, and advanced markers such as global longitudinal strain when available. The article also highlights common pitfalls, the role of serial imaging, and special considerations in HFpEF, valvular heart disease, and acute decompensation.

Keywords

Heart failure; echocardiography; HFpEF; HFrEF; diastolic dysfunction; strain imaging; pulmonary hypertension; valvular disease.

Introduction

Heart failure is not a single disease but a syndrome that reflects structural and functional cardiac abnormalities, often with overlapping ischemic, hypertensive, valvular, arrhythmic, infiltrative, and cardiomyopathic mechanisms. Echocardiography is indispensable because it links symptoms to anatomy and physiology in a way that is rapid, portable, and widely available.

Guidelines from major societies recommend echocardiography as the primary imaging test in the initial evaluation of heart failure and in reassessment when clinical status changes. Older practical frameworks already emphasised the value of a structured checklist approach, and newer

guidance has extended this concept by updating the assessment of diastolic function and HFpEF-related parameters. For physicians, the key challenge is not merely obtaining an echocardiogram but ensuring that the study answers the clinical question in a reproducible and complete manner.

Checklist for physicians

1. Confirm the clinical question

Before scanning or interpreting, define whether the patient has suspected new heart failure, worsening chronic heart failure, unexplained dyspnea, valvular disease, cardiomyopathy, or treatment follow-up. The interpretation should be framed

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by the pretest probability and the specific clinical decision being addressed.

2. Measure left ventricular size and systolic function

Document left ventricular end-diastolic and end-systolic dimensions or volumes, and report left ventricular ejection fraction using a consistent method. This remains fundamental for distinguishing HFrEF, HFmrEF, and HFpEF phenotypes and for tracking response to therapy.

3. Assess regional wall motion

Regional wall motion abnormalities may suggest ischemic cardiomyopathy, prior infarction, or acute coronary syndrome. In a heart failure patient, this finding should immediately prompt correlation with symptoms, ECG, biomarkers, and coronary evaluation when appropriate.

4. Evaluate diastolic function

Diastolic assessment is essential, particularly when ejection fraction is preserved or only mildly reduced. The updated ASE framework emphasises more refined estimation of left atrial pressure, grading of diastolic dysfunction, and specific application to HFpEF evaluation. In practice, the checklist should include mitral inflow, tissue Doppler e' , E/e' ratio, left atrial volume, tricuspid regurgitation velocity, and contextual interpretation rather than reliance on a single variable.

5. Inspect left atrial size and function

Left atrial enlargement is a marker of chronic elevation in filling pressures and long-standing diastolic burden. It is also useful for tracking cumulative pressure-load exposure in hypertension, valvular disease, atrial fibrillation, and HFpEF.

6. Examine the right heart

Right ventricular size and function, right atrial size, and estimated pulmonary artery pressure should be part of every heart failure echocardiogram. Right heart involvement is prognostically important and may reflect pulmonary hypertension, RV ischemia,

volume overload, or advanced left-sided disease.

7. Look carefully at valves

Functional mitral regurgitation, tricuspid regurgitation, aortic stenosis, and mixed valvular lesions can both cause and worsen heart failure. A structured echo report should state lesion severity, mechanism where possible, and whether the lesion is likely contributing materially to the syndrome.

8. Search for pericardial and congenital causes

Pericardial effusion, constriction, and unrecognised congenital abnormalities are less common but important reversible or contributory causes. These should be actively considered when the clinical picture is disproportionate to left ventricular systolic findings.

9. Use strain imaging when available

Global longitudinal strain adds sensitivity for subclinical myocardial dysfunction and can be particularly useful in infiltrative disease, cardiotoxicity, and cardiomyopathies with preserved ejection fraction. ASE's recent strain-focused consensus has reinforced its broader role in contemporary echocardiography practice.

10. Integrate the data into phenotype-based management

The final report should not end with numbers alone. It should state whether the study supports HFrEF, HFmrEF, HFpEF, valvular heart failure, RV-predominant failure, or an alternative diagnosis, and whether repeat imaging, advanced imaging, or invasive hemodynamic evaluation is warranted.

Practical interpretation

A checklist-based echocardiographic approach is particularly valuable in patients with dyspnoea, oedema, atrial fibrillation, obesity, and hypertension, where HFpEF may be under-recognised. The 2025 ASE update places greater emphasis on diastolic function and HFpEF diagnosis, reflecting the clinical need to go beyond a simple "preserved EF" label. In such patients, a

“normal EF” should never be interpreted as “no heart failure” without filling-pressure assessment and structural correlation.

In HF_rEF, serial echocardiography helps document reverse remodelling, persistent severe dysfunction, worsening functional mitral regurgitation, or emerging RV failure. In valvular or device-treated patients, repeat studies should answer whether intervention changed chamber loading, pulmonary pressures, and clinical trajectory.

Pitfalls

Several common errors reduce the value of echocardiography in heart failure. These include overreliance on ejection fraction, failure to assess diastolic indices, ignoring image quality limitations, and interpreting single measurements without clinical context. Another frequent pitfall is assuming that normal resting filling pressures exclude HF_pEF, especially in patients with exertional symptoms and high pretest probability.

Conclusion

Echocardiography remains the cornerstone imaging tool in heart failure because it provides a complete structural and hemodynamic profile in a single examination. A checklist approach improves consistency, strengthens diagnostic accuracy, and ensures that crucial elements such as diastolic function, right heart assessment, and valvular contribution are not missed. With the updated

ASE guidance on diastolic dysfunction and HF_pEF, physicians should interpret echocardiograms as integrated clinical reports rather than isolated measurements.

References

1. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.
2. 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. *J Am Coll Cardiol*. 2022;79(17):e263-e421.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-3639.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129-2200.
5. Nagueh SF, Anand IS, Dzakova P, et al. Echocardiographic assessment of patients with heart failure: a practical checklist. *Acta Cardiol*. 2008;63(6):783-789.
6. American Society of Echocardiography. ASE guidelines and recommendations. 2026. Available from: <https://www.asecho.org/practice-clinical-resources/ase-guidelines>.

CONFLICT OF INTEREST: NONE

INFORMED CONSENT: NOT APPLICABLE

TYPE OF MANUSCRIPT: REVIEW ARTICLE

QUIZ

Dr. K K Perumal

QUESTIONS

INFECTIOUS DISEASE

Q 1. A 30 year –old male patient complaints of fever and sore throat for several days.

The patient presents to you today with additional complaints of hoarseness, difficulty breathing and drooling.

On examination,

The patient is febrile and has inspiratory stridor.

Which of the following is the best course of action?

- a. Begin outpatient treatment with ampicillin.
- b. culture throat for Beta hemolytic streptococcus.
- c. admit to intensive care unit and obtain otolaryngology consultation.
- d. schedule for chest x-ray.
- e. obtain Epstein-Barr serology.

This patient with the development of hoarseness, breathing difficulty and stridor, is likely to have acute epiglottitis.

Because of the possibility of impending airway obstruction,

The patient should be admitted to an intensive care unit for close monitoring,

The diagnosis can be confirmed by indirect laryngoscopy or soft tissue X-rays of the neck, which may show an enlarged epiglottis.

Otolaryngology consultation should be obtained.

The most likely organism causing this infection is Haemophilus influenza.

Many of these organisms are Beta lactamase producing and would be resistant to ampicillin.

The clinical findings are not consistent with the presentation of streptococcal pharyngitis.

Lateral neck film is more useful than a chest X-ray.

Classic findings on lateral neck films would be the thumbprint sign.

Q 2. The treatment of choice for a 20 –year –old college student with a history of upper and lower respiratory symptoms, bullous myringitis, a negative sputum Gram stain, and patchy lower lobe infiltrates on chest X-ray is which of the following?

- a. Erythromycin.

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- b. supportive therapy.
- c. Ceftriaxone.
- d. Cefuroxime.
- e. Penicillin.

The treatment of choice for mycoplasma infection is Erythromycin.

Newer Macrolides such as AZITHROMYCIN OR Clarithromycin are also effective.

Treatment decreases the number of symptomatic days.

Mycoplasma does not have a cell wall membrane, so neither penicillin nor ceftriaxone would be effective therapy.

Q 3. A 40 year old airplane pilot is hospitalized with shortness of breath.

He experienced fever, chills, and myalgia for several days prior to his breathing problems.

He has returned from the Far East, where he visited Singapore and Hong Kong.

He is found to have hypoxic, and chest X-ray shows diffuse opacification of both lung fields.

Sputum and blood cultures are negative.

Rapid testing for influenza A and B are also negative.

Which of the following is the most important next step in management?

- a. Begin treatment with amantadine.
- b. respiratory isolation for corona virus infection.
- c. treatment for acute bacterial pneumonia.
- d. High resolution CT scan.
- e. obtain Ventilation-perfusion scan.

Severe acute respiratory syndrome (SARS) was first recognized in mainland China in 2002.

It eventually spread to other countries.

The initial symptoms of the disease are similar to influenza. With myalgia, fever and malaise.

The disease progresses to shortness of breath and ARDS and many patients require mechanical ventilation.

The organism is now known to be a coronavirus (SARS-CoV).

Treatment is supportive with no anti-viral therapy.

Respiratory isolation is extremely important.

Chest X-ray in the advanced disease shows a diffuse opacification of the lungs.

Q 4. A previously healthy lady, music teacher, 25 year old, develops fever and a rash over her face and chest.

The rash is itchy and on exam involves multiple papules and vesicles in varying stages of development.

One week later she complains of cough and is found to have an infiltrate on X-ray.

Which of the following is the most likely etiology of the infection/

- a. Streptococcus pneumonia.

- b. Mycoplasma pneumonia.
- c. Pneumocystiscarini.
- d. Varcella virus.
- e. Chlamypssitacii.

Varicella pneumonia develops in about 20% of adults with Chickenpox.

It occurs 3 to 7 days after the onset of the rash.

The hallmark of the chicken pox rash is papules, vesicles and scabs in various stages of development.

Fever, malaise and itching are usually part of the clinical picture.

The differential can include some coxsackievirus infections which might present with pneumonia and vesicular rash.

Rickettsialpox, a rickettsial infection, has also been mistaken for chickenpox.

RHEUMATOLOGY

Q 1. A 43 year old man with diabetes and cardiomegaly has had an attack of pseudogout.

He should be evaluated for which of the following?

- a. Renal disease.
- b. Hemochromatosis.
- c. Peptic ulcer disease.
- d. Lyme disease.
- e. Inflammatory bowel disease.

Pseudogout is part of the spectrum of calcium pyrophosphate deposition disease.

It is usually an acute monoarthritis or oligoarthritis caused by calcium pyrophosphate crystals in the joint.

Pseudo gout may be associated with hemochromatosis.

Since the patient has a history of diabetes mellitus and cardiomyopathy, hemochromatosis must be considered.

Serum iron saturation should be measured.

Ferritin may also be a usual measure of iron stores.

pseudo gout has also been associated with hyperparathyroidism.

Inflammatory bowel disease, Lyme disease and peptic ulcer disease do not predispose to pseudogout

NEPHROLOGY

Q 1. Which one of the following systemic disorders is LEAST associated with glomerulonephritis?

- a. Malaria.
- b. Goodpasture's disease.
- c. Sarcoidosis.
- d. Wegener's granulomatosis.
- e. Henoch-Schönlein purpura.

Clinically apparent primary renal involvement in Sarcoidosis is rare although tubular, glomerular and renal artery diseases have been reported.

More commonly, but still in only 1-2% of all cases, there is a disorder of calcium **metabolism with hypercalciuria with or without hypercalcaemia.**

If chronic, nephrocalcinosis and nephrolithiasis can result.

Q 2. Which one of the following, when seen in a pregnant woman, is not likely to be physiological?

- a. Glycosuria.
- b. Haematuria.
- c. Ketonuria.
- d. Plasma osmolality 277 mOsmol/kg.
- e. Ureter dilatation.

There is reduced renal reabsorption for glucose in pregnancy, which may cause glycosuria.

However patients with persistent glycosuria should be investigated with a glucose tolerance test at around 24 weeks.

Ketonuria may also be seen in normal pregnancy as a result of the increased metabolic requirements.

Early in pregnancy, the plasma osmolality falls by an average of 10 mOsmol/kg.

This is principally due to hyponatremia.

The osmotic thresholds for ADH release are reduced, so that ADH is not suppressed.

Dilatation of renal pelvises and ureters is seen in 90% women by the third trimester.

NEUROLOGY

Q 1. Which one of the following features is most typical of cavernous sinus thrombosis?

- a. Double vision on looking upward.
- b. Papilloedema is an early feature.
- c. Loss of pinprick sensation around the chin area.
- d. Difficulty in swallowing.

Cavernous sinus thrombosis is usually due to a suppurative process in the orbit, nasal sinuses or upper half of the face usually caused by staphylococcus aureus infection.

The condition is severe with high fever, headache, malaise, nausea, vomiting and convulsions.

Chemosis, oedema and cyanosis of the upper face occurs due to obstruction of the ophthalmic vein.

Ophthalmoplegia is secondary to damage to the third, fourth, and sixth cranial nerves

Eye pain and hyperaesthesia of the forehead (not the chin) is due to damage to the first division of the trigeminal nerve.

Retinal haemorrhage and papilloedema are late events.

Q 2. Which one of the following is MOST suggestive of essential tremor?

- a. Often associated with cogwheel rigidity.

- b. Improves with intentional movement.
- c. Made worse with alcohol.
- d. Strong familial tendency.
- e. Tends to improve with age.

Essential tremor manifests as tremor of the hand, head and least frequently the voice..

Compared to Parkinson's tremor, it is more rapid and occurs on volitional movement.

It is not associated with rigidity or hypokinesia.

It is suppressed by alcohol and beta-blockers.

There is strong family history and the incidence distributed as an autosomal dominant trait.

Though it manifests in the elderly, the age of onset varies and it can start as mild tremor in the third decade and worsen with advancing age.

BASIC SCIENCES

Q 1. which of the following statements are true of coronary artery anatomy/

- a. Right bundle branch block in acute anterior myocardial infarction suggests obstruction prior to the first septal branch of the left anterior descending coronary artery.
- b. The posterior descending artery is usually a branch of the circumflex artery.
- c. The sinus node is supplied by a branch of the right coronary artery in over 90% of subjects.
- d. The AV node is supplied by the left anterior descending coronary artery.
- e. The left main stem is about 4 cm long.

The posterior descending artery is most often (85%) A BRANCH OF THE RIGHT CORONARY ARTERY.

The sinus node artery is a branch of right coronary artery in 60% cases.

The AV NODE SUPPLIED FROM THE POSTERIOR DESCENDING CORONARY ARTERY.

The left main stem is much shorter than 4cm.

Q 2. A 73 year-old man presents with an abrupt onset of double vision and left leg weakness.

Examination shows weakness of abduction of the right eye, Right-sided facial weakness affecting upper and lower parts of the face.

He also has a left hemiparesis.

Where is the lesion?

- a. Left frontal lobe.
- b. Left lateral medulla
- c. right corpus striatum.
- d. right mid brain.
- e. right pons.

The abducent nucleus is next to the facial nucleus in pons, they usually coexist.

In a pontine CVA.

Hemiparesis is also a common feature of pontine lesion.

Q 3. In which of the following **is mental retardation an expected finding ?**

- a. Alkaptonuria.
- b. Cystinuria.
- c. Glycogen storage disease.
- d. Lactose intolerance
- e. Maple syrup urine disease.-

Mental retardation

Fragile X SYNDROME –COMMONEST male cause.

Hypoxia at birth,

Intraventricular haemorrhage, rhesus disease,

Congenital infections, toxoplasmosis, CMV, rubella, herpes, hypoglycemia, meningitis, hypothyroidism (cretinism, tuberous sclerosis, Down's, Tay-

-Sachs, s, Comella De Lange, Hartnup-biochemical, treatable with diet.-homocystinuria, phenylketonuria -maple syrup urine disease, tryptophanuria- galactosaemia.

Q 4. The following statements with regard to postpartum thyroiditis are true EXCEPT?

- a. Typically occurs in the first week after delivery.
- b. Characterised transient hyperthyroidism.
- c. Spontaneous recovery is expected in 90% of cases.
- d. Anti-microsomal antibodies might be elevated
- e. Radioactive iodine uptake is reduced.

Typically occurs in the first week after delivery.

Postpartum thyroiditis may occur in 5% of postpartum women, at least three months after delivery and characterized two phases:

1. The hyperthyroid phase occurs alone in half of the cases with mild symptoms and may be associated with a small painless goiter. It can be differentiated from Graves. by the absence of thyroid stimulating and a low radioactive iodine uptake.-uptake antibodies
2. The hypothyroid phase manifests, four to eight months after delivery which may or may not be preceded by the hyper thyroid phase.

Prospects of developing expertise in transfusion Medicine as a career choice in India.

Dr. Kinjalka Ghosh

Abstract

Postgraduation in Transfusion medicine is an excellent career choice. After MBBS and internship a 3 year MD course or DNB course in transfusion medicine takes one into league of superspecialists. There are 60 transfusion medicine MD seats in addition to seats in AIIMS Delhi and PGIMER Chandigarh in India more over quite a few DNB seats in the same subject is available across the country. The subject has evolved considerably in our country with greater recognition of need for component therapy, transfusion transmitted infections, management of chronic transfusion programme in thalassemics and in many patients with other haemoglobinopathies and MDS. More than 400 corporate hospitals doing ever more complicated surgeries and various kind of transplantations have increased needs for these experts. More than 700 medical colleges in India where each of them needs to keep blood bank and few transfusion medicine experts immediately translates into big job opportunities. At present in any transfusion medicine centre a person with transfusion medicine degree gets first preference. Increased demand for Apheresis technology in preparative work and for patient management puts transfusion medicine experts in great advantage. Future dimension of cryopreservation of stem cells and other cells along with preparation of cells for cell therapy purpose is increasingly opening new chapters in transfusion medicine based patient management. India needs many of you now and in future.

Key words:

Transfusion Medicine, Stem Cell banking, Tissue antigens, Registry, clinical dimension, research and development, cell therapy, molecular medicine.

Introduction

Many doctors and of course many parents have no idea whether a postgraduate degree in transfusion medicine is a good career option for a doctor in training. Classically doctors after their graduation prefer to be a cardiologist, neurologist, gastroenterologist etc or superspecialists like neurosurgery, cardiothoracic surgeon, plastic surgeon or urologist in surgical specialities.

Very few graduates want to take up preclinical subject eg Anatomy, Physiology, Pathology, Microbiology etc. Pharmacology as a subject always has some demand and as few centres are offering superspecialisation in Clinical pharmacology, this para clinical subject has seen lot of interest amongst students. One of the important reason for interest in Pharmacology lies in good job prospect in pharmaceutical industry, which has a very strong base in This country.

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Specialities which by itself had great demand yesterday is slowly falling out of individual preference ie today nobody wants to stop at MD medicine or MS surgery unless forced to. Subjects like obstetrics & gynecology is unlikely to lose its interest or money earning potential. Similarly ophthalmology, ENT etc has a small following but is indispensable in any medical set up. Orthopedics and Radiology of late has seen intense competition. But how about transfusion medicine? In this paper I will try to focus on the scope of this subject in India and in International health care along with some indications on various ways this subject has made progression.

Transfusion Medicine (Blood Banking) In India Yesterday:

Transfusion medicine as it was called blood banking was not a sought after subject even by the pathologists who mentored this subject during its early development in this country. Blood was obviously required for many clinical indications and surgical and gynecological procedures, hence blood bank was a necessity in any medical college or in any big hospital. The donor population was often paid donors, replacement donors and in some states of India the major sources of blood donation was from the jails of the states where a convict used to get few days relief if he donated blood. The techniques were elementary hence it was not difficult to induct any body into blood banking system with few days training. For doctors it was often a punishment posting and there was very little enthusiasm to do anything positive. Most of the time only whole blood was available, few blood components were produced in the elite blood banks of the country. Blood banks were mostly thought as blood supply centre, nothing more than that. The infectious complications of transfusion was rampant as was also various complications as glass bottles in which blood was collected and transfusion sets through which blood used to be given was repeatedly sterilized before use ie no disposable plastic sets. There was very little awareness of scope and applicability of this important branch of medicine as very little of the subject was taught and is still taught in main stream medical curriculum. Hence there was very

little interest in making blood banking a career in the past. However several pioneers of blood banking in the country worked under challenging conditions to improve the situation and today it is one of the most rapidly expanding area of medical science. It may not be out of place to mention here that world's 2nd (some body will say 3rd) blood transfusion centre was established in the Campbell Medical School campus (Now Nilratan Sarkar Medical college, Kolkata) way back in 1938 by the discoverer of treatment of Kala-azar Sir (Dr.) UC Bhramachari.

Evolution of transfusion Medicine In India :

Transfusion Medicine in India evolved in this country through several steps. Indian council of Medical Research was aware of the inadequacies of facilities, reagents and trained manpower in transfusion medicine in post independent India and understood that these hindrances need to be surmounted to improve the transfusion Medicine service in the country. With that idea a Blood group reference Centre (BGRC) was started at KEM hospital Mumbai in 1957.[1] BGRC within a short time became a nucleus of training in blood bank operations and training in production of ABO and RhD antisera in the country. Most of the transfusion medicine experts of yesterday in some way was associated with the centre and the centre regularly trained 20-30 person on blood bank technology and serology over last 60 years paying attention to those parts of the country where such expertise was lacking.

With the demonstration of Hepatitis B as one of the important transfusion transmitted disease and its identification by Counter current immunoelectrophoresis or Red cell haemagglutination inhibition test a layer of safety was established in collected blood units.[2] This technique was also regularly taught in BGRC for its widespread use. Plasma could be separated from blood easily and was made available in some centres even in early days of blood banking in India. But with the availability of plastic bags (initially imported) and disposable transfusion systems much of the nonhaemolytic febrile reaction to transfusion could be eliminated.

Later on India started producing its own

disposable plastic bags. Now several Indian companies produce good quality plastic bags cheaply. Introduction of multiple plastic bags connected with a mother bag allowed production of multiple blood components easily. Some of the other machineries like blood bank freezers, deep freezers, centrifuges was also started to be produced in this country.

A simple process for production of cryoprecipitate was discovered and the product was tested only in 1965 in USA[3]. However in India cryoprecipitate could not be produced till early 1980s in this country when a multicentric study funded by ICMR standardized production of cryoprecipitate [4,5,6]. Now many blood banks in the country produce blood components including cryoprecipitates.

One of the most important chapter in developing good quality transfusion medicine service in India was voluntary blood donation movement initiated at several places in the country in early 1970s till it became an All India Movement, Dr J G Jolly, Ms Moolgaonkar, West Bengal voluntary blood donor association are some of the pioneers in this movement[7].

Today there are innumerable voluntary blood donor organizations across the country doing a very commendable job. Apart from Indian Red Cross with its various branches across the country running blood banks, many charitable blood banks under the patronage of influential and well meaning citizens of this country. Most of these blood banks supported voluntary blood donation movement and plays a very important role in serving the transfusion needs of this country.

Presently India collects about 10 million units of blood per year. Some of the centres collect blood to the tune of 30-100,000 units per year. These blood banks can only work efficiently and supply the product in time if good automation in various sections of blood bank is available. After India opened up to the rest of the world in early 1990s various types of automation instruments in grouping cross matching infection determination has become available easily and is extensively used by various blood banks. To utilize all the blood components from a bag of blood the blood bag should be kept at 4 °C as soon as it is collected and should be processed within 4-6 hours of collection.

This has been made possible with the availability of blood mobiles with refrigeration capability. These mobiles has been extensively distributed by Government of India across various blood banks in the country.

Tailor made blood products for the patients :

Already many blood banks in India are making blood components and providing apheresis single donor products in the form of single donor plasma, platelets etc. It is possible to develop a rare blood donor registry across the country involving all the properly endowed blood banks, this will serve difficult to crossmatch patients, patients requiring rare blood group red cells like Red cells from Bombay phenotype. In a similar way cryopreservation of rare donor red cells can be accomplished and ready made rare donor blood will be available from such blood banks.

HIV infection and rise of National Aids control organization (NACO):

First HIV infection was documented in India in 1986[8]. Following that Government of India Established an organization called NACO to look after and develop strategies to control progress of HIV infection in the country. As blood transfusion was one of the important route for HIV transmission the whole Blood banking process came under its control. Around that time freeze-dried plasma products produced by one Indian company lead to spread of HIV infection in many of its recipients, quite a few of them were haemophiliacs. This has important repercussions in the way PWH in India wanted to be treated and a haemophilia patients along with thalassemia patients movement also contributed to the need for quantum improvement in functioning of blood bank operation in this country.

This had the salutary effect of developing organizational set up, quality control, and overseeing of various blood banks in India substantially improving their performance. NACO took leading part in providing instruments, reagent kits and training both doctors and technicians in various facets of improving infectious transmission and quality of product development in blood banks in this country. Meanwhile Drug controller

General of India (DCGI) considering blood as a therapeutic product developed rules and norms for licensing blood banks. Norms were also set up on the degrees and nature of training which will be required for the doctors and technicians to serve in the blood banks. To improve qualities of blood bank activities further National Accreditation Board for Hospitals (NABH) also developed their norms for transfusion medicine centres and encouraged all blood banks to accept periodic NABH audit.

Rise of Corporate hospitals :

Over last 30 years few hundred high quality corporate hospitals have come up in this country. These corporate hospitals have state of the art surgical units and cardiology units practicing various types of surgery particularly cardiac surgeries, cancer surgeries, neurosurgeries, hip and knee joint surgeries requiring tailor made transfusion support and these corporate hospitals were paying good salaries to transfusion medicine experts. Many such hospitals also incorporated HLA typing centres within blood banks. In addition to surgery these hospitals also cater for dialysis, Intensive care unit of various sorts where requirement of different kinds of blood products have increased and so also the role of transfusion medicine experts as complicated haemotherapy in many such patients require sound advice from transfusion medicine experts.

Bone marrow and Solid Organ transplantations :

Few good government centres, charitable hospitals and mostly many corporate hospitals are increasingly involved in complicated organ transplantation Kidney being the frequent but substantial number of liver transplantation and few cardiac transplantation is taking place in this country. Blood group mismatched kidney, bone marrow both related and mismatched unrelated donor transplantation is taking place in this country. All these transplantations require high degree of expertise in transfusion medicine in not only providing tailor made products and different products at different time points of transplantation, the proper management also needs dialogue between transplant, medical specialist managing

these cases and transfusion medicine expert. In these scenario Transfusion medicine expert not only functions as provider of a service and product, he/ she functions as a clinical consultant advising the colleagues. Many situations in transplantations and in neonatal, Intrauterine, premature baby transfusion also needs irradiated blood products and blood irradiators are now available in quite a few hospitals in the country.

Molecular biology and transfusion Medicine :

Increasingly molecular biology based testing is entering in the arena of transfusion medicine. NAT testing is an example. HLA typing is other example. In future the red cells are going to be genotyped for transfusion using a variety of molecular biology platforms.[9]. Moreover molecular biology based detection of many more infectious diseases in blood is going to be the norm in future. Some of the complexities of Rh Gene in Indian population has been unravelled through the agency of molecular biology [10].

Umbilical cord cell banking:

Over last 15 years many cord cell banks cryopreserving cord blood has come up in the country. These cord blood banks also offer opportunities for exciting work for Transfusion medicine expert. As many cord blood banks with good laboratory and manufacturing practice has expertise in cell culture, cell expansion and stem cells and different types of differentiated cells and bioengineered cells are going to be utilized for a variety of therapy in future in this area of Transfusion medicine experts has exciting career ahead [11].

Apheresis preparative and therapeutic :

In this procedure blood is collected in a continuous or discontinuous flow in a closed circuit and is processed outside the body for either preparation of various therapeutic products like single donor platelets, Plasma for fractionation, mononuclear cells either as stem cells or for donor lymphocyte infusion for immunomodulation etc or for therapeutic purpose like plasma pheresis, erythrocytapheresis etc. This procedure requires

trained personnel and a doctor. Even transfusion medicine doctors should train themselves to do this procedure. This procedure is extensively used now a days to manage many dreaded complications across various specialities and are also used to produce important therapeutic products.

Scope of research in Transfusion medicine in India :

Transfusion medicine offers exciting scope of research for those interested in research work. In addition to exploring the complex distribution of various blood group antigens across the population diversity in Indian subcontinent and its direct medical application through creation of rare blood donor registry, Various association studies of different blood group antigens with different diseases and complex genetic traits, their serological and biochemical foundation for occurrence of such disease and the evolutionary biology of complex evolution of such complicated and often polymorphic system is but a few lines of research avenues available to the Transfusion medicine experts [12-16]. Better management of donors, recipient, inventory, human resources, finances and infrastructure using modern tools of Artificial Intelligence and other heuristic softwares offer interesting possibilities of original and operational research. In addition to what was described transfusion medicine centres collect blood from apparently healthy person for various transfusion purpose. Presently in India more than 12 million blood units are collected across more than 3000 recognised blood banks. In a properly constructed ethically vetted project a small part of this sample which is collected for serology testing can also be analysed for various health parameters of the nation, progress of unrecognized infection in the community and so on.

MD and DNB in transfusion Medicine:

This is a superspecialist degree but one gets the degree by working 3 years less than those working for DM or MCh degree. DM in haematology has only 25 seats in the country whereas there are 60 MD transfusion Medicine seats across the country and almost half as many DNB seats for the same purpose. Transfusion medicine is an extremely

good and satisfying career choice and is one of the subjects in medicine with lots of possibilities. At present in India there are 246 National Medical Commission recognized MD transfusion medicine seats and 23 DNB in Transfusion medicine openings available across the country.

Conclusion :

Transfusion medicine evolved in India as it did across the world. Development in apheresis technology, automation, molecular biology as applicable to the subject, automation in the laboratory, Infectious organism detection and control, rise of corporate hospitals with ever increasing load of complicated operations and transplants, Stem cell preservation and therapy and other cell therapies are spawning a development of transfusion medicine it has never seen. Moreover the need for transfusion medicine experts in 800 medical colleges, 750 civil district hospitals and in many private and corporate hospitals as well as stand alone transfusion centres offer good job opportunities. To be in this speciality at present is very exciting as a career of choice.

Conflict of interest : None.

Acknowledgement : Professor Kanjaksha Ghosh MRCPI, Fmr Director National Institute of Immunohaematology, for idea and content.

Funding : None

References

1. Bhargava PM & Chakarabarti C. The saga of Indian Science since Independence in a nutshell. Pp168 table 2. Universities press, Hyderabad 2003.
2. Joshi SH, Baxi AJ, Bhatia HM. Prevalence of hepatitis-B surface antigen by rapid passive haemagglutination inhibition technique. Indian J Med Res. 1979 ;69:978-80.
3. Pool JG, Shannon AE. Production of high-potency concentrates of antihemophilic globulin in a closed-bag system. N Engl J Med. 1965 30;273:1443-7.
4. De M, Banerjee D, Chandra S, Bhattacharya DK. A simple method for preparation of good quality cryoprecipitate. Indian J Med Res. 1989 ;90:32-5.
5. Nanu A, Taneja N, Madan N, Sood SK. Preparation and standardization of fresh frozen plasma and cryoprecipitate in a developing blood bank. Indian J Pathol Microbiol. 1980 ;23:235-40.
6. Chudgar UH, Chandy M, Pulimood RB, Khanduri U. Slow

- thaw siphon technique for cryoprecipitate production. *Indian J Med Res.* 1989 ;90:295-9.
7. Neelam Marwaha Voluntary blood donation in India: Achievements, expectations and challenges *Asian J Transfus Sci.* 2015 Apr; 9(Suppl 1): S1-S2.
 8. Simoes EA, Babu PG, John TJ, Nirmala S, Solomon S, Lakshminarayana CS, Quinn TC. Evidence for HTLV-III infection in prostitutes in Tamil Nadu (India). *Indian J Med Res.* 1987;85:335-8.
 9. Ray S, Gorakshakar AC, Kashivishwanathan V, Agarwal S, Nadkarni A, Ghosh K. Molecular characterization of weaker variants of A and B in Indian population--the first report. *Transfus Apher Sci.* 2014 ;50(1):118-22.
 10. Fichou Y, Parchure D, Gogri H, Gopalkrishnan V, Le Maréchal C, Chen JM, Férec C, Madkaikar M, Ghosh K, Kulkarni S. Molecular basis of weak D expression in the Indian population and report of a novel, predominant variant RHD allele. *Transfusion.* 2018 ;58(6):1540-1549.
 11. Ghosh K. Advancement of transfusion Medicine with emphasis on cellular therapy in 'A text book on laboratory and clinical transfusion medicine.' Eds Choudhury N & Bharucha ZS. Volume 3, Chapter 18 pp 411-429. Nova science Publisher, Nova biomedical, N York 2016.
 12. Mishra KK, Patel K, Trivedi A, Patel P, Ghosh K, Bharadva S. Risk of hepatitis-E virus infections among blood donors in a regional blood transfusion centre in western India. *Transfus Med.* 2021 Jun;31(3):193-199.
 13. Shah A, Jariwala K, Gupte S, Sharma P, Mishra K, Ghosh K. Pattern of distribution of 35 red cell antigens in regular voluntary blood donors of South Gujarat, India. *Transfus Apher Sci.* 2018 Oct;57(5):672-675.
 14. Gorakshkar AC, Ghosh K. Subclinical iron deficiency is a silent epidemic amongst voluntary blood donors. *Transfus Med.* 2012 Aug;22(4):300-1.
 15. Shaikh R, Kanjaksha G, Gorakshakar A. Duffy Binding Protein Ligand (PvDBP) gene duplication in Indian P. Vivax Malaria isolates: implication for malaria research. *Curr Genet.* 2024 Nov 9;70(1):18. doi: 10.1007/s00294-024-01304-7.
 16. Das Biswas A, Bhattacharya P, Banerjee S. Non-secretor status as a saliva-based risk marker for cancer susceptibility: a hypothesis. *Medical Hypotheses* 2026;212:112012. <https://doi.org/10.1016/j.mehy.2026.112012>.

Pre-Eclampsia: Anticipation, Prediction and Prevention.

Dr. Rajiv Dhall

Abstract

One of the greatest scourges that can afflict pregnant women and is peculiar only to the pregnant state is pre-eclampsia. In its severest form it can cause widespread multi-organ disruptions in the mother and leave behind residual implications for her future health including future pregnancies. It also contributes significantly to perinatal morbidity and mortality and also has future implications for the health of the child thus born. This, combined with the fact that anticipation, prediction and prevention of pre-eclampsia is not always foolproof, makes the condition even more challenging. This article depicts the current status of anticipation, prediction and prevention of pre-eclampsia and also explores the future possibilities.

Key words:

Pre-eclampsia, Risk assessment, Prediction models, Biomarkers, Uterine artery Dopplers.

Introduction:

Pre-eclampsia, by definition, is new onset hypertension after 20 weeks of gestation with features of maternal organ or uteroplacental dysfunction or proteinuria.¹ It has wide prevalence worldwide though more common in certain ethnic groups and causes significant maternal and perinatal morbidity and mortality, often with persistent or future morbidity in the mother. Also, in the offspring, long-term sequelae like hypertension and altered vascular function have been ascribed to pre-eclampsia in the mother.

Epidemiology:

Preeclampsia is a disorder peculiar to pregnancy and involves multiple systems including hepatorenal and coagulation systems. The incidence is about 2% to 8% of pregnant women. It may eventually lead to pulmonary edema, kidney injury, cerebrovascular

accidents and eclampsia in the mother and also placental abruption and fetal growth restriction. In the long run, women with pre-eclampsia are prone to chronic hypertension, brain strokes, end-stage renal disease and cognitive impairment. Even babies born to such mothers may develop neurodevelopmental problems, hypertension, coronary heart disease and diabetes mellitus in later life.² Pre-eclampsia is usually encountered in the third trimester of pregnancy.³

Aetiopathogenesis:

The underlying pathophysiology of preeclampsia indicates that it develops in two stages. Stage I usually arises in the first trimester and is characterized by inadequate trophoblastic invasion, the underlying causes being genetic factors [fms-related tyrosine kinase 1 single-nucleotide polymorphism and trisomy 13], maternal factors and co-morbidities

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and immunological factors (imbalance between decidual natural killer cells and regulatory T-cells). Stage II results from reduced placental perfusion wherein oxidative stress stimulates the release of inflammatory cytokines and antiangiogenic factors; the widespread endothelial dysfunction so caused brings about the ultimate clinical manifestations. In Stage I of the pathophysiology of the disease, there is incomplete spiral artery remodelling and poor trophoblastic invasion and in Stage II release of anti-angiogenic factors like sFlt-1 [soluble fms-like tyrosine kinase 1] and soluble Endoglin and maternal endothelial dysfunction are encountered.² The acronym 'fms' comes from the fms oncogene which was originally discovered in Feline McDonough Sarcoma.

A dynamic prediction model is imperative as the risk assessment is updated with evolving changes in clinical parameters and availability of relevant blood biomarker and ultrasonographic results. A high MAP (Mean Arterial Pressure) in the first trimester increases the risk of preeclampsia. Uterine artery Doppler studies may be performed between 11 weeks and 13 weeks and 6 days of gestation at the time of the Combined first trimester screening test (for fetal aneuploidies) but may also be performed in the second trimester. Impaired placental perfusion is indicated by increased uterine artery resistance, increased pulsatility index and a persistent early diastolic notch.

Defective placental vasculogenesis and widespread endothelial dysfunction are the hallmarks of preeclampsia. A circulating antiangiogenic protein namely sflt-1 probably has an important role in the pathogenesis of preeclampsia.⁴ PlGF (Placental Like Growth Factor) belongs to the VEGF (Vascular Endothelial Growth Factor) family, is produced by trophoblastic cells and is proangiogenic and proinflammatory. Soluble Endoglin (sEng) and sFlt-1 are two antiangiogenic proteins involved in the pathogenesis of preeclampsia. Enhanced platelet and complement activation point towards systemic inflammation as an important underlying factor in the development of preeclampsia.

In preeclampsia the uterine spiral arteries fail to change into low-resistance vessels because of defective differentiation and invasiveness

of trophoblasts thereby resulting in increased impedance in the uterine arteries. This is reflected by increased pulsatility index and increased resistance index detected on Doppler studies on the uterine arteries.³

Appropriate vascularization of the placental bed is very important for fetal development. Failure of the physiological transformation of the successive branches of the uterine arteries in this area forms the anatomical basis for reduced perfusion to the intervillous space in preeclampsia. Defective deep placentation is ascribed to defective or absent transformation of the myometrial segment of the uteroplacental arteries, atherosclerotic lesions in the defective myometrial segment and acute atherosclerosis in the basal decidua and is associated with the great obstetric syndromes including preeclampsia, fetal growth restriction, preterm labour, preterm premature rupture of membranes and placental abruption.⁵

Risk assessment and anticipation :

The maternal factors which increase the risk of preeclampsia in the index pregnancy include preeclampsia in a previous pregnancy, family history of preeclampsia, nulliparity, long interpregnancy interval (more than 10 years), maternal age above 35 years, obesity, low socioeconomic status, pregnancy resulting from 'Assisted Reproduction Technology', multifetal pregnancy, pre-existing (chronic) hypertension, chronic kidney disease, anti-phospholipid syndrome, diabetes mellitus, heritable thrombophilias and auto-immune diseases.² Risk factors for preeclampsia include in vitro fertilization with donor eggs. Because of the heterogeneous nature of preeclampsia, solitary clinical, imaging or biochemical factors are not sufficient enough for risk-prediction and robust algorithms are required.³

Of all the prediction models currently available, Maternal history, MAP, UtA-PI (Uterine Artery Pulsatility Index) and PlGF together constitute the most accurate model. The sFlt-1/PlGF is useful in excluding preeclampsia in symptomatic women especially after 20 weeks of gestation. It is also useful in assessing disease severity and in prognostication.

Investigations and Prediction:

Various first trimester prediction models have been proposed for screening for preeclampsia based on maternal risk factors such as those from the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE). However, a more reliable prediction model in terms of detection rates and prediction of early and preterm preeclampsia has been proposed by the FMF (Fetal Medicine Foundation) in the form of the 'triple test' which involves a combination of maternal factors and measurements of MAP, UtA-PI and serum PlGF. Another important maternal blood marker in this regard is PAPP-A (Pregnancy Associated Plasma Protein A).

Using the FMF triple test, the Number Needed to Screen (NNS) to prevent one case of preterm preeclampsia is 250. Obviously, adherence to standardized protocols for biomarker measurements and maintenance of regular quality assessment is essential for retaining optimal screening performance.²

Among the biochemical markers, a low PlGF and an elevated sFlt-1 suggest placental dysfunction and endothelial injury. Other important biochemical markers include PAPP-A, Placental protein-13 (PP-13), Inhibin-A and Activin-A.

The blood flow in the uterine artery is normally of high pulsatility with a high systolic and a low diastolic flow. As a greater trophoblastic invasion of myometrium takes place in pregnancy, the resistance to blood flow gradually drops. However, a high resistance can persist in preeclampsia. Resistive Index (RI), Pulsatility Index (PI) and the presence of persistent diastolic notching are the parameters to assess uteroplacental blood flow.⁶ In preeclampsia, an increased sFlt-1/PlGF ratio can be detected in the second half of pregnancy and this finding can precede the onset of clinical disease and can also have prognosticating implications. A ratio of less than 38 rules out preeclampsia for at least 1 week. If the ratio is more than 85 or 110, early onset or late onset preeclampsia respectively is likely.⁷

A combination of maternal factors, UtA Doppler studies, MAP, maternal serum PAPP-A and PlGF at 11 to 13 weeks of gestation serves as an effective

screening for preterm preeclampsia.⁸

With a history of severe preeclampsia in a previous pregnancy, any recurrence in a subsequent pregnancy usually occurs 2 – 3 weeks later in gestation and is of lesser severity. In women with such a history tests for antiphospholipid syndrome, factor V Leiden mutation, Protein S, Protein C, hyperhomocysteinuria and antithrombin deficiency may be required.³

Preventive Management:

Preventive measures for preeclampsia include advice for smoking cessation, appropriate dietary advice and optimization of pre-existing diseases like hypertension and chronic kidney disease.³ Prophylactic use of low-dose aspirin can bring down the prevalence of preeclampsia in women at risk for this condition.⁸

The simplest and the most effective preventive strategy is low-dose oral aspirin (75 – 150 mg daily) ideally started before 16 weeks of gestation. Oral calcium supplementation, which is normally routinely given in pregnancy anyway, is also an important preventive intervention. Lifestyle interventions include weight optimization and balanced nutrition. Regular antenatal surveillance and management of comorbidities is obviously of paramount importance.

Metformin has been found to reduce sFlt-1 and sEng secretion possibly by inhibiting the mitochondrial electron transport chain and thereby to reduce endothelial dysfunction and to induce angiogenesis. Metformin therefore holds the potential to prevent or treat preeclampsia.⁹

Discussion:

Preeclampsia is a multisystem disorder and is characterized by uteroplacental dysfunction which may culminate in fetal growth restriction, preterm delivery and intrauterine fetal death. Early-onset preeclampsia (developing before 34 weeks of gestation) and late-onset preeclampsia (developing at or after 34 weeks of gestation) have been recognized as two different disease entities with different biochemical markers, heritability, clinical features and obstetric outcomes.¹⁰

Ongoing research is looking at the possible preventive role of statins (particularly pravastatin),

antioxidants and angiogenic factors. Personalized risk prediction using Artificial Intelligence is also being explored. Because of its unpredictable course and serious complications, anticipation, prevention, early detection and optimal management of preeclampsia continue to pose a tough challenge in obstetric practice.

Many tests have been developed for predicting preeclampsia in pregnancy and newer tests involving metabolomics are on the horizon.³

As the pathophysiology of preeclampsia is complex, no single biomarker is sufficiently effective in screening. The search for further predictive models must continue with this in mind. Early-onset and preterm pre-eclampsia are prone to more adverse events than term preeclampsia.²

An optimal approach to women at risk for pre-eclampsia is the employment of a multi-marker algorithm followed by the identification of treatable risk factors to offer the required benefit.¹¹

Conclusion:

Pre-eclampsia constitutes one of the main contributors to maternal and perinatal morbidity and mortality worldwide. Importantly, early-onset preeclampsia is a larger contributor in this regard because in some of these cases, in the best interest of the mother and the baby, the pregnancy may have to be terminated before full maturity is attained. Consequently, the early identification of pregnant women at risk for developing preeclampsia is more rewarding as it allows more time for preventive and therapeutic intervention.²

Conflict of Interest: None to declare.

References

1. Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring. *J Clin Med*. 2019 Oct 4;8(10):1625.
2. Chaemsaihong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. *Am J Obstet Gynecol*. 2022 Feb;226(2S):S1071-S1097.e2
3. English FA, Kenny LC, McCarthy FP. Risk factors and effective management of preeclampsia. *Integr Blood Press Control*. 2015 Mar 3;8:7-12.
4. Maynard SE, Venkatesha S, Thadhani R, Karumanchi SA. Soluble Fms-like tyrosine kinase
5. Brosens I, Puttemans P, Benagiano G. Placental bed research: I. The placental bed: from spiral arteries remodeling to the great obstetrical syndromes. *American journal of obstetrics and gynecology*. 2019 Nov 1;221(5):437-56.
6. Gaillard F, Knipe H, Hacking C, et al. Uteroplacental blood flow assessment. Reference article, Radiopaedia. org (Accessed on 04 Aug 2026) <https://doi.org/10.53347/rID-2247>
7. Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, Klein E, Lapaire O, Llurba E, Ramoni A, Vatish M, Wertaschnigg D, Galindo A. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. *Ultrasound Obstet Gynecol*. 2015 Mar;45(3):241-6.
8. O'Gorman N, Wright D, Rolnik DL, Nicolaides KH, Poon LC. Study protocol for the randomised controlled trial: combined multimarker screening and randomised patient treatment with ASpirin for evidence-based PREeclampsia prevention (ASPRE). *BMJ Open*. 2016 Jun 28;6(6):e011801
9. Brownfoot FC, Hastie R, Hannan NJ, Cannon P, Tuohey L, Parry LJ, Senadheera S, Illanes SE, Kaitu'u-Lino TJ, Tong S. Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. *Am J Obstet Gynecol*. 2016 Mar;214(3):356.e1-356.e15.
10. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv*. 2011 Aug;66(8):497-506.
11. Gabbay-Benziv R, Oliveira N, Baschat AA. Optimal first trimester preeclampsia prediction: a comparison of multimarker algorithm, risk profiles and their sequential application. *Prenatal diagnosis*. 2016 Jan;36(1):34-9.

Answers

Infectious disease

1. The answer is c.
2. The answer is a.
3. The answer is b.
4. The answer is d.

Rheumatology

1. The answer is b.

Nephrology

1. The answer is c.
2. The answer is b.

Neurology

1. The answer is a.
2. The answer is d.

Basic sciences

1. The answer is a.
2. The answer is e.
3. The answer is e.
4. The answer is a.



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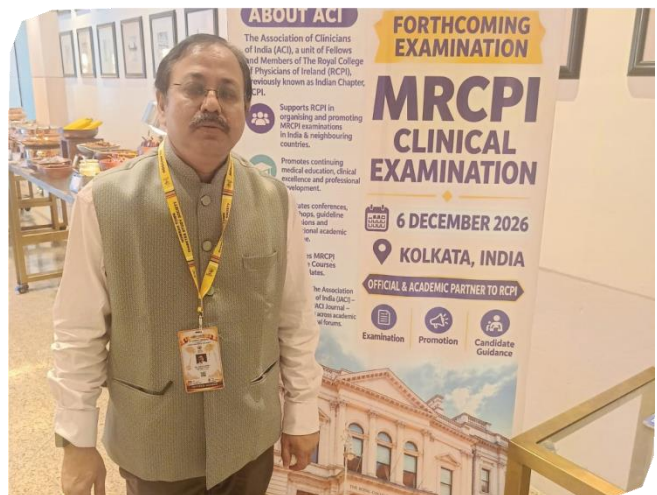
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