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COVER PHOTO: In 1733, Sir Stephen Hales performed the first recorded direct measurement of blood pressure on an anaesthetised horse. He inserted a fine brass tube connected to a 9-foot vertical glass tube into the horse's carotid artery, observing the blood rise over 8 feet and fluctuate with the heartbeat. This was the foundation of modern blood pressure measurement.

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From Chairman's Desk

As the preparation for the first edition of 2026 is in the final stage, I am delighted to announce that Dr. Diarmuid O'shea, the President, Royal College of Physicians of Ireland is arriving in Kolkata on 6th March 2026 along with Dr. Geoff Chadwick, International Examination Convenor, Sinead Lucey, Director of Business Development & Examinations, Sinead Freeman, Senior Manager, Examinations and Global Training to conduct MRCPI Clinical exam on 7th March.

President Dr. O'shea and Dr. Chadwick will participate by president's oration and delivering lectures in the International Master Class on 8th March Along with Eminent speakers like Prof. Sanjay Badada and Prof. Gourdes Chaudhari. The President will also launch The Journal of Association of Clinicians of India (JACI) in front of the august gathering during the Master Class program. Subsequently, multi -disciplinary CME will continue in Internal Medicine, Paediatrics and Obstetrics +Gynaecology until 6 pm

In keeping with our commitments, the editorial team have been working tirelessly. I would like to extend profuse thanks and gratitude to Editor in Chief, Prof Kanjaksha Ghosh, Joint Editors, Dr. Kaushik Ghosh and Dr. Mainak Mukhopadhay, all members of Journal team and secretaries Mr. Debashis Chakraborty and Ms. Basabpriya Das for their sincere effort, perseverance and determination for fulfilling their task on time. We would like to continue publication of this Journal twice a year.

I extend the season's greetings and best wishes to all for the year ahead.

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
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View Point

Any medical association in the world has one or several ways of communications to its members, other doctors and sometimes to the lay public. In present day of multiple electronic communication systems (video, audio AI embedded systems) these are also utilized or embedded in many widely read medical journals.

Associations of Clinicians of India draws its inspiration from the great tradition of Irish Medicine and most of the members of the society are either Fellows or Members of The Royal College of Physicians of Ireland.

The current issue of the journal presents a mixture of review articles, recent advances, original article, medical quiz etc. One of the important article is the instruction for postgraduate trainees on how to prepare for the Membership examination particularly the pattern of examination. The journal also presents authors from both Ireland and India bringing a distinct flavour in the articles. A forward by the current president of the Royal College adds to the importance of this collection. I have been helped by two of my Joint Editors Dr. Koushik Ghosh and Dr. Mainak Mukhopadhyay for final compilation and editing of the articles.

I hope this journal will be received with enthusiasm by the practicing doctors and the students alike. Particularly students will be benefitted by gaining new knowledge and skills after reading this journal.

Prof. (Dr) Kanjaksha Ghosh
Editor-in-Chief
Former Director, National Institute of Immunohaematology (ICMR)
Hon Prof., Clinical Haematology and Transfusion Medicine
KEM Hospital, Mumbai, India.

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MRCPI EXAMINATION IN 2026

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	:	16th April 2026
MRCPI Part I (General Medicine) Written	:	20th August 2026
MRCPI Part I (General Medicine) Written	:	10th December 2026
MRCPI Part II (General Medicine) Written	:	19th March 2026
MRCPI Part II (General Medicine) Written	:	18th June 2026
MRCPI Part II (General Medicine) Written	:	29th October 2026
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MRCPI Part II (General Medicine) Clinical	:	29th May – 30th June 2026 (Ireland)
MRCPI Part II (General Medicine) Clinical	:	18th Sept – 23rd October 2026 (Ireland)
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MRCPI Part II (General Medicine) Clinical	:	7th March 2026
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MRCPI Part II (Paediatrics) Written	:	13th March 2026
MRCPI Part II (Paediatrics) Written	:	21st August 2026
MRCPI Part II (Paediatrics) Clinical	:	29th May – 5th June 2026 (Ireland)
MRCPI Part II (Paediatrics) Clinical	:	29th May – 5th June 2026 (Ireland)
MRCPI Part II (OBGYN) Written	:	5th March 2026
MRCPI Part II (OBGYN) Written	:	4th September 2026
MRCPI Part II (OBGYN) Clinical	:	7th Feb & 8th Feb 2026 (Dubai)
MRCPI Part II (OBGYN) Clinical	:	22nd May & 23rd May 2026 (Dublin)
MRCPI Part II (OBGYN) Clinical	:	22nd May & 23rd May 2026 (Muscat)

Message from President of RCPI

It is my great pleasure to add this foreword to the forthcoming Journal of Association of Fellows and Members of the Royal College of Physicians of Ireland. Participated in by authors from both India and Ireland. The journal plays a very important role in the overall academic activities in addition to many CMEs, Conferences, case presentations and training.

I am looking forward to be in Kolkata along with Dr Geoff Chadwick, International Examination convenor RCPI along with Ms Sinead Lucey, Director of Business Development & Examinations, Sinead Freeman, Senior Manager, Examination and Global Training, Royal College of Physicians of Ireland, for participating in the MRCPI clinical examination in General Medicine on 7th March 26 followed by Master class in Medicine on the following day.

We wish for the continued success of the ACI in the academic activities, Clinical examinations and publication of Journal with the participation of the College."

Dr. Diarmuid O'Shea
President
Royal College of Physicians of Ireland

CONTENTS

REVIEW ARTICLE

Obesity-related Pulmonary Disease – A Growing Burden

Geoffrey Chadwick

Obesity is a growing disease

Obesity has often been referred to as "an epidemic" in recent years. It is the most common metabolic disease in the world, and it has been well documented that the prevalence of obesity is increasing worldwide, with significant health and socioeconomic implications[1–6]. Globally, the prevalence of obesity between the years 1980 to 2013 has increased 27.5% in adults, and 47% in children, with 2.1 billion people in the world classifying as overweight (body mass index (BMI) >25 kg/m^2), while over 500 million are classified as obese (BMI >30 kg/m^2)[7]. While the rise in obesity has been attenuated somewhat in developed countries, with improved public health education, it continues unabated in developing countries; however, obesity and obesity-related disease are projected to increase in all European countries by 2030[2]. In developed countries, obesity is most prevalent in lower socio-economic groups, where public education initiatives may not have the same yield, and the population may have poorer access to fitness facilities, fresh fruit and vegetables, and overall more difficulty making healthy lifestyle choices[3].Obesity continues to rise due to a worldwide change in our regular diet with increased caloric intake, decreased physical activity, and a shift in the gut microbiome.

In Ireland, about 1 in 4 of both the male and female population qualify as obese[7], with around 2 out of 3 of the population qualifying as overweight. Childhood obesity rates are higher than the European Union (EU) average, and if current rates of obesity rise continue, it is estimated that by 2030, 48% of men and 57% of women will be obese, while over 80% of both men and women will be overweight;this is similar to the projection for future rates of obesity in the United States4. The reasons for Irelands rates of obesity are, again, many-fold; Ireland has the fourth-highest insufficiently active adult population compared with other EU member states; Ireland also has the lowest insufficiently active adolescent population, but this still ranges up to 80%; Ireland is thebiggest consumer for sweets and confectionary in the EU, and are middle-of-the-pack in terms of soft drink consumption, while consumption of fruit and vegetables are low compared with other EU member states[8].

Obesity has substantial health consequences, with six common obesity-related diseases identified as hypertension, diabetes mellitus type 2, coronary artery disease (CAD), cerebrovascular disease (CVD), cancers including oesophageal, colon and cholangial, and osteoarthritis. The majority of deaths related to obesity are cardiovascular. In 2010, over 3.4 million deaths were due to obesity-related disease, along with 3.9% of years of life lost, and 3.8% of Disability Adjusted Life Years (DALYs)[7]. In addition to the increased morbidity and mortality, obesity has a significant healthcare

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cost burden. Obesity generally accounts for up to 2.8% of a country's healthcare costs[9], and an obese individual incurs medical costs up to 30% more than normal1. In contrast, obesity and obesity-related disease amounted to approximately 30% of total healthcare spending in Ireland in 2011[4]. A study by Dee et al evaluated the healthcare costs related to obesity in Ireland, and found that in 2009, direct healthcare costs related to obesity totalled €399 million; these included direct healthcare utilisation such as GP costs, hospital inpatient costs, and drug costs. Meanwhile, indirect costs totalled €729 million; these include missed work days and productivity losses due to the increase in morbidity and mortality related to obesity[6]. In the same year, the total direct healthcare costs of the six obesity-related diseases totalled €2.5 billion. If current obesity projection rates continue into 2030, it is estimated that direct obesity healthcare costs will amount to €5.4 billion, with indirect costs reaching €9.8 billion4. More than 90% of this will be accounted for by coronary and cerebrovascular disease.

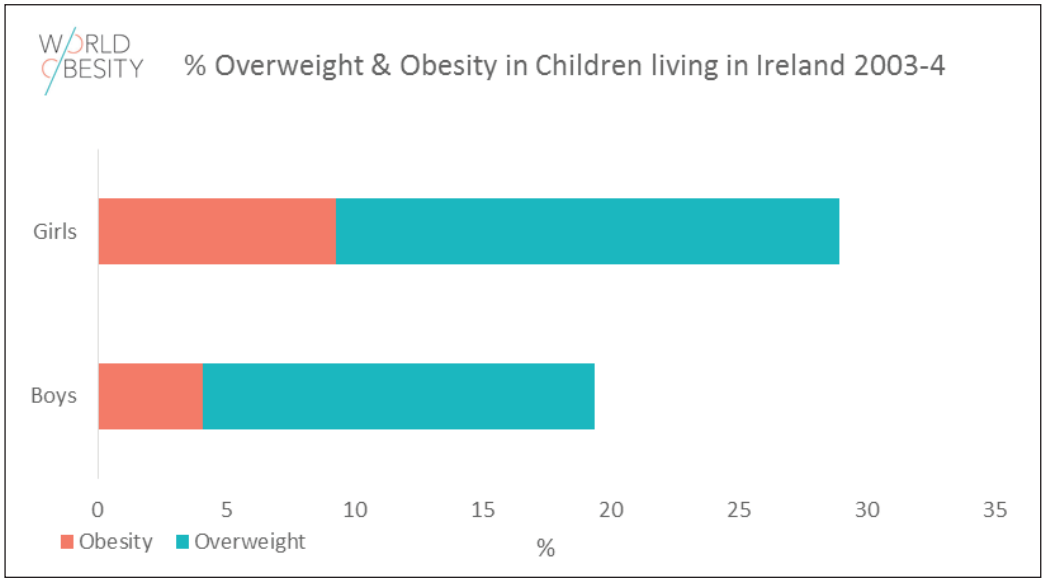

Fig. 1 Childhood rates for overweight and obese 2003-4 (Permission needed)

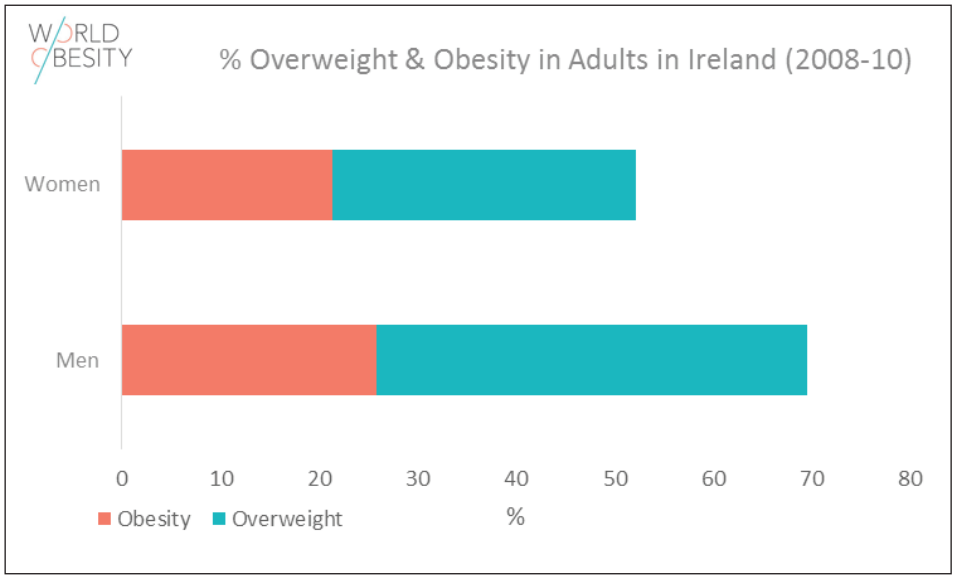

Fig. 2 Adult rates for overweight and obese 2008-10 (Permission needed)

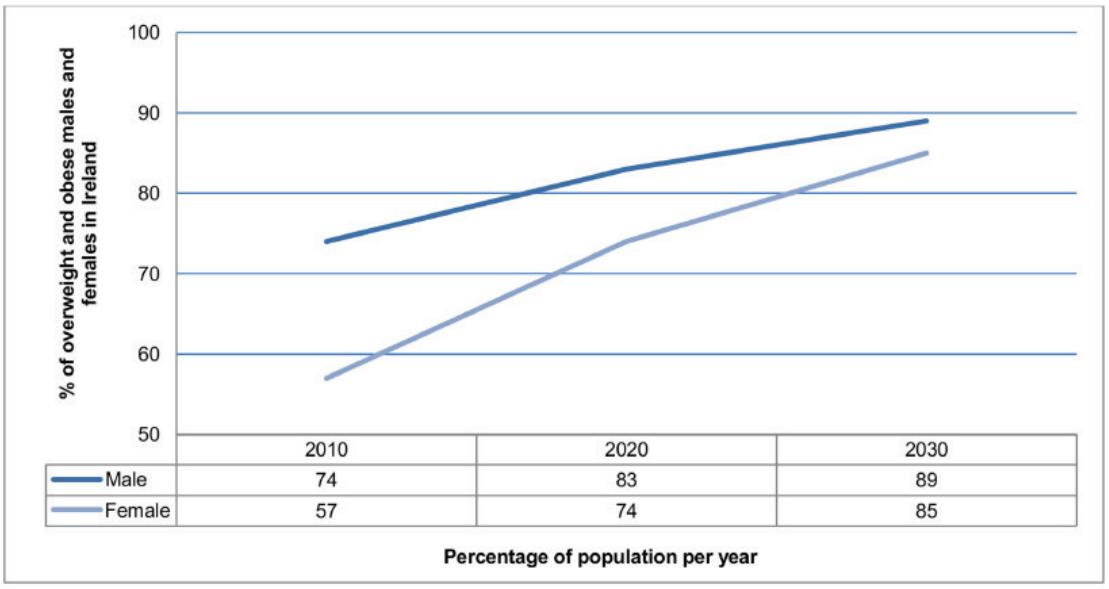

Fig. 3 Projected prevalence of overweight and obesity in the Irish population (PLOS, 2013)

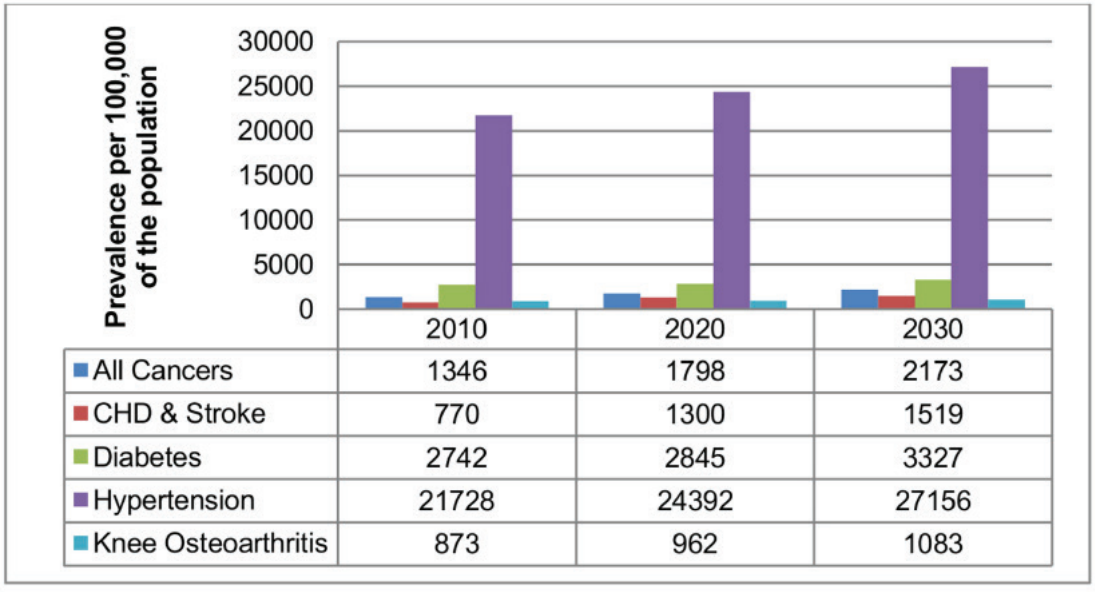

Fig. 4 Projected prevalence of disease per 100,000 population from 2010 - 2030 (PLOS, 2013)

Despite these estimates of increasing prevalence, projections of obesity-related effects based on population BMI reduction are encouraging. A 1% reduction in population BMI could lead to an average reduction of 365/100,000 cases of coronary or cerebrovascular disease, and up to 1,317/100,000 cases with a 5% reduction in population BMI[2]. It is estimated that if Ireland reduces the BMI on a population level by 1%, by 2030, healthcare spending will reduce by €143 million; if Ireland reduces the BMI by 5% on a population level, by 2030, healthcare spending will reduce by €495 million4..

Pulmonary disease related to obesity

Obesity's effects on the lungs are well recognised,

but not as well publicised as the cardio- and cerebrovascular effects. Obesity can result in various "phenotypes", due to a difference of body composition and fat distribution patterns, but Babb et al reported that differences in respiratory mechanics correlated as strongly with BMI as with chest wall fat distribution patterns[10]; therefore, for the purposes of this review article, we will continue to use BMI as a marker for obesity severity.

The effects of BMI on the lungs are complex and diverse. We know that BMI is inversely proportional to the forced expiratory volume in 1 second (FEV1) as a predictor of all-cause mortality, but the effect of BMI on lung function in general can vary from person to person, likely as a result of differences in fat distribution[3]. Truncal obesity is most associated with the mechanical effects of lung restriction associated with obesity, such as lower lung volumes, reduced lung and chest wall compliance, and a reduced end-expiratory lung volume (EELV)[3,10,11]. In contrast, subcutaneous and visceral fat is associated with a higher cardiovascular risk, and furthermore, neck circumference, independent of BMI, is a predictor for obstructive sleep apnoea[3,11]. Aside from the mechanical effects, adiposity causes in increase in circulating adipokines, resulting in systemic inflammation that has its own effects on the lungs[3,12,13].

The mechanical effects of obesity on the lung

The mechanical effects of obesity result from adipose tissue deposition, particularly on the abdomen and chest well. This results in reduced compliance, increasing static elastic recoil pressure of the lung, and reducing the lung volumes14the prevalence of both chronic obstructive pulmonary disease (COPD. While there is certainly reduced compliance of the chest wall due to excess adiposity, there is also reduced compliance of the lung itself, as the reduced lung volume results in a compressive bibasal atelectasis and airway closure. This causes heterogenous air-trapping, and an increase in intra-thoracic blood volume, all of which contribute to the lungs' stiffness. In addition, the lower lung volumes result in a lower EELV, effectively placing the tidal volume at the lower (and less compliant) end of the lung's pressure-volume curve, and increasing the work of breathing[3,14] the prevalence of both chronic obstructive pulmonary disease (COPD. BMI and EELV have been shown to be inversely proportional, with an EELV decline until a BMI of over 35 kg/m^2, when the EELV plateaus at what is likely a "minimal operational" value, as a critical mass of smaller airways close15. The total lung capacity (TLC) is relatively preserved, and in the context of a reducing EELV, the inspiratory capacity increases as the EELV reduces, to reflect this. This continues until morbid obesity, at which stage the EELV reaches its minimal operational value, both the TLC and IC start to decline.

Sleep disordered breathing

These mechanistic effects contribute to the development of obstructive sleep apnoea (OSA), which is defined as repetitive collapse of the upper airway, at a rate of more than 5 apnoeic or hypopnoeic events per hour (AHI). This causes episodic hypoxia (and possibly hypercapnoea), dynamic changes in intrathoracic pressure, and changes in blood pressure. This results in poor quality sleep, and obstructive sleep apnoea syndrome (OSAS) is defined as an AHI > 5 with clinically significant excessive daytime somnolence. In addition to the chest wall and truncal adiposity, neck adiposity significantly contributes to the development of OSA, and, independent from BMI, neck circumference has been shown to be the anthropometric most closely associated with OSA[16]. Increased neck fat causes increased intraluminal pressure, resulting in a crowded and collapsible upper airway. The abdominal obesity and reduced lung volumes also contribute to the upper airway collapse by reducing longitudinal upper airway traction11. Obesity is the most significant risk factor for OSA, responsible for 30-50% of the AHI variance, and the only modifiable risk factor[17]. Weight gain in particular is associated with an increase in AHI; Peppard et al reported a 70% increase in AHI with a 20% weight gain, while a 20% weight loss resulted in only a 48% reduction in AHI[18].

In addition to the mechanical factors of obstruction described above, obesity contributes to hypoventilation. Normal sleep is associated with hypoventilation and mild, transient hypercapnoea, as response to ventilatory stimuli is reduced, muscle tone is reduced, EELV is reduced in a

supine position and gas exchange is reduced. In obesity, this is exaggerated, as lung volumes are compromised due to adiposity, and chest wall compliance is impaired. Gas exchange and airflow obstruction are both worsenedas a result of atelectasis and airway closure, and work of breathing is increased. This respiratory muscle dysfunction may lead to significant hypoventilation, and obesity hypoventilation syndrome (OHS) is seen when the nocturnal hypoventilation is significant enough to cause diurnal hypercapnoea, in the setting of obesity, without an alternative cause[11]. This process can be a vicious cycle; obese eucapnoeic patients can maintain an increased respiratory drive to meet the increased ventilatory requirements, however hypercapnoeic patients lack this drive, and the hypoventilation worsens without treatment[17].Leptin resistance in obesity may contribute to worsening hypoventilation, as the hormone normally assists in increasing the respiratory drive to meet its workload[11]. OHS prevalence in obesity is estimated at 11-38%, and in hospitalised obese patients, 31% had daytime hypercapnoea[19]. OHS is associated with a significantly higher morbidity and mortality compared to OSA, mainly from cardiorespiratory compromise[20]. Uncontrolled OHS results in pulmonary and systemic hypertension, and more frequent presentations with decompensated right heart failure. Hospitalisation rates and health service usage are significantly higher in patients with OHS, even when compared with eucapnoeic morbidly obese patients.[21] These patients are also more likely to require admission to intensive care if hospitalised, and more likely to need mechanical ventilation. 18-month mortality, post hospitalisation, is shown to be increased (23%) in patients with OHS, versus 9% in uncomplicated obese patients.[22]

The mainstay of treatment for sleep disordered breathing is nocturnal positive airway pressure, which splints open the upper airways, increases lung volumes, and improves gas exchange. OHS is part of a spectrum of sleep-disordered breathing phenotypes, and in fact, very few patients have sustained, non-obstructive hypoventilation[23]. As a result, many patients can effectively be treated with continuous positive airway pressure (CPAP), or at least an initial run of bilevel positive airway pressure (BiPAP) to resolve the hypoventilation, followed by CPAP. Mandibular advancement devices can be used for milder disease or patients with smaller jaws, however these are likely insufficient in the context of obesity. Weight loss should always be recommended, as it will improve respiratory muscle function, improve gas exchange, as well as haemodynamic function, but this is rarely enough to eliminate the sleep-disordered breathing entirely. Weight loss in obesity may simply convert non-positional OSA to positional OSA (as AHI, snoring, and hypoxia are all worse in the supine position). Buchwald et al reported, in a meta-analysis, that bariatric surgery led to an 86% resolution in OSA, however in severe OSA surgery may only lead to improvement, rather than resolution[24]. Treatment is also important on a biochemical level. OSA perpetuates the cycle of inflammation seen in obesity, as increased sympathetic activity and oxidative stress (due to intermittent hypoxia) cause a cytokine response and increased levels of IL-6, TNF-α and CRP, like what is seen in the obesity response. Finally, poor sleep is seen to lead to an increase in ghrelin (which signals hunger) and a reduction in leptin (which signals satiety), leading to an increase in appetite, and high calorific food intake, showing that sleep disordered breathing itself has a feedback response on obesity[25].

Asthma

Asthma prevalence rises with obesity, and, in the context of rising obesity prevalence, has risen 2.5 fold from 20 years ago[12]. Several studies have reported a correlation between BMI and asthma symptoms[26–28]. It should be noted, that most studies focus on self-reported rather than physiologically defined asthma. Obesity is associated with smaller lung volumes, reducing the diameter of smaller airways, and causing increased airflow obstruction. However, Rönmark et al found that obesity increased the odds ratio for asthma by 2.7, and this was confirmed by bronchoprovocation[28]. In fact, the data regarding asthma in obesity is conflicting; obesity is certainly associated with increased asthma symptoms, but whether there is increased airway hyperresponsiveness is unclear. We know that there are increased circulating levels of leptin in obesity, in the context of increased leptin resistance[29]. Mouse models have shown

reduced levels of leptin production and leptin receptors, as well as reduced carboxypeptidase E, both of which can contribute to increased airway hyperresponsiveness[30]. In addition, leptin has been shown to enhance the inflammatory response in the lungs in animal models[31], while adiponectin, reduced in obesity, has been seen to reduce inflammation and airway hyperresponsiveness in animal models[12,32,33]. Huang, et al, found an increased BMI was associated with an increased dose-dependent risk of atopy in Taiwanese girls[34], however, von Mutius et al, found no significant relationship between BMI and atopy, although they did find a positive relationship between BMI and asthma symptoms[35].

Despite the lack of significant causal data, weight loss has been shown to improve clinical and physiological parameters, such as reduce diurnal peak expiratory flow variability, increase EELV, and reduce airflow obstruction[36]. Aaron et al showed an improvement in FEV1 and forced vital capacity (FVC), but no change in airway hyperresponsiveness[37]. Bariatric surgery has been shown to reduce asthma symptoms and improve lung function, but with no demonstrable change in fractional exhaled nitric oxide (FeNO)[38]. The link between obesity and asthma may not be directly causal at all; obesity is associated with increased gastro-oesophageal reflux disease, as well as sleep-disordered breathing, both of which could contribute to asthma-type symptoms. In addition, obesity is associated with increased circulating levels of inflammatory markers such as leptin, IL-6 and TNF-α, which are associated with glucocorticoid insensitivity and may attenuate response to treatment. Ultimately, the combination of obesity and asthma is associated with more frequent emergency department visits, longer stays in the emergency department, and more hospitalisation[39].

Current Practice and Future Possibilities

Obesity-related pulmonary disease in Ireland is managed largely in general practice (GP) surgeries and general respiratory outpatients. Obesity and weight management clinics exist in Dublin and Galway, and are managed with a focus on endocrinology and general medicine. However, neither have dedicated respiratory input. Obese patients with asthma-type symptoms are often managed empirically by their GPs. Patients with symptoms suggestive of OSA or OHS are referred to local sleep clinics for assessment, either by their GP, or by the weight management service when they are seen.The issue here is the prolonged waiting time that is associated with a referral to most public health services; for a person who has already been waiting upward of two years for their weight management appointment, another six months to two years wait for a sleep assessment is an unacceptable amount of time to lapse with a clinical condition associated with potentially significant morbidity or mortality. The single biggest referrer to the St. Vincent's University Hospital sleep service is the St. Columcille's weight management service, who see up to 200 new patients annually, the majority of whom symptomatic of untreated sleep-disordered breathing. Once patients are seen in the sleep clinic, the next wait is one for an inpatient sleep assessment. This has additional implications for the local hospitals, in costs such as bariatric beds for the morbidly obese patients, or increased healthcare expenditure for patients presenting with right heart failure due to untreated sleep disordered breathing.Finally, as more patients are being referred with symptoms of sleep disordered breathing and being started on positive airway pressure, there is no way of effectively monitoring compliance and efficacy of the nocturnal devices, without bringing return patients into already overloaded clinics. As 46 to 83% of patients may be non-adherent to CPAP devices[40], this can result in suboptimally managed sleep-disordered breathing, as well as increased cost incursions to the taxpayers in the form of potentially unused sleep devices rented from (paid for by) the HSE, or indeed indirect costs such as missed productivity or work days, or even road traffic accidents. Currently, the Irish public health service does not have the infra-structure to manage the burden of obesity-related pulmonary disease, not to mention future projections. .

There are improvements that can be made towards future practice. Firstly, as obesity is a growing epidemic, current data on the prevalence of obesity-related respiratory disease should be sought. Current data will allow for improved service provision, in both in- and outpatient

settings, in terms of staff and resource allocation. For example, if the need for sleep studies in the bariatric population far exceeds the resources for inpatient sleep assessment, services should utilise the available domiciliary sleep studies facilitated by sleep company providers. Home sleep studies have been externally validated, and provides similar diagnostic efficacy at a lower cost[41–43].Another potential solution would be the implementation of an electronic patient record system for sleep services, to which patient sleep devices are linked, with data viewable remotely by sleep services to monitor efficacy and compliance, rather than overloading already-busy outpatients. Finally, in the context of a growing cohort of patients with obesity-related respiratory disease, these patients could be seen in a clinic dedicated to these issues. By centralising these patients care, they are reviewed by physicians who are familiar with common respiratory complications of obesity, in outpatientsfurnished with bariatric equipment, with easy access to services such as domiciliary sleep studies.

Conclusion

Obesity-related respiratory disease is, along with obesity itself, a growing issue. The obesity epidemic is complex, with multifactoral solutions that need to be implemented on a national level, with obesity-related respiratory disease in particular havinghealth, resource and economic implications for both patients and health service providers. Despite public health initiatives, the prevalence of obesity continues to rise, andby recognising the prevalence of common obesity-related disease such as sleep disordered breathing and asthma, the Irish health system will be better able to plan for the future.

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REVIEW ARTICLE

Evolution in the Management of Al Amyloidosis

Philip Murphy

Headline: AL amyloidosis is the most common systemic amyloidosis. The use of targeted therapies has resulted in marked improvement in prognosis. The use of monoclonal antibodies to degrade amyloid deposits holds great promise for the future.

Systemic light chain (AL) amyloidosis is a monoclonal plasma cell proliferative and clinical manifestations are due to extracellular deposition of abnormal protein fibres (amyloid fibrils) formed by either kappa (k) or lambda (L) immunoglobulin light chains secreted by the plasma cells. Amyloid fibrils, thus, accumulates in various tissues leading to organ damage. At present, therapy includes supportive management of organ dysfunction as well as anti-plasma cell therapy to reduce the amyloidogenic light chain levels as rapidly as possible. New treatments, such as monoclonal antibodies, aimed at clearing deposited amyloid fibrils from damaged organs, are in clinical trials and, if successful, could revolutionize the treatment of AL amyloidosis.

Incidence and diagnosis

The approximate annual incidence of AL amyloidosis is 10 cases per million persons. The insidious organ-dependent clinical presentation often leads to delayed diagnosis and a majority of patients will have multiple organ involvement when finally diagnosed. The most frequently affected organs include kidneys and heart, followed by the liver, gastrointestinal tract and the autonomic nervous system. Myocardial infiltration leading to heart failure results in worse outcomes. Serum cardiac biomarkers NT-pro-BNP and troponin T reflect the extent of cardiac involvement.

Diagnosis is made by a tissue biopsy stained with Congo red demonstrating amyloid deposits with confirmatory typing by immunofluorescence or mass spectrometry. Adjunctive laboratory tests include assaying for organ dysfunction and directly measuring the light chains circulating in the peripheral blood. AL amyloidosis must be distinguished from other types of systemic amyloidosis in which protein-based infiltrate is deposited into tissues, as treatments for each type are completely different. For example, in transthyretin (TTR) amyloidosis, transthyretin, an abundant protein produced by the liver, is prone to misfold when in monomeric form, leading to gradual deposition as amyloid deposits. Tc-pyrophosphate nuclear imaging is helpful in distinguishing AL from TTR cardiac amyloidosis. Serum amyloid P component (SAP) scintigraphy, available at the National Amyloid Centre, Royal free Hospital, London, provides a clear picture

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of the location and quantity of the AL amyloid deposits in organs throughout the body and is useful at diagnosis and at follow up.

Supportive care

Patients with cardiac failure or renal involvement can be treated with salt restriction and diuretics. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are helpful for nephrotic syndrome, whilst dialysis may be necessary for progressive renal disease. As there is a high prevalence of conduction disease in cardiomyopathy due to AL amyloidosis, amiodarone or an implantable defibrillator may be required.

Current anti-plasma cell therapies

Targeted systemic anti-plasma cell therapies are similar to those used in multiple myeloma and are influenced by the patient's performance status and level of organ dysfunction. Improvements in therapy have increased 5 year survival rates from 15% in the 1980s to nearly 50% in the mid 2010s. In newly diagnosed patients requiring induction therapy, combination therapy with daratumumab, a monoclonal antibody targeting plasma cells, together with cyclophosphamide, bortezomib and dexamethasone (Dara-CyborD) is now the new standard of care in many developed countries. Immunomodulatory drugs tend not to be used frontline due to tolerability issues. Only a small minority of patients are fit enough for the most effective treatment, autologous haematopoietic stem cell transplantation. BCL-2 inhibitors may be useful for relapsed/refractory patients whose plasma cells have chromosomal translocation t(11;14).

Future direction

Birtamimab and anselamimab are monoclonal antibodies which are currently in clinical trials. They target the light chains making up the amyloid fibrils, causing degradation of amyloid deposits. If proved effective, these monoclonal antibodies will revolutionize the treatment of AL amyloidosis, especially for patients with more severe forms of cardiac amyloidosis, for whom prognosis currently remains poor.

MEDICAL HISTORY

Sir Dominic Corrigan: The Man Who Showed the Secret Door—Legacy and Impact on Irish Health care

Kaushik Ghosh

Abstract

Abstract: Sir Dominic John Corrigan (1802–1880) was among the most influential physicians in nineteenth-century Ireland, making enduring contributions to cardiovascular medicine, medical education, and public health. Born into a modest family in Dublin, Corrigan rose to prominence through exceptional clinical observation, academic leadership, and sustained engagement with the social determinants of disease. He is best remembered for his classical description of aortic regurgitation, later termed Corrigan's pulse, which remains central to bedside cardiovascular examination.Corrigan's influence extended beyond clinical practice. He played a significant role in reforming medical education, strengthening professional standards, and shaping health governance during a period of major social and political change. His career coincided with the Great Irish Famine, during which he emerged as an important medical voice linking poverty, malnutrition, and disease, and advocating for systemic responses to public health crises.Contemporary accounts depict Corrigan as an exceptionally busy practitioner, balancing clinical work, teaching, institutional responsibilities, and public service. An anecdote describing his occasional departure from his consulting chamber through a secondary exit has acquired symbolic significance, reflecting the pressures and adaptive strategies of nineteenth-century medical practice.This paper situates Corrigan's life and work within Irish medical history, examining his clinical contributions, educational reforms, and public engagement. It argues that his legacy lies not only in enduring clinical descriptions but also in an integrated vision of medicine that combined scientific rigor with social responsibility.

Keywords:

Corrigan pulse, cardiovascular medicine, Irish healthcare, medical education, public health

Obesity is a growing disease

Sir Dominic John Corrigan, 1st Baronet (1802-1880), is one of the most eminent physicians in Ireland whose work has made significant contributions to cardiovascular medicine (Fleetwood, 1951). Born into a modest family of an agricultural tools dealer in Thomas Street, Dublin, Corrigan is a true story of the rise of the poor boy to a medical genius that can be witnessed in post-Catholic Emancipation Ireland. His legacy runs deep in clinical signs that are named after him; the influence of Corrigan has infiltrated reforms in medical education, government policy on health, and the institutional frameworks that persist in defining Irish healthcare.

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Childhood and Health Development

Corrigan was initially educated at St. Patrick's College, Maynooth; the college physician encouraged him to get involved in medicine (Widdess, 1963). After his apprenticeship with local doctor Edward Talbot O'Kelly, Corrigan was formally trained in medicine at Dublin but went to Edinburgh Medical School, where he was awarded his Doctor of Medicine diploma in August 1825. On returning to Dublin, he opened a private practice some time later, shifting to the elegant Merrion Square West that was the center of high-end medical practice in Ireland in 1837 (O'Brien, 1987).

Fig. 1 Sir Dominic Corrigan

Contributions to Cardiology as Revolutionary

The most notable medical accomplishment of Corrigan was the result of his careful observations with regard to patients having valves of the aorta. He described aortic regurgitation in his 1832 seminal article in the Edinburgh Medical and Surgical Journal, where he described the typical observable pulsations of the head and upper extremity arteries, the cardiac murmur, and pulse quality (Corrigan, 1832). His description was so accurate and clinically important that the eponymous terms "Corrigan pulse" and "Corrigan disease" are still used to refer to the phenomena across the globe (McGee, 2021).

The importance of the work of Corrigan was not limited to the description. He clarified the physiological processes that occurred in aortic insufficiency and how the regurgitation of blood into the left ventricle created the usual arterial collapse. The name Maladie de Corrigan should be given to aortic heart disease in honor of the credit that this Irish doctor gave to the study of the heart (Fleetwood, 1951). Further contributions to his reputation as a methodical clinical researcher were his articles on cirrhosis of the lung (1838), aortitis as the cause of angina pectoris (1837), and mitral stenosis (1838).

The innovations in diagnostics introduced by Corrigan were based on the study of the poor population of Dublin and great clinical practice. He worked at the Charitable Infirmary Jervis Street (1830-43) and House of Industry Hospitals (1840-66), where he had access to large groups of patients with advanced disease and thus could perform clinical-pathological correlations that formed the basis of his research (Widdess, 1963).

Service During the Great Famine and Public Health

The unswerving effort of Corrigan was quite noticeable in the Great Famine of Ireland (1845-1852). Corrigan also became a member of the Central Board of Health formed in 1846 to deal with the public health disaster that had accompanied mass starvation (Ó Gráda, 1999). His endorsement of the recommendations of the Board, especially on the issue of physician compensation, caused friction with the heads of the medical profession, who later opposed his appointment to be an honorary fellow in the King and Queen College of Physicians in Ireland.

The experience of working in the country throughout the famine shaped Corrigan into realizing how malnutrition, overcrowding, and social disturbance led to disease transmission, which would later guide contemporary views of social determinants of health in public health (Kelly, 2017). In his Lectures on Fevers (1853), he shed a lot of light on epidemic diseases, showing that he had a deeper insight into the role of the physician, who was not only supposed to heal but also to deal with the wider conditions that prevailed in society and influenced the state of health.

"**Fig. 2** Medicine Amid Hunger: Corrigan's Compassion and Clinical Courage During the Irish Famine

Medical Education Reform and Institutional Leadership

Corrigan showed great strength and political skill, though he was unsuccessful in 1846. He overcame the opposition of the College of Physicians by being entered alongside new qualified doctors in the licentiateship examination in 1855 and becoming a fellow in 1856 and, in 1859, the first Catholic president of the institution (Coakley, 1988). His election to this prestigious office four times, the first time in the history of the college, was fundamentally changing the college. The Irish College of Physicians was the first place in the British Isles where women were admitted to the license examination in his presidency (Kelly, 2010).

Corrigan was a member of the General Medical Council and a great reformer of medical education, having been a member of it for more than twenty years. Since the 1840s, he was a senator in the senate of Queen's University and was made the vice-chancellor in 1871 (O'Brien, 1987). His seven-year tenure as a Liberal Member of Parliament from 1870 to 1877 in Dublin gave him the opportunity to lobby for education reform in Ireland and campaign for the early release of Fenian political prisoners.

Corrigan was named physician-in-ordinary to Queen Victoria in Ireland in 1847, the first Catholic to be so honored. His establishment as baronet in 1866 was an appreciation of his work in the field of medicine as well as his service to the society (Fleetwood, 1951). There is a statue of Corrigan by the sculptor John Henry Foley that is a place of honor in the Graves Hall of the Royal College of Physicians of Ireland in commemoration of his institutional leadership and professional accomplishments.

The Contemporary Irish Healthcare Legacy

The impact of Corrigan on modern healthcare in Ireland has many dimensions. His clinical observations form the direct part of medical education and practice. The pulse of Corrigan is still taught in cardiac physiology and clinical

examination courses to medical students all over the world (McGee, 2021). The signs of diagnosis that he has provided are the basic elements of cardiovascular examination, and they show how attentive clinical observation will be regarded as still useful even in the era of technology in medical imaging.

In his honor, there is a cardiology ward in the Corrigan Ward at Beaumont Hospital, Dublin. Beaumont Hospital, in its turn, is a symbol of the institutionalized legacy of the hospitals in which Corrigan worked, having already taken over the Charitable Infirmary Jervis Street and the Richmond Hospitals upon its inauguration in 1987. The hospital has a Corrigan Faculty, which is devoted to medical education and postgraduate training.

In Ireland, medical education and professional standards are still the elements that focus on the Royal College of Physicians of Ireland, which Corrigan led with such dignity (Royal College of Physicians of Ireland, 2021). The progressive policies that the college has been practicing, such as admitting women to professional examinations early, demonstrate the values that Corrigan stood up for. His campaign for better medical education was the basis of advanced medical education programs that currently define Irish medical education.

The focus on clinical observation by Corrigan as opposed to pure theoretical knowledge appeals to the modern focus on evidence-based medicine and clinical competency. His statement that the shortcomings of physicians were not related to their lack of knowledge but to their lack of clinical observation foreshadows modern beliefs on excessive dependence on technological investigations to the detriment of clinical examination (Elder et al., 2017). The concept of close observation of the patient, history taking, and the ability to diagnose the patient by examining them—all these issues are still stressed by medical educators in the footsteps of Corrigan.

Corrigan's Secret Door: A Metaphor for Physician Wellbeing

One of the most persistent metaphorical legacies of Corrigan is probably not his clinical descriptions, but a concept that has come to embody the idea of physician wellbeing and survival in the challenging environment of medical practice: a notion of Corrigan's secret door. Corrigan, in his outpatient clinic at the Charitable Infirmary Jervis Street, was so overrun that he needed an escape door in his consulting rooms to avoid the constantly increasing queues (Woywodt et al., 2010). Although the historians cannot confirm that this door was actually there physically, as the Charitable Infirmary was later replaced by a shopping centre, the metaphor has gained a tremendous standing in the medical culture. Published in the Oxford Handbook of Clinical Medicine, the concept teaches generations of British-trained doctors that even in the medical profession, a metaphorical backstage entry into the serene world of the inner is essential to survival. The concept has become especially timely in the face of modern-day challenges of physician burnout, work-life balance, and mental health among medical personnel. The metaphor informs the clinicians that having their own refuge, be it in music or art, family, or whatever they wish, is not a luxury but an essential part of their work. It is important to note that in the age when the rate of physician burnout is at a crisis level, the secret door of Corrigan is an indication of the vital line between professionalism and personal survival, and in today's world, it is as applicable as it was allegedly in nineteenth-century Dublin.

Medical Education and Teaching Impact

The work of Corrigan is especially relevant to modern medical education. The medical students he lectured to during his career were a mixture of private practice and public hospital positions and allowed him to teach clinically. His approach to teaching focused on bedside education, whereby students were made to observe, analyze, and compare clinical observations with pathology (Widdess, 1963). It was a revolutionary method, the pioneer of which set the principles of clinical medical education.

Corrigan belonged to the so-called Golden Age of Irish medicine that occurred in the middle of the nineteenth century when doctors such as Graves, Stokes, and Corrigan made their work known internationally through their innovative approaches to medicine and clinical practice (Coakley, 1988). These physicians of Dublin worked out organized methods of clinical instruction that impacted the

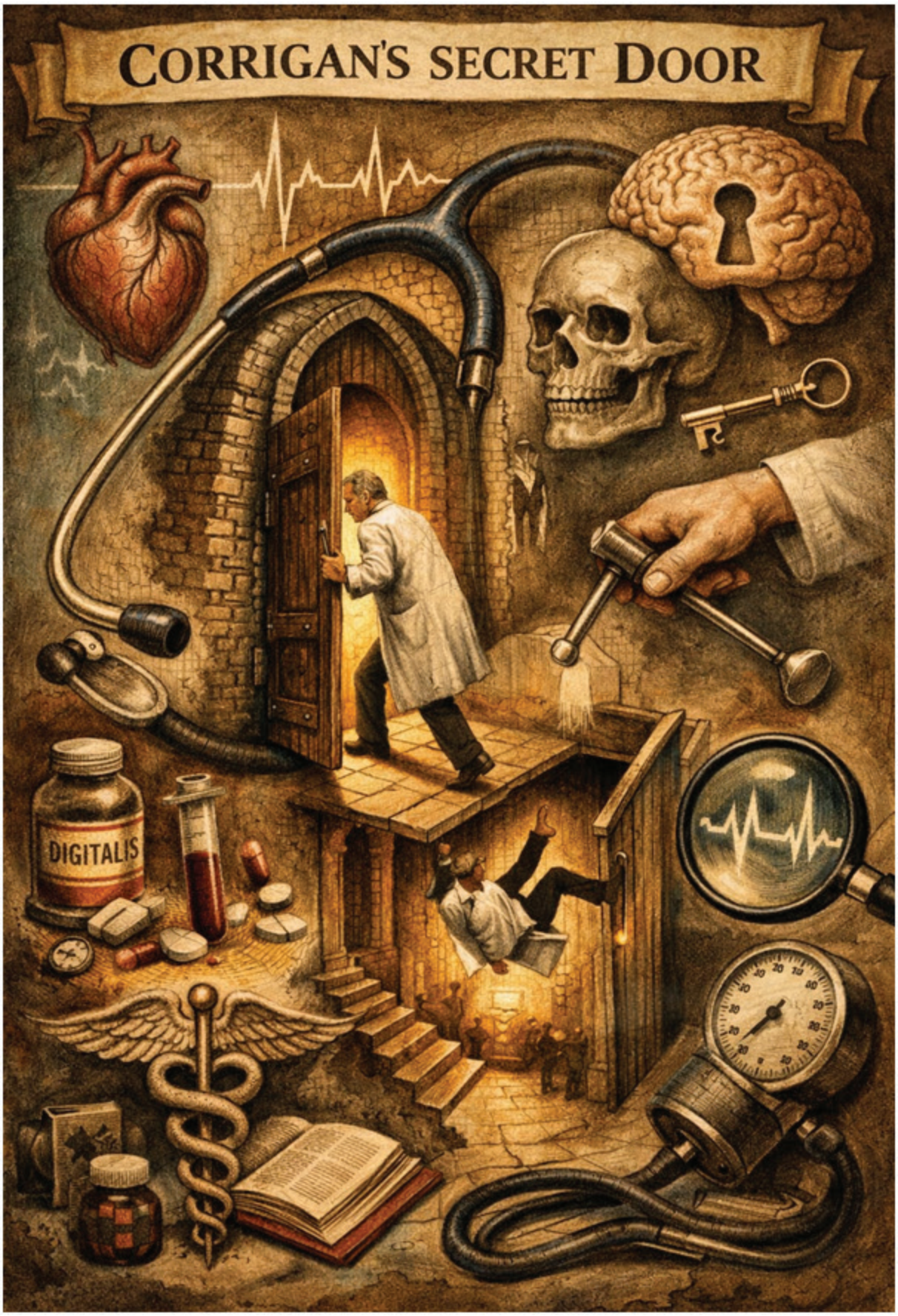

Fig. 3 He did not force the door; Corrigan listened, and it opened.

training of medicine worldwide. Their focus on systematic clinical observation, comparison with the post-mortem results, and publication of results made Dublin one of the key centers of medical innovation.

The institutions of education that Corrigan assisted in the formulation of are still used to influence Irish medical training. Ireland's medical schools still focus on clinical skills and scientific knowledge, as a balanced curriculum is still applied as Corrigan did (Kelly, 2017). His desire to increase access to education is what today would be called diversification of the medical student body and removal of obstacles to medical careers.

Relevance to Modern Medical Practice

There are various elements of the career of Corrigan that are of particular importance to modern medicine. To begin with, his methodical way of clinical observation is a fine example of scientific method usage in medical practice. His keen attention to documenting signs and symptoms and the association with underlining pathology and publication of findings gave patterns that have become fundamental to clinical research (McGee, 2021). Second, the institutional leadership of Corrigan showed the way in which physicians can define the healthcare systems and professional standards. His life as the president of the Royal College of Physicians helped in reforms such as the admission of women in examinations, which set a precedent for professional inclusivity (Kelly, 2010). Even modern medical leaders are still struggling with the dilemma of professional standards and entry into medical professions and have to strike a balance between tradition and the required innovation. Third, the clinical excellence, teaching, research, and public service activity of Corrigan are vivid examples of the various roles that academic physicians should perform. Contemporary medical professions also require a more and more active combination of patient care, education, research, and administration roles (Elder et al., 2017). Fourth, his perseverance to overcome professional challenges and discrimination is a source of hope to any doctor who encounters problems. His fellowship application was blocked instead of killing his career, and this encouraged him to think creatively to solve problems, which was eventually beneficial to him. His success in becoming the college president despite being sidelined at first showed that merit and perseverance could go around institutional racism, which is applicable to the modern-day physicians of disadvantaged backgrounds (O'Brien, 1987).

Conclusion

The legacy of Sir Dominic Corrigan includes not only the clinical signs that he gave his name to but also the contributions he made to the cardiovascular medical field, as well as the way he transformed the leadership of medical institutions in Ireland. His dedication to medical education access, work with poor patients, and promotion of public health has laid standards applicable to modern medical issues. To contemporary Irish medicine, the life of Corrigan can provide lasting lessons: the focus on clinical observation in his practice reminds us of the continuing significance of bedside skills regardless of technological progress, whereas his career as an institutional leader can teach physicians how to bring a systematic change to the existing system. His care of various populations and his service with clinical excellence exemplify the way equity and good care should be incorporated into one another. Since the Irish healthcare industry is striving to deal with the aging population, chronic illness, sustainability of the workforce, and technological implantation, the case of Corrigan is inspirational as well as instructive. The fact that he emerged as an observer, reformer, and pioneer of change in Irish medicine despite his humble beginnings is applicable even now since the issues that he solved, such as clinical uncertainty, access to education, professionalism, and healthcare equity, are the same things that are experienced today.

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ORIGINAL ARTICLE

Efficacy and Safety of the Patients Treated with Colloidal Bismuth Subcitrate (CBS)

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Abstract

Patient with chronic dyspepsia presents with symptoms like abdominal pain, discomfort, heartburn, bloating, nausea, etc.On UGI endoscopy,lesions i.e. peptic ulcer disease (PUD), erosions or gastritis/duodenitis are found .
Major PUD risk factors include Helicobacter pylori infection,chronic NSAID ,Aspirin use, Steroids and SSRI particularly if taken with NSAID, Anticoagulants, Clopidogrel,addictions like Smoking, Ethanol,excess severe stress, environmental i.e.water borne,overcrowding.
Standard triple therapy for H. pylori eradication now has declining efficacy due to antibiotic resistance. Consensus guidelines recommend bismuth-containing quadruple regimens as first-line therapy.
In our single-center, retrospective cohort (June 2020 –June 2025), 325 adults with chronic dyspepsia (clinical + endoscopic evidence) received a two-weekBismuth-based quadruple regimen (PPI+CBS+ Antibiotic+Probiotic). We evaluated efficacy (symptom relief, ulcer/erosion healing, H. pylori eradication) and safety (adverse effects).
Overall, CBS-based therapy was effective and well-tolerated for H. pylori-associated dyspepsia as well as mucosal protectant.

Introduction

Chronic dyspepsia,characterised by epigastric pain/discomfort, early satiety, bloating,nausea or vomiting, heartburn, regurgitation correlates with peptic ulcer disease (PUD) or gastritis/duodenitis. Patients with gastric ulcers, pain are often aggravated by ingestion of food whereas duodenal ulcer,pain usually more in empty stomach.

Over last decade, global prevalence of H pylori has declined by 43.7% in adults.Remarkable reduction of H pylori prevalence as well as gastric cancer was observed in adults in the Western Pacific, Southeast Asian and African regions.

In India and subcontinent prevalence has reduced significantly from 90% to 69% over a10 years period (2008-2018).[1]

In dyspeptic patients, 'Test and treat' guideline for H. Pylori has been recommended, assuming that will significantly increase healing of ulcers and reduce of risk of gastric cancer. Unfortunately, steadily increasing resistance to the antibiotics like Amoxicillin, Clarithromycin, Metronidazole resulted the reduced effectivity of thestandard PPI based triple therapy+ kit significantly from initial about 80% to only around 30%.[2]

Cephalosporine derivatives i.e. Cefuroxime is

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quite useful and safe alternative to Amoxicillin or Fluroquinolone class of antibioticsin a quadruple therapy regimen.[3]

Bismuth compounds were used for medicinal purposes for more than 200 years. Before the antibiotic era, used for traveler'sdiarrhea. Colloidal Bismuth Subcitrate (CBS) is a water-soluble bismuth salt widely used to treat PUD and dyspepsia. Bismuth has a significant anti H pylori property, It works by a) damaging the bacterial wall b)Inhibits H. pylori Urease by blocking the active site of the enzyme, c) Interfere with adhesion of H pylori to the gastric epithelium, as well as inhibiting the organism›s Urease, phospholipids and proteolytic activity d)Protect gastric mucosa byprostaglandin E2 production and alkali secretion in the mucosa which inactivates pepsin, binds bile salts and promotes mucus/bicarbonate output.

In fact, Bismuth compound was recommended as a part of triple therapy regimen ever since the guidelines in world congress in 1990[4].Currently, in a high resistance setting, most of international consensus recommend bismuth-containing quadruple regimens as first-line in high-resistance settings resulting in 75-90 % eradication rate[5].

Objective

This Retrospective observational study of patient with chronic dyspepsia Aimed at:

- Endoscopic evaluation of the patients
- Determine efficacy and safety of Colloidal Bismuth Subcitrate in the management.

Study Design

- This study includes all patients attending the clinic for last 5 years from June 2020 till June 2025
- 325 patientsof chronic dyspepsia were endoscopically evaluated for the evidence of gastritis, erosions,ulcers, Helicobacter Pylori (H. Pylori) infection as well asmucosal protection.
- UGI endoscopy and Rapid Urease Test (RUT) was carried out in all patients included in this study.
- Data of the demographic and clinical and endoscopic details recorded and analysed during each follow up visit at the clinic.
- For H. Pylori positive patients,2 weeks course of Quadruple therapy with Antibiotic, PPI, CBS, Probiotics prescribed.
- For H. Pylori negative patients,PPI and CBS were continued for 4 weeks
- Relevant investigation reports were included.
- In order to look for eradication of H. Pylori or healing of the above-mentioned lesions repeat endoscopy were done 4-6 weeks after completion of therapy
- Adverse effects experienced by the patients were evaluated and documented

Eligibility criteria

The inclusion and exclusion criteria for the subjects to be recruited are detailed below.

Inclusion criteria

- Diagnosis of chronic dyspepsia was based on clinical findings.
- Above 18 years
- CBS given to patients for H-pylori eradication and also for mucosal protection

Exclusion criteria

- Below the age of 18 years
- Lost follow up
- Didn't continue the medications for the stipulated period
- Unable to continue due to adverse effect

Outcome expected

- Significant improvement by CBS
- Medications well tolerated
- No serious adverse effect.

Materials and Methods:

- Patients were recruited as per inclusion criteria. In this cohort of 325 dyspeptic patients (mean age 45 years, both genders included), for H. Pylori Positive patients 14 days CBS based

quadruple therapy was prescribed. H. Pylori negative subjects were given PPI with CBS for 1 month.

- Patient records were reviewed for demographics (age, sex), clinical symptoms, endoscopic findings (gastric/duodenal erosions or ulcers), H. pylori test (RUT) results, and laboratory reports.
- Each follow-up visit (at 4–8 weeks post-therapy) was assessed for symptom improvement and adverse events.
- A repeat endoscopy with biopsy or urease breath test was performed to confirm H. pylori eradication and mucosal healing.
- Usual side effects (nausea, vomiting, abdominal pain, diarrhea, dark stools, metallic taste, rash, etc.) were noted.

Results:

MALE	198
FEMALE	127
TOTAL	325

TABLE 1: SEX DISTRIBUTION

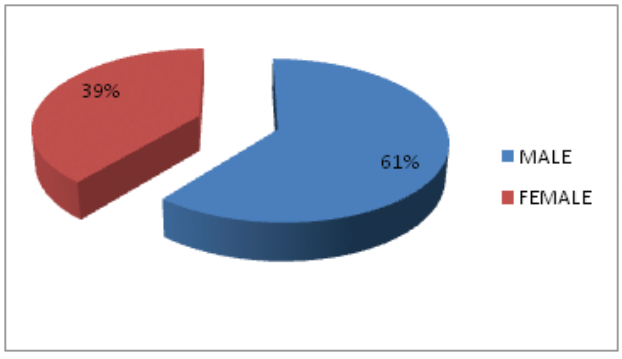

DIAGRAM 1: SEX DISTRIBUTION

(POSITIVE (H.PYLORI	133
NEGATIVE(Mucosal (Protectant	192
TOTAL	325

TABLE 2 : H PYLORI POSITIVITY AMONG THE PATIENTS

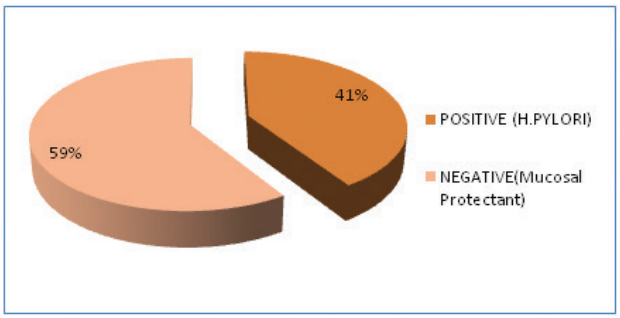

DIAGRAM2 : H PYLORI POSITIVITY AMONG THE PATIENTS

Total number of patients for mucosal protectant is 192 (41%). Among them 17% patient treated for Bile Reflux and 83% patient treated for erosions.

Total Mucosal Protectant Patient	192
BILE REFLUX	17%
EROSIONS	83%

TABLE 3:DISTRIBUTION OF PATIENTS TREATED FOR MUCOSAL PROTECTANT

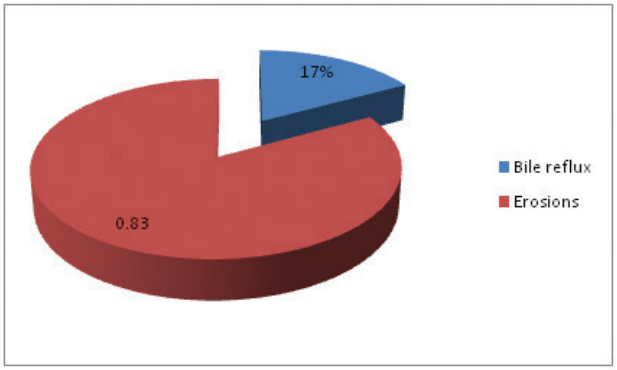

DIAGRAM 3:DISTRIBUTION OF PATIENTS TREATED FOR MUCOSAL PROTECTANT

Evaluation:

Clinical

Symptomatic Relief: Pain resolution, improved appetite, was reported by most participants. These outcomes reinforce that CBS addition yields high cure rates even with antibiotic resistance

Endoscopic

Eradication of H.Pylori

Healing of mucosal lesions

Safety and Tolerability:

- Adverse events were generally mild and transient.
- About ?60–70% of patients reported at least one minor side effect (similar to other studies).
- Side effects resolved after treatment; compliance was high (>90% medications taken by most)
- The most frequent were gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain, metallic taste) pruritus and benign bismuth effects (blackened stool), similar to other studies No serious toxicities occurred.
- One patient had severe pruritus. Hence CBS therapy had to be discontinued.

Discussion:

In all global and regional studies, H. pylori infection has been found to be common worldwide and is a very important cause of peptic ulcer disease and gastric cancer.

In functional dyspepsia, often not investigated, H. pylori may also have a significant role. Hence appropriate evaluation including UGI endoscopy and appropriate eradication regimen is essential. In order to ensure efficacy, previous history of Macrolide use must be obtained, before including Clarithromycin in triple therapy[6].

In Maastricht V/Florence consensus conference, 43 experts from 24 countries, emphasized eradication of H. Pylori withmultidrug therapy and suggested efficacy of supplementationwith Probiotics like Lactobacillus, Saccharomyces boulardi in reducing side effects associated with antibiotic-based H. pylori eradication therapies, enhanced effects and reduce adverse effects[7].

In a multicentre trial of India Thyagarajan *et.al* reported that in Indian population, the effect of eradication therapy is deeply influenced by antimicrobial resistance particularly very high to Metronidazole, moderate to Clarithromycin and Amoxicillinand low to Ciprofloxacin and Tetracycline.Following CBS treatment, the relapse rates of gastric and duodenal ulcers are significantly reduced and delayed due to its mucosal protective property.[8,9]

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CASE SERIES

Faces of a Failing Adrenal Axis

A Case Series Highlighting Diverse Etiologies of Adrenal Insufficiency from a Tertiary Care Centre in Eastern India

Tanmay Ghosh[1], Sujoy Roy Chowdhury[2]
Prabuddha Mukhopadhyay[3], Ajitesh Roy[4]

Abstract

Background: Adrenal insufficiency (AI) is a potentially life-threatening endocrine disorder with a wide spectrum of clinical presentations, often resulting in delayed diagnosis.

Objectives: To highlight the clinical heterogeneity, diagnostic challenges, and etiological spectrum of adrenal insufficiency encountered in a tertiary care hospital in Eastern India.

Materials and Methods: This retrospective case series included five patients diagnosed with adrenal insufficiency between January 2025 and December 2025 at a tertiary care teaching hospital in Kolkata.

Results: Etiologies included tuberculosis, histoplasmosis, autoimmune APS-2, empty sella syndrome, and steroid withdrawal.

Conclusion: Early diagnosis and hormonal replacement significantly improved outcomes.

Keywords

Adrenal insufficiency, Addison's disease, Tuberculosis, Empty sella, Steroid withdrawal, Case series

Introduction

Adrenal insufficiency (AI) is characterized by inadequate secretion of glucocorticoids, with or without mineral ocorticoid deficiency. The non-specific nature of symptoms such as fatigue, weight loss, gastrointestinal disturbances, and electrolyte imbalance often leads to delayed recognition. Although autoimmune Addison's disease is the predominant etiology in Western countries, infectious and infiltrative causes continue to be significant contributors in developing nations like India.

Materials and Methods

This retrospective observational case series was conducted at RKMSP-VIMS, Kolkata. Five patients diagnosed with adrenal insufficiency were included. Diagnosis was based on clinical features, morning serum cortisol levels, plasma ACTH levels, and radiological evaluation.

Case Descriptions

Case 1

A 17-year-old male presented with high-grade

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Case 1 – Primary Adrenal Insufficiency due to Disseminated Tuberculosis

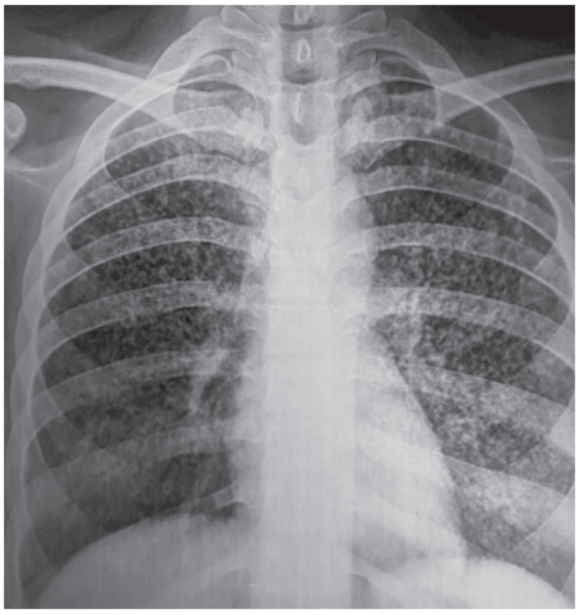
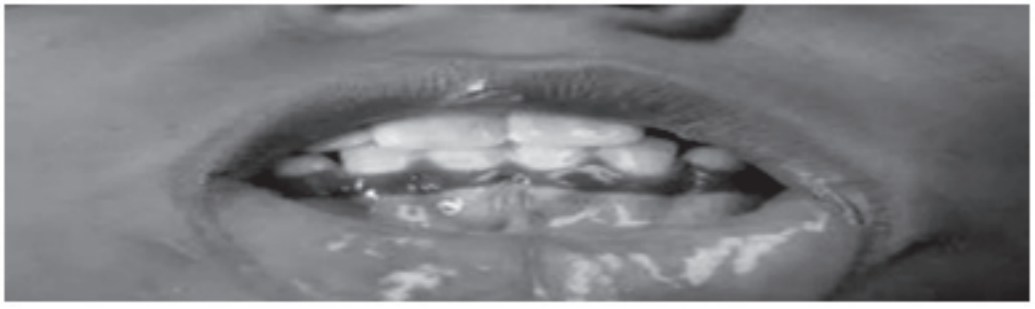


Fig. 1A ChestX-ray showing bilateral diffuse miliary nodularopacities.

intermittent fever and cough for three weeks, associated with generalized hyperpigmentation and postural hypotension. Laboratory evaluation revealed hyponatremia (Na+128 mEq/L), hyperkalemia (K+ 5 mEq/L), anemia (Hb 8.2 g/dL), and low morning cortisol (5.51 μg/dL) with markedly elevated ACTH (>2000 pg/mL). Chest radiograph showed miliary shadows. BAL GeneXpert detected Mycobacterium tuberculosis. CT abdomen revealed bulky adrenal glands with calcifications. A diagnosis of primary adrenal insufficiency due to adrenal tuberculosis was made.

Case 2

A 55-year-old diabetic female presented with prolonged relapsing fever and recurrent hospitalizations for dyselectrolytemia. Investigations revealed hyponatremia (Na+ 130 mEq/L), hyperkalemia (K+ 5.3 mEq/L), low cortisol (9 μg/dL), and elevated ACTH (41.9 pg/mL). CT adrenal showed diffusely enlarged adrenal glands with heterogeneous enhancement, suggestive



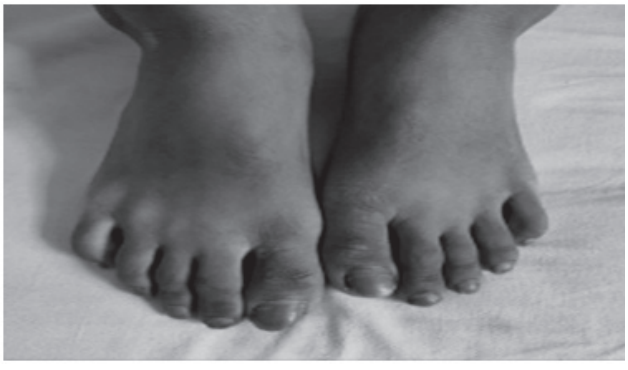


Fig. 1B Mucocutaneous hyperpigmentation involving lips, toes, and hands.

of infiltrative adrenal disease. Fungal work-up confirmed histoplasmosis.

Case 2 – Primary AdrenalIn sufficiency due to Histoplasmosis

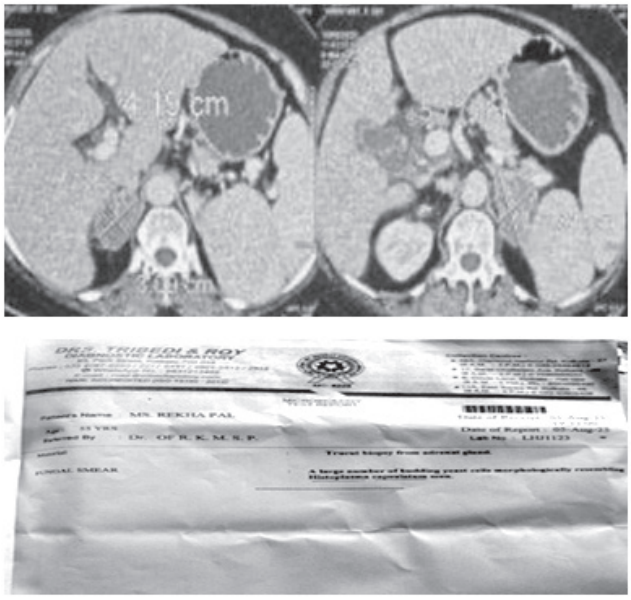


Fig. 2 Contrast-enhanced CT abdomen showing bilaterally enlarged adrenal glands.

Case 3

A 48-year-old postmenopausal woman presented with recurrent vomiting, depression, and loss of body hair for six months. She had severe hyponatremia (Na+110mEq/L), low cortisol (6μg/dL), and low pituitary hormones. MRI pituitary showed an enlarged empty sella. She was diagnosed with secondary adrenal insufficiency due to panhypopituitarism.

Case 3 – Primary Adrenal Insufficiency due to Histoplasmosis

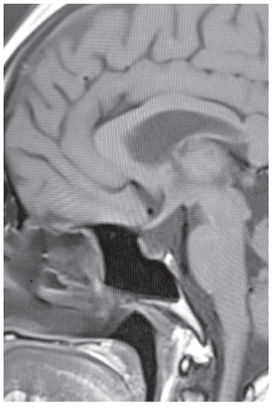


Fig. 3A MRI brain T1-weighted sagittal image showing empty sella.

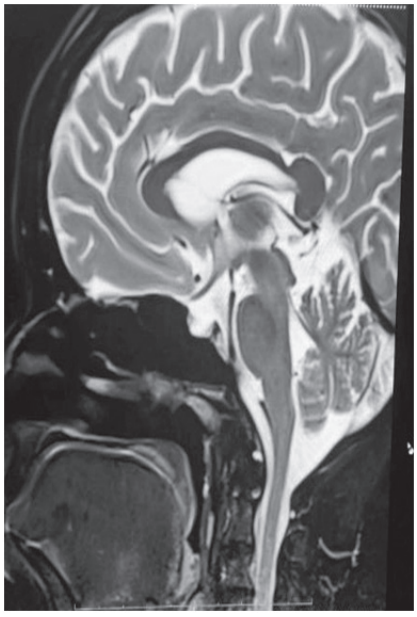


Fig. 3B MRI brain T2-weighted sagittal image showing CSF-filled sella with flattened pituitary gland

Case 4

A 60-year-old male presented with progressive generalized hyperpigmentation, vitiligo, and hoarseness of voice.

Investigations revealed anemia with macrocytosis, vitamin B12 deficiency, hypothyroidism, low cortisol (4.79 μg/dL), low DHEAS, and positive anti-TPO and anti-parietal cell antibodies. CT adrenal showed bilateral adrenal atrophy. A diagnosis of autoimmune polyglandular syndrome type 2 was made.

Case 5

A 55-year-old female presented with severe vomiting following abrupt withdrawal of oral dexamethasone taken for knee pain for three months. Laboratory evaluation showed low cortisol (3 μg/dL), low ACTH, and low DHEAS. She was diagnosed with secondary adrenal insufficiency due to exogenous steroid suppression.

Case 4 – Autoimmune Adrenal Insufficiency (Response to Treatment

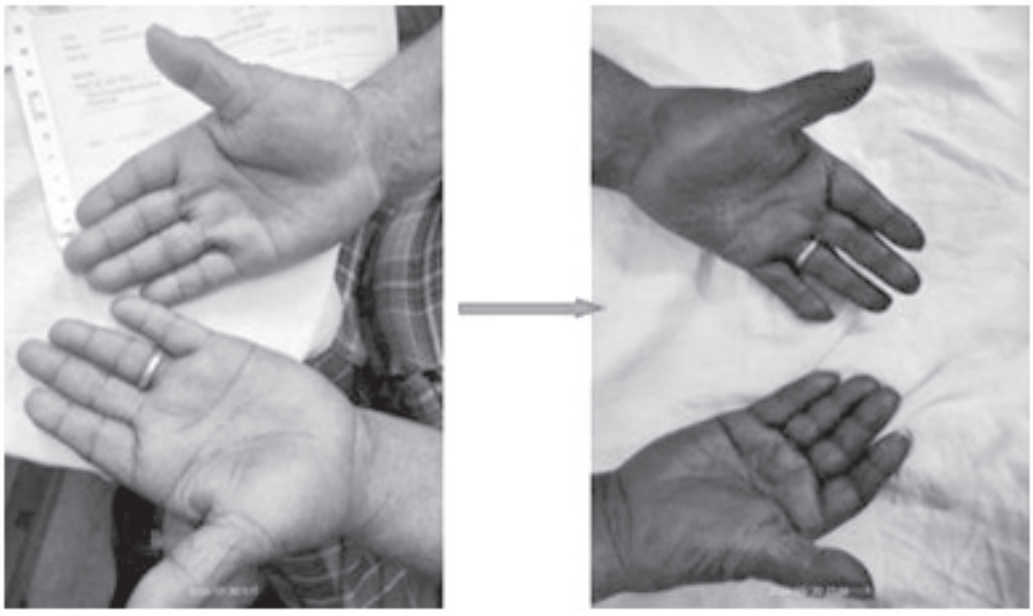


Fig. 4 Clinical photographs showing palmar-hyperpigmentation before treatment and normalisation of skin pigmentation after treatment (arrow indicating response)

Table 1. Comparative Summary of Cases

Case	Age/ Sex	Key Presentation	Type of AI	Etiology	Imaging
1	17/M	Fever, cough, hyperpigmentation	Primary	Adrenal TB	Bulky adrenals, calcification
2	55/F	Relapsing fever, dyselectrolytemia	Primary	Histoplasmosis	Bilateral enlarged adrenals
3	48/F	Vomiting, depression	Secondary	Empty sella	Enlarged empty sella
4	60/M	Hyperpigmentation, vitiligo	Primary	APS type 2	Bilateral adrenal atrophy
5	55/F	Vomiting post steroid withdrawal	Secondary	Steroid suppression	—

Results

Hyponatremia was the most common biochemical abnormality. Primary adrenal insufficiency was observed in three patients, while two had secondary adrenal insufficiency. Prompt initiation of glucocorticoid replacement led to rapid clinical improvement in all patients.[2]

Discussion

This case series highlights the heterogeneity of adrenal insufficiency in the Indian context. Infectious etiologies such as tuberculosis and histoplasmosis remain relevant, unlike Western populations where autoimmune causes predominate. Secondary adrenal insufficiency due to pituitary pathology and iatrogenic steroid withdrawal is increasingly encountered.

Conclusion

Adrenal insufficiency presents with varied clinical manifestations and diverse etiologies. A systematic approach
incorporating clinical suspicion, hormonal

evaluation, and imaging is essential for early diagnosis. Timely hormone replacement therapy significantly improves outcomes.

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Ethical Approval and Declarations
Ethical Approval: Institutional Ethics Committee approval was obtained for this study.
Informed Consent: Written informed consent was obtained from all patients for publication.
Conflict of Interest: None declared.
Funding: None.

REVIEW ARTICLE

Reprint

Bedside Medicine – A Forgotten Art

B. M. Hegde

"One kind word can warm three winter months."
Japanese saying.

"Art" wrote, Henry David Thoreau "is that which makes another man's day". One kind word on the bedside can cure many ills. The art of medicine is that which should make the patient's day. Infact, the summit of all efforts in the field of medical care delivery is the coming together of two human beings—the one who is ill or imagines to be ill and the other in whom the first has confidence. This is called medical consultation. All else in medicine should really flow from this summit. "Know your patient better than his disease" was the opinion of the father of modern medicine, Hippocrates. Having worked under some of the giants of clinical medicine both in India and abroad, I feel sorry for the patient as also for the doctors of today who think that the hi-tech investigations give them the diagnosis and management strategies.

Hardly anyone talks with the patients thèse days. Most of the big bosses make what they call the "chart rounds" in the ward side rooms where all the details of the patients, including the scanners and X-rays are kept. Little time is spent on the bedside. The present jargon for good medical practiceis "euboxic medicine" where all the right boxes should be ticked in the computerised cases heet. Whether the patient feels better or worse is of no consequence. "Patient doing well, do not interfere" wrote Sir William Osler, a great clinician of the last Century. "God give me deliverance from treating suffering human beings as cases, not letting the well alone, and making my interventions worse than his disease," was the daily prayer of Hutchinson. If you talk to a present day sub-specialist, he / she would say that all those ancient timers did n't have the array of scopes and scanners that we have to day!

Recently a triple blind, computerized, prospective study was undertaken in London by some of the great teachers in different medical schools there-John Mitchell, John Hampton, Michel Harrison and Carol Seymour, to name a few of them to study the role of listening to the patient and reading there ferral letter from the family doctor vis-àvis examining the patient phvsically and investigating the patient with all the gadgets including the positron emission to mography, in the diagnosis of medical out-patients. Thè sergiants were all students of Lord Plattatthe University College Hospital, London. Platt had written in 1949 that if one were to listen to the patient long enough the patient would give away his /her diagnosis." Patt's students, who now have access to all hi-tech stuff, wanted to check varacity of his statement.

This study was published in the British Medical Journal. The study showed, to every one's delight, that 80% of the accurate final diagnosis and one hundred percent of the future management strategies could be arrived at, at the end of listening to the patient and reading the referral letter. This could only be refined 4% more by all the physical examinations and only 8% by all the investigations including the PET scanner! A very

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strong message there from a very robust study, indeed. This will be a boon to all doctors ready to practice even in a remote village. Unfortunately, all our doctors are trained with in the four walls of the five star hospitals where their teachers rely only on the modern gadgets. It is not a surprise that such doctors tomorrow will feel frustrated to practise medicine without those gadgets. The new trend is being propped up by the industry through the irindirect advertisements under the guise of scientific data.

Every disease, in a manner of speaking, is "slightly mental". Diseases start in the human mind and also end there. If one wants to get a grip on the patient's problems one will have to have a ninkling in to the patients mind-his worries, his anxieties, his fears, his obsessions, his spirituality, his environment, his family ties and his problems-all of which will have a say in the final outcome. These important aspects of the disease management could only be gauged by listening to the patient. In his beautiful book "Talking with Patients", Prof. Calnan, who was Emeritus professor of Plastic Surgery at the S R Smith Hospital, London goes to great lengths to show that "talking with" or listening to patients is an art that mastered every medical student.

In our days we were to follow the foot steps of our teachers by observing how they talked to and listened to patients in meet patients as also on the bed side. This is absent in today's atmosphere. That breed of teachers is almost extinct like the dinosaurs. Even the so called bed-side clinics are now conducted in what they call the ward side teaching rooms where another mini didactic lecture takes place on the patient's problems! Real beside clinics should happen on the bedside where the patient could be observed carefully even while he is talking. His facial expressions, showing his internal turmoil, could be a pointer sometimes to the final diagnosis. Sir William Osler had a prescription for all doctors to have two great qualities on the bed side-imperturbability and aequanimitas-equanimity and the capacity not be perturbed under any circumstances on the bed side. These two, in their absence, could send wrong signals to an anxious patient.

Some of the important clinical research data in the field of modern medicine have emanated from the bed side. Genuine clinical research is nothing but a question on the bed side and the effort to go as far away from the bed as needed to get an answer! Some of my original works, reported in the prestigious journals abroad, have come from the bed side. Time spent by the students on the bedside will bear fruit in the long run to make them very good humane doctors. Every patient is another human being in distress and needs to be understood with compassion before being treated with drugs or surgery. A good doctor knows how to treat from the books, a better doctor would know when to treat from the books again, but the best doctor knows when not to treat from his bedside experience only. Our present biggest problem is over treatment, resulting in adverse drug reactions and over interventions.

In conciusion, one could easily say that if one trains himself/herself to be a good bedside clinician one would have achieved great success in dealing with patients. One must learn to listen a very difficult art, indeed. Medicine is basically an art based on the scientific foundation that seems to be shaky. If doctors have done any good to the suffering humanity that was mainly because of their bed side skills and not based on the faulty science of reductionism. "Cure rarely, comfort mostly, but console always" was the advice of Hippocrates and still remains valid to this day of hi-tech stuff. To practice each one of them the doctor must be a great communicator. Pain and suffering were the problems for our ancestors in medicine and they are our problems today and will remain the problems for the future generation of doctors as well.

So bed side medicine will remain the sheet anchor of medical management for all times to come. Time was when medicine was purely paternalistic where the doctor was considered God and he/she did what he/she wanted. Today it is gradually becoming more of an equal partnership where the patient takes part in his /her management. It is more important today to know one's patient than it was in the day's gone by-all the more reason why today's doctors should be better bedside clinicians and communicators. Long live the fine art of doctoring.

POEM

INFLAMMATION

Kanjaksha Ghosh

Calor, dolor, rubor,
Tumor, loss of function,
Still rings in our ear
From the first day of
Pathology class.
Driven into our ear the
Inflammation song is
All pervading bass.
Reaction of the
Tissue to injury being
The defining character, physical, chemical,
Biological or of their varied mixture could
Be the deciding factor.
Idiopathic shouts
Some other teachers,
It means we are
Ignorant of the inciting
Cause and dither.
Subsequent chapters
In general pathology
Was numerous to mention, Degeneration,
Granulation, neoplasia
Are a few that come to attention.
Neoplasia attracted our undivided attention,
Progressing from
Metaplasia,dysplasia
And finally neoplastic
Development.
Benign or malignant
Are two extremes of
This neoplastic process,
Its progression from
One to another is still
Conjectural in many case(s).
Progression at each
Step is due to
Mutation somatic,
Donot forget the
Guiding value of
Microenvironment fantastic.
After studying so
Much we come back
To the chapter of
Inflammation,
The overarching principle which guides
Almost every pathological
Denomination.
Necrosis and gangrene
Comes to another extreme
Of the spectrum .
Atrophy, hypertrophy,
Aplasia,desmoplasia
Are other some other names,
Pathology surprises
Us with this naming games.
Correlating all these
Events into a rational
Story is doctors' conundrum.

REVIEW ARTICLE

Artificial Intelligence (AI) in Medicine: A Revolution Underway

Kanjaksha Ghosh

Abstract

Abstract: Over last two decades AI is bringing about a revolution in health care in all its dimension. While there are different depths and levels at which AI works both in the form of embedded and non embedded systems, broadly this vast area of artificial intelligence is being applied in health careeg. patient management, laboratory and imaging embedded systems, health assistance, Electronic health records, drug discovery, research, communication, data analysis, projection of epidemics etc,Direct to person systems involve health improvement instruments like continuous glucose monitoring (CGM). More than 399999 such instruments, algorithms are available to consumers directly.

There are AI programmes meant for health business and administration and finally there are also hybrid AI programmes which does a mix of all these. AI is continuously evolving over time and will take another one ortwo decade to reach the level of human cognizance and intelligence. However there are theoretical challenges and challenges in the area of ethics .AI hallucinations and mistakes, AI inducing Lazy doctor syndrome etc,are examples.

AI can be applied in medicine optimally if doctors are trained on nuances of AI and how to use it from the beginning of undergraduate medical curriculum. At school level elementary principles of AI should be taught in a graded manner so that the transition to individual specialised demands of AI in different section of the society becomes smooth. Many AI applications in medicine has not been properly vetted by licensing authorities, How these systems should be analysed by licensing authorities and what kind of field trial results should be adequate for such purpose is evolving.

Key words

AI-Artificial Intelligence–health care-Ethics-utility-danger-education-licensing-legal implication.

Introduction

Last few years if one looks at standard English language International medical Journals like Lancet, BMJ, Annals of Internal Medicine and New England Journal of Medicine to name a few and many specialized medicine journals, it will be seen to be discussing/ publishing on various facets of artificial intelligence, its development and possible impact on health care.

Number of such articles and discussion in audio/ video platforms are too large to be mentioned. Though these are still early days and AI in medicine is evolving but this branch of computer science is already used over many areas of human activity ie agriculture, communication, banking, business to name a few. Many of us who were trained in medicine in 1970s-90.s and in the first decade of 21st century have hazy ideas about AI's area of

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application in medical sciences.

In this discourse attempt will made to discuss evolution and current position of AI, its use in medicine, possible evolution in future and the caution and dangers that may be associated with its use in the face of immense utility in this area.

Evolution and Development:

Evolution and development of AI is intimately associated with development of the Concept, Hardware and Software(language, grammar, coding /decoding, intrinsic consistency, reasoning and logic platform, deep learning concept, big data analysis, image recognition tools, verbal cognizance tools) over time.

It is difficult to say at what point of human civilization this evolution started but beginning from a simple Abacus as a counting machine, mechanical simple calculators, development and miniatiarisation of complex circuits, production of simple controllers for machines that are used day to day ie cars, AC, washing machines, Babbage's computing Machine, Eniac of IBM and finally progression of desktop computers with progressively increasing computing powers from 286 processors to the present Pentium architecture of the hard ware and continuous evolution of software and its integration with Telecommunication system via internet leading to world wide web created a situation where with present day computers/ mobiles, one can easily perform straight forward works of searching literature, writing on what one wants to write like word processors, commanding the machine to do a large number of complex work all are possible. However all of this was simply an input and an output on whatever software algorithm commanded the machine to do. The machine was not producing an output via its thinking and logical reasoning. Some more advances needed for developing a thinking machine. This needed development of pattern recognition software, voice interactive software and need for extreme speed of computing process so that ocurrences can be played in real time .

All these in last two decades developed from the demand of different gaming programmes and finally development of computer programmes which could play and outwit chess grand masters(deep Blue).Personal helping assistant which respond to voice like Alexa cameto many homes today.

It is evident that to be able to analyse and be able to give rational intelligent response AI software needs access to already existing huge medical knowledge data base, this is already available . Subsequently depending on specific purposes of the diagnostic system or management etc Individually the software needs to be trained. For example to be able to confidently analyse Chest xrays, the software needs to be trained with thousands of normal and abnormal chest xrays, an algorithm needs to be introduced how the chest xraysare read by gifted radiologists and finally with each chest xray the description and diagnosis reached.

This feeding constitute trainining the software. Then its outputs are vetted by a number of expert radiologists and they offeralternative diagnosis in addition to the diagnosis offered maintaining the inner logical consistency in the software for diagnosis. This is a supervised learning protocol for the software then this software with its pattern recognition capability is fed thousands of chest xrays without diagnosis being given, the software gives the diagnosis via pattern recognition, analysis, observation from its library with confirmed diagnosis and finally gives the diagnosis, this is unsupervised learning and this can be improved via several cycles of this learning process by the machine.

Once acceptable accuracy is reached the software of that AI can be used in randomised trial applications for real world diagnostic or other applications and finally can be released to the market after licensing authorities of the the country are satisfied. This process is true for many investigations, treatment algorithms, sorting out best possible management, research discovery, Community medicine, and so on.

Artificial Intelligence: basic understanding:

Post computer and telecommunication revolution involving world wide web, many search engines were developed for various purposes, the field was ready for the machines to become intelligent so that it can start behaving like human brain. To

be able to do that we needed to emulate human brain in the machine leading to its functionality . The term Artificial intelligence cover some-total of all the machine related knowledge developed so fat and it includes

i.Machine learning: In this case one or several inputs follow a particular algorithm and provide the output. Several In puts may interact in a given way as suggested by the said algorithm.

ii.Generative Transformers: Here The software can generate incorporating various informations like voice, Image, written information in a creative form and by interacting with the huge store of information already in its archives which has been vetted in innumerable pretrained sessions can now give its own unique output depending on the problem and /question stated. Classical example being ChatGPT/ Gemini. This is a truly Generative artificial intelligence programme can learn from its in puts using various types of Neural networks.

iii.Deep convoluted Neural Network: This area of network in artificial intelligence can become more and more complex in its architecture where the input surface which may be consisting of an array of different acceptor of information called nodes (nodes are like collection of nerve cells as in ganglion) from this input area information go through several layers of hidden nodes (remember our brain which is consisted of deeply interacted cells of three to six layers) where extensive interactive connections feeds to out put layer of the programme which also could be consisting of many nodes. AI often use a combination of the softwares as described above.

iv. Agentic AI. Here the artificial intelligence programme incorporates inputs from the surroundings without needing any prompts by human and work for the purpose for which the programme is produced.

AI for Medicine: Broadly medicine has diagnostics(laboratory and Imaging Science), Monitoring, Prognosis and Management, Education, research, Epidemics projection,Community health Health Economics and Business, Medical research in its various forms and documentation archiving for future use. Infact there is no area of health Science that is not touched by AI. All these informations again will be different for different specialities of Medicine.

AI for medicine can be considered withfollowing groups of programmes.

i. Programmes for diagnosis, prognosis, management, Education Research, prescription writing, Electronic Health record writing and maintenance, machine health assistance, Embedded AI programmes in Different Diagnostic machines .

ii. Direct to Consumer programmes: There are more than 300,000 such programmesthat are available basically for health education and health improvement, health monitoring for patients in different branches of medicine like 24 hour blood glucose monitoring, blood pressure monitoring,etc. Many such programmes have low levels of AI in the form of algorithmic machine learning . However many such machines have not been vetted . scientifically evaluatedor licensed by licensing authorities of the countries where it is available.

iii.Health Business: largely used by hospitals, doctors offices for Billing, Tracking usages of different resources. Future projection of work load, Profit margins, areas of improvement etc.

iv. Hybrid AI programme:In this programme both health care related office tasksie billing, advertising, account keeping, auditing etc are simulataneously available with various health care related diagnostic and management softwares. These kind of programmes are often useful for whole hospital information and management systems.

v. Individual programmes directed for specific disease detection, management, follow up and prognosis. Many doctors and specialists in particular fields will be able to use this programme for management of their patients. Some of these programmes can also list which of the patients are not doing well with a given management and needs alternative or modified management.

vi.Embedded AI programmes, these programmes are embedded with different machines used for patient care and management, Most of them are based on machine learning principles. Voice, Image and written prompt recognition is part of the system leading to acquiring, comparing the patient data in the requisite software, then diagnosis, possible further investigation and production of final repost comes from the embedded software of

AI. These programmes also allow final editing and modification by those experts who are cleared to do so.

AI enabled computers: Because of increasingly complex work involving big data acquisition and real time analysis, computation with very high memory and speed is increasingly required so also its connection with uninterrupted highspeed communication network. Hence AI software enabled computer with current generation of highspeed processor and current software is getting available in the market . These programmes are also getting adapted to current generation of android and internet mobile phones.

Ethics, Challenges and dangers associated with AI:Though it is believed that in current scenario and in not too distant future most of the functions and medical services will be provided in association with some sort of AI either embedded in the instrument or as an independent standalone systems.

With adventof AI, which is still in its infancy,there are also concerns related to ethics in medicine ie how the data of individual patients can be protected from unintended use by others ie insurance company, black mail etc. If there is some diagnostic error associated with particular programme who is supposed to be responsible and hence legally prosecutable? Is it the company who marketed the AI programme, are they the ones who wrote the software, loaded the training material, properly coded the training material, those who purchased the system, hospital authorities, or the licensing agency that licensed the software (was the due diligence observed)? Unfortunately the details of how the licensing agency should evaluate the system, how post marketing surveillance of such AI programmes should be conducted and how long it should go on is still evolving .

Another real disaster is once there is really a mistake / fault in the system it will affects thousands of people across the continents where this programme is being used. If there is some delay in spotting the error millions of lives may be affected.

Some of the AI software is also evolving for Psychiatric assessment or management of such patients and claims to provide equivalent of Cognitive BehaviouralTherapy(CBT), a cornerstone of management of many psychiatric conditions. Many operations are increasingly being carried out with assistance with AI driven robots(e.g Da-Vinci), complications following use of these robots are inevitable and may be compounded by surgeon doing the operation sitting thousands of miles away with few experts around the patient. The graver the complications with use of such systems accountability fixation becomes difficult without a laid down SOP which is also at its infancy.

It has now become apparent that AI systems can hallucinate ie gives an output which may not be related to the challenge for which its service is requested. Such dangers can only be averted if the doctor who is applying this system has requisite knowledge of AI and is aware when using it.

This brings us to our original expectation that with development of AI its service can be remotely applied in areas where expert knowledge is not available ! However in current scenario optimum use of AI is only possible if those who are applying this system has at least modest knowledge of AI system that is going to be applied.

AI education in medical Curriculum.The above account of application of AI in medicine clearly demands that education on application of AI should start with early years of medical teaching and should be a part of lifelong CME programmes. As the AI itself is evolving, the current AI is only current in terms of its last revision date. The serving grace in the AI education is that many school going students who will become future medical students is already taking elementary education in this required field. As AI is getting extensively involved in every sphere of human activity and day to day living, so the syllabus for whole school education needs to be revamped with AI teaching in mind, this will also have beneficial impact on AI teaching as medical assistance in medical schools.

Doctors in AI era: Lazy doctor syndrome!Once AI pervades every area of health activity including understanding, pathophysiology and natural history of diseases, management, documentation etc, there is real possibility that doctor's complete dependence on such a system could make him/her lazy and will not make much effort to acquire core knowledge required to practice medicine properly. Once that day arrives, whether AI based

information for a particular patient is working properly or not will be difficult for that doctor to tell. One must develop adequate safe guard on the way against these scenarios.

Doctors getting redundant and outdated: Already in the current scenario due to progress in pattern recognition software and algorithmic machine learning process,doctors who contribute a lot in Imaging science like radiodiagosis, cytology, histopathology, laboratory haematology, biochemistry and microbiology is facing redundancy in many institutions.

May hospitals are getting remotely this report done from expert sitting in another country, taking the advantage of day–night differences due to geographical distance.There is also a monertary angle to it. With progress of AI there isa fair chance that other areas of medicine will also be equally affected. However with advent of every technology this challenge of those who could not/ did not get trained with advanced technology is likely to lose their job but simultaneously newer avenues of profession or completely new profession emerge.

AI in medical research/ Drug discovery/ Research paper writing: This area of AI is already very eloquent. Major impact in drug discovery by showing, designing newer molecules, indicating possible side effects of developing molecules in Silico . quite early in the cycle of drug development will quicken drug discovery.

Repurposing thousands of already existing molecules for management of other diseases will also become more frequent. Serendipity in discovery of drugs will be minimized. Similarly newer signs and symptoms may be discovered when electronic history records of thousands of patients with given disease label will be analysed by AI.

Many research papers and reviews are written with the help of such AI programmes like ChatGPT/ Gemini. This creates a new challenge for the editors of well known medical journals to decide how much of the write up is authors own and how much of it is contributed by AI. New AI algorithms are available to editors to detect this quantum of mixups.

The idea is that basic work should be investigators own. Research and other papers in todays journal looks much better with better figures and photographs, references that are also made immediately available to authors using AI programmes . These can be arranged as per Journals requirements also by the system . All these facilities tremendously increase the speed with which a paper may be written and published or rejected.

Discussion and Conclusion:The above write up is a small account how AI is influencing medical care, research, education today .

Like all human knowledge AI gets its power from the quantum and quality of the information uploaded in its memory and the way it is trained repeatedly as to how this information can be churned into useful knowledge. Coding and decoding along with repeated deep convolutional interaction is in the core of AI function. As out of several thousands of languages that exists on earth and every day few disappears because of non usage, finally dominant language gets enriched. In a similar way depending on who is uploading what kind of message in AI programmes, the dominant system will finally determine what thought will persist and others will perish. In medical parlance many investigations, algorithms, understanding of the disease, medicines and methods of management changes. Some of the techniques in different branches of medicine (e g Alt Medicine) may eventually vanish as a knowledge source if due care is nor taken for their proper inclusion in AI data base. What one use in any AI system ie Machine learning and embedded system is only current upto the time when the information was loaded into the system. Hence all AI systems needs to be on perpetual overhaul. Chat GPT which we are using already underwent four or more editions. As the AI programme in medicine is slowly replacing many areas of human activity particularly in Imaging and laboratory science, specialists in this area is likely to get redundant, health administrators and government of the day has a duty to find out how this challenge is going to be addressed. There are innumerable direct to customer programmes in embeded machines with AI component, they have not been properly vetted by licensing authority and details of how these system should be analysed for day to day application is still evolving. There are

ethical challenges with AL application in medicine . Hallucination can introduce mistakes or there could be minor fault. Virus attack, cyber-frauds. Coding defects,which may not be immediately apparentbut may compromise the health care delivery across the globe and in very many different populations at the same time. This looming danger with AI application needs addressing and relevant protection needs to be initiated .

AI in medicine is going to stay influencing all its branches ieeducation, service, management, research, discovery etc . It is our duty to know about this important ally as much as possible. Without good knowledge of its application best output cannot be obtained. Hence the feeling that AI will make most of the human activity unnecessary is still not correct. The final decision on any medical activity, management, intervention has to be human. It is believed that AI will need another one or two decade to develop the level of human cognizance and intellect,by that time the application of AI in medicine is going to be mind boggling. We must not forget AI in the end of the day is an expression of ingenuity of human mind.

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Undertaking

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REVIEW ARTICLE

Acute Kidney Injury in Critical Care

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Abstract

Acute Kidney Injury (AKI) is one of the most frequent and deadly complications in the intensive care unit. It is now recognized as a complex, systemic syndrome rather than a single disease process. Modern understanding has shifted from a purely creatinine-based definition to the KDIGO framework, incorporating staging and duration to predict outcomes. Early diagnosis is improving through biomarkers and functional tests such as the Furosemide Stress Test. Phenotyping and biological subtyping are redefining AKI as multiple syndromes with distinct mechanisms, helping explain why traditional drug trials failed. Management remains supportive, centred on haemodynamic precision, balanced fluid therapy, avoidance of nephrotoxins, and timely renal replacement therapy. Continuous modalities are preferred for hemodynamically unstable patients, with dose guided by evidence rather than intensity. Emerging tools, including real-time GFR monitoring, bio-artificial kidneys and predictive analytics, signal a move toward personalized therapy. Prevention and early intervention remain the key determinants of long-term renal and survival outcomes.

Keywords:

Acute Kidney Injury, Biomarkers, Critical Care, Fluid Stewardship, KDIGO, Renal Replacement Therapy, Subphenotypes, CRRT

Introduction

Acute Kidney Injury (AKI) has emerged as one of the most significant challenges in contemporary critical care. It is not only a reflection of illness severity; it contributes directly to morbidity and mortality. Approximately half of all ICU admissions develop some degree of AKI, and the incidence increases to nearly 60% among patients with sepsis[1].

Historically, renal function was viewed in narrow, mechanical terms as a passive filtration system that occasionally failed, and treatment focused primarily on correcting biochemical abnormalities or initiating renal replacement therapy. This concept is now changed. AKI is recognized as a complex, systemic disease process. The injured kidney becomes an active source of inflammatory mediators and cytokines, which contribute to multi-organ involvement, including acute lung injury and ARDS, cardiac dysfunction consistent with cardiorenal syndrome type 3, and neurological impairment.

Importantly, even mild AKI carries prognostic weight. Small increases in serum creatinine are associated with higher mortality risk. Apparent recovery can be misleading; a return to baseline creatinine often masks a permanent loss of renal reserve. A single episode of AKI during critical illness is a major risk factor for future CKD and end-stage kidney disease, with many patients progressing to long-term dialysis dependency[2].

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This chapter focuses on clinically meaningful aspects of AKI relevant to critical care practice. It integrates current definitions, evolving phenotypes, pathophysiological insights, and bedside management strategies, especially in situations where conventional therapies offer limited benefit. It also highlights the broader implications of AKI on long-term outcomes and the importance of early recognition to prevent irreversible injury.

Definition

For years, progress in AKI research and management was hindered by the lack of a unified definition. More than 30 diagnostic descriptions were in circulation, ranging from mild reductions in urine output to severe azotemia. This inconsistency contributed to variability in clinical practice and prevented meaningful comparisons across studies. The introduction of consensus criteria brought needed uniformity.

The current global standard is the kidney disease: Improving Global Outcomes (KDIGO) definition, which integrates and refines elements from the earlier RIFLE and AKIN classifications[3]. According to KDIGO, AKI is diagnosed when any of the following criteria are met (Table-1):

Table 1. KDIGO Diagnostic criteria for AKI

An increase in serum creatinine (SCr) by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours.
An increase in SCr to ≥ 1.5 times the baseline value, known or presumed to have occurred within the previous 7 days.
Urine output < 0.5 mL/kg/h for at least 6 hours

Limitations of the Current Definition

Despite its widespread acceptance, the KDIGO framework is built on two imperfect markers: serum creatinine and urine output.

a) Creatinine is a delayed and insensitive biomarker. Its concentration is influenced by multiple variables like muscle mass, liver function, and volume status. Critically ill patients often have sarcopenia and significant fluid overload, which may mask true renal dysfunction. In such individuals, a serum creatinine of 0.8 mg/dL may coexist with a severely reduced glomerular filtration rate. Up to 50% of kidney function may be lost before creatinine rises above the normal range, making KDIGO a largely retrospective diagnosis[3].
b) Urine output lacks specificity. Oliguria can occur as an adaptive response to intravascular depletion or vasodilation, or it may signal intrinsic renal injury such as acute tubular necrosis. KDIGO does not differentiate between these pathophysiological states, and urine output alone may be misleading in patients receiving diuretics or vasopressors.

Although KDIGO is imperfect, consistent application improves early recognition and standardizes clinical communication and research methodology. It remains the most practical and validated diagnostic approach available.

Classification

Once AKI is identified, staging becomes essential. Staging is not simply a descriptive exercise; it has direct prognostic value. Increasing stage correlates strongly with morbidity and mortality, and patients with Stage 3 AKI face a substantially higher risk of death than those with Stage 1 disease (Table-2).

Table 2. KDIGO Staging of AKI

Stage	Serum Creatinine Criteria	Urine Output Criteria
Stage 1	1.5–1.9 x baseline, OR ≥ 0.3 mg/dL increase	< 0.5 mL/kg/h for 6–12 hours
Stage 2	2.0–2.9 x baseline	< 0.5 mL/kg/h for ≥ 12 hours
Stage 3	3.0 x baseline, OR SCr ≥ 4.0 mg/dL, OR Initiation of RRT	< 0.3 mL/kg/h for ≥ 24 hours, OR Anuria for ≥ 12 hours

Note: If creatinine and urine output map to different stages, always assign the worse stage.

A. AKI as a Disease Continuum

Classification extends beyond severity alone. Duration of kidney dysfunction now forms an important framework, linking acute injury to long-term outcomes[4]:

- AKI: renal dysfunction lasting ≤ 7 days.
- Acute Kidney Disease (AKD): dysfunction persisting between 7 and 90 days. This interval is critical, as targeted interventions may still prevent irreversible nephron loss and progression to chronic disease.

- Chronic Kidney Disease (CKD): persistence beyond 90 days.

Understanding AKI within this continuum recognizes that kidney injury does not resolve at discharge. It evolves, and timely intervention during the AKD phase may significantly influence long-term renal and survival outcomes.

B. Phenotypes, Sub Phenotypes and Endotypes

The modern approach to AKI recognizes that it is not a single disease entity. Patients may have identical serum creatinine values but develop AKI through entirely different mechanisms. Treating these diverse processes as one condition has contributed to the failure of numerous therapeutic trials. Precision medicine in AKI now focuses on classifying patients based on clinical context, biological behaviour, and molecular pathways.

1. Clinical Phenotypes: Clinical phenotypes group patients according to the primary disease process driving AKI. Key categories include:

- Septic AKI: The most frequent phenotype in the ICU. Unlike classic pre-renal states, renal blood flow may be normal or increased. Injury is thought to result from microvascular dysfunction, inflammatory activation, mitochondrial impairment, and loss of autoregulation, rather than simple hypoperfusion[5].
- Cardiorenal Syndrome (Type 1): Acute cardiac dysfunction leading to renal injury. Venous congestion, reflected by elevated central venous pressure, is now recognized as a principal mechanism. Increased renal interstitial pressure and impaired renal perfusion may occur even when cardiac output is acceptable.
- Hepatorenal Syndrome: A distinct pre-renal physiology associated with advanced cirrhosis and profound systemic vasodilation. Marked splanchnic pooling and neurohormonal activation eventually lead to severe renal vasoconstriction and rapidly progressive renal failure.

These phenotypes illustrate that AKI arises from highly specific physiological disturbances rather than a universal mechanism.

2. Subphenotypes (Inflammatory vs. Non-inflammatory AKI): Latent class analyses from large critical care cohorts have identified biologically distinct AKI sub phenotypes that appear clinically similar at presentation[6]:

- Subphenotype 1 (Non-inflammatory): Characterized by lower systemic inflammatory activity and generally associated with better outcomes.
- Subphenotype 2 (Pro-inflammatory): Defined by elevated cytokines and inflammatory mediators, including IL-6, IL-8, and TNF-receptor-1. These patients demonstrate higher mortality and respond differently to therapies. For example, observational data suggest a potential benefit of vasopressin in this inflammatory subgroup, whereas its advantages are not seen in non-inflammatory patients.

These findings highlight the potential for biomarker-guided therapy and explain why "one-size-fits-all" interventions frequently fail.

3. **Endotypes:** Endotypes classify AKI based on specific biological mechanisms responsible for renal injury[7]:

- Ischaemic Endotype: Driven by ATP depletion, tubular epithelial injury, and microvascular hypoperfusion typical of acute tubular necrosis.
- Nephrotoxic Endotype: Direct cellular injury from exogenous or endogenous toxins, including aminoglycosides, radiocontrast agents, and chemotherapeutic drugs such as cisplatin.
- Pigment Nephropathy: Injury caused by myoglobin or haemoglobin deposition in rhabdomyolysis or haemolysis, respectively.

Clinical Relevance

Identifying the correct phenotype and endotype has practical implications. In septic AKI with an inflammatory endotype, aggressive fluid administration will not reverse mitochondrial dysfunction or immunometabolism failure. Conversely, in pigment-induced AKI, timely volume expansion and alkalinization may be lifesaving. Understanding these distinctions is central to developing personalized treatment strategies and improving outcomes in critically ill patients with AKI[8].

Table 3. Diagnostic Approach to AKI in the ICU

Diagnostic Component	Key Elements	Clinical Meaning
History & Exam	Hypotension: MAP < 60 mmHg (even briefly)	Can precipitate renal injury, especially in elderly patients
	Nephrotoxins: ACEi + Diuretics + NSAIDs; Vancomycin + Piperacillin–Tazobactam	Drug-associated AKI; synergistic toxicity risk
	Raised Intra-abdominal Pressure: IAP > 20 mmHg	Renal vein compression → Compartment Syndrome of the Kidney
Urinalysis & Microscopy	Muddy brown casts	Suggest acute tubular necrosis (structural injury)
	Hyaline casts	Suggest concentrated urine → pre-renal physiology
	White cell casts	Points toward interstitial nephritis or pyelonephritis
Functional Testing: Furosemide Stress Test (FST)	Dose: 1.0–1.5 mg/kg IV furosemide	Assesses tubular integrity
	Pass: > 200 mL urine in 2 hours	Indicates preserved tubular function; good prognosis
	Fail: < 200 mL/2 hours	Predicts progression to severe AKI and need for RRT

Diagnosis

Diagnosing AKI in the ICU requires continuous surveillance supported by targeted investigation[7,8]. The primary diagnostic task is to distinguish functional, potentially reversible reductions in filtration (pre-renal physiology) from structural tubular injury (intrinsic disease) (Table-3).

Biomarkers

Relying on serum creatinine to diagnose AKI is clinically insufficient. Creatinine rises late, often after substantial structural injury has already occurred. The need for earlier detection has driven the development of novel biomarkers that identify kidney stress before overt dysfunction becomes measurable. These tests allow recognition of "subclinical AKI," where cellular injury is present despite normal creatinine[9,10]. (Table-4)

Table 4. Key AKI Biomarkers

Biomarker	Mechanism	Clinical Utility
NGAL (Neutrophil Gelatinase-Associated Lipocalin)	Released from injured tubular epithelial cells within hours of stress.	Early AKI detection; helps differentiate pre-renal states (low NGAL) from intrinsic injury/ATN (high NGAL).
TIMP-2 • IGFBP7 (NephroCheck®)	Cell-cycle arrest markers indicating tubular stress.	FDA-approved predictive test; values > 0.3 identify patients at high risk for moderate to severe AKI.
Cystatin C	Constant production; freely filtered and independent of muscle mass	More accurate GFR estimation in sarcopenic or fluid-overloaded ICU patients.
Proenkephalin A	Biomarker correlating closely with measured GFR.	Less influenced by inflammation or hemodynamics, potentially useful in sepsis and shock states

These biomarkers aim to close the gap between structural renal stress and creatinine-based diagnosis, allowing earlier intervention and improved prognostication.

The Concept of "Renal Angina"

The term renal angina draws a parallel with myocardial infarction diagnostics: combining clinical risk with early biomarkers improves diagnostic accuracy. In a high-risk ICU patient, such as one with sepsis, vasopressor dependence, or mechanical ventilation, a positive early biomarker strongly suggests AKI even before creatinine rises[11].

Identifying renal angina supports immediate initiation of kidney-protective measures, often referred to as a "kidney-sparing bundle," including hemodynamic optimization, avoidance of nephrotoxins, careful fluid management, and early nephrology involvement. This biomarker-based approach moves AKI diagnosis from reaction to prevention and represents an important step towards precision management in critical care nephrology.

Prevention

There is no proven therapy that reverses established acute tubular necrosis. Tubular necrosis cannot be pharmacologically repaired, and renal recovery depends on time and supportive care. Prevention therefore remains central to AKI management in the ICU.

1. Hemodynamic Optimization: The kidneys receive almost one quarter of cardiac output and are highly sensitive to oxygen delivery and perfusion changes.

- Arterial pressure targets: A MAP above 65 mmHg is adequate for most critically ill patients. However, in individuals with chronic hypertension, autoregulatory thresholds are higher. In the SEPSIS-PAM trial, targeting a MAP between 80 and 85 mmHg in septic shock patients with chronic hypertension reduced the need for renal replacement therapy[12].
- Venous decongestion: Renal perfusion is determined by both inflow and outflow. Elevated venous pressures impair glomerular filtration as effectively as hypotension. A CVP of 20 mmHg can significantly restrict renal blood flow. In patients with right-sided cardiac failure or fluid overload, diuresis or ultrafiltration to reduce venous congestion may improve renal function.

2. **Fluid Stewardship:** Fluid therapy should be individualized. Excess or inappropriate fluids contribute to renal injury.

- Choice of crystalloid: High-chloride solutions such as normal saline may provoke renal vasoconstriction and worsen metabolic acidosis. The SMART and SALT-ED trials reported lower rates of major adverse kidney events with balanced crystalloids such as Lactated Ringer's and Plasma-Lyte[13]. More recent trials (PLUS and BASICS) showed smaller effects, but balanced solutions remain preferred for large-volume resuscitation[14,15].
- Avoidance of fluid overload: Once hemodynamics are stable, unnecessary fluid administration should be discontinued. Fluid overload, typically defined as more than 10 percent increase in body weight, is independently associated with mortality and poorer renal outcomes.

3. **Nephrotoxin Stewardship:** Minimizing exposure to nephrotoxins is one of the most effective preventive strategies[16,17].

- Suspend ACE inhibitors and ARBs during shock or active renal hypoperfusion.
- Replace nephrotoxic antimicrobials, including aminoglycosides, when suitable alternatives exist.
- Contrast media risk has been overstated in the modern ICU setting. While caution is reasonable, delaying essential imaging for fear of contrast-associated injury may be more harmful. In conditions such as pulmonary embolism or mesenteric ischemia, timely imaging outweighs theoretical renal risk.

Treatment-Medical/Intervention (CRRT)

Once AKI is established, treatment focuses on supporting the patient while the kidneys recover. Management targets complications, prevents further damage, and maintains homeostasis through haemodynamic stabilization, electrolyte control, and renal replacement therapy when indicated[18,19].

A. Medical Management

1. Hyperkalemia: The most immediate life-threatening complication. Treat with

intravenous insulin and dextrose to shift potassium intracellularly. Administer calcium to stabilize myocardial membranes. Oral potassium binders may help, but their onset is slow and should not delay definitive therapy.

2. Metabolic Acidosis: Aim to maintain a pH above 7.20. Intravenous bicarbonate can be used as a temporary measure, but persistent acidosis despite optimization of ventilation and perfusion usually requires dialysis.
3. Nutrition: AKI is a hypercatabolic state. Protein restriction to control urea is harmful and promotes muscle loss. Provide standard protein intake (1.2 to 1.5 g/kg/day); if urea levels rise excessively, renal replacement therapy can remove nitrogenous waste.

B. Renal Replacement Therapy (RRT)

When renal function is insufficient to maintain metabolic and fluid stability, extracorporeal support becomes necessary.

1) Indications

The traditional AEIOU framework remains clinically useful when interpreted within context [20]:

- Acidosis: Severe metabolic acidosis (typically pH < 7.1 to 7.2) unresponsive to medical therapy.
- Electrolytes: Hyperkalemia > 6.5 mEq/L, especially with ECG changes or rapid rise.
- Ingestions: Removal of dialysable toxins such as methanol, ethylene glycol, lithium, or salicylates.
- Overload: Fluid overload causing refractory hypoxia or pulmonary oedema.
- Uremia: Clinical manifestations including encephalopathy, pericarditis, or bleeding.

2) The Timing Debate

For years, early initiation of RRT—before conventional indications developed—was believed to improve outcomes. However, the AKIKI [19] and IDEAL-ICU [21] trials demonstrated that prophylactic initiation in Stage 3 AKI without urgent indications does not reduce mortality. Early RRT is associated with increased risk of hypotension, catheter-related infection, and unnecessary dialysis exposure.

- Practical approach: Wait for a clear AEIOU indication or approximately 72 hours of persistent severe AKI. Many patients will recover without dialysis, avoiding procedural complications altogether.
- Exception: Severe fluid overload compromising oxygenation should prompt earlier initiation. In patients with refractory hypoxemia, particularly when PO2/FiO2 falls below 200, delaying RRT may worsen outcomes, and early fluid removal through continuous modalities is justified [22].

3) Modalities of Renal Replacement Therapy

Modality to use Renal Replacement Therapy (RRT) in the ICU is individualized according to haemodynamic stability, neurologic status, solute burden, and local resource availability. No single modality is intrinsically superior; the goal is to match treatment characteristics to the patient's physiology (Table-5).

4) Continuous RRT Techniques

CRRT can be delivered through three main processes: CVVH, CVVHD, and CVVHDF [23,24,25]. CVVH uses convection to remove solutes and fluids via a pressure gradient, efficiently clearing larger molecules. CVVHD employs diffusion across a semipermeable membrane to eliminate smaller toxins through concentration gradients. CVVHDF combines both convection and diffusion for maximal clearance of small and middle molecules. In all methods, blood continuously circulates through an extracorporeal filter, maintaining fluid, electrolyte, and toxin balance in critically ill patients.

- CVVH (Hemofiltration): Convection-based removal; better for middle molecules and fluid clearance.
- CVVHD (Hemodialysis): Diffusion-based removal; efficient for small solutes (urea, potassium).
- CVVHDF (Hemodiafiltration): Combination of diffusion and convection; most commonly used for broad solute clearance and flexible fluid control

Table 5. Modalities of Renal Replacement Therapy

RRT Modality	Description	Clinical Strengths / Best Use
Intermittent Hemodialysis (IHD)	High blood and dialysate flow rates over short sessions (typically 3–4 hours). Allows rapid solute and potassium removal.	Suitable for hemodynamically stable ICU patients. Excellent for urgent hyperkalemia due to rapid potassium clearance. Also preferred for rapid correction of acidosis or intoxication.
Continuous Renal Replacement Therapy (CRRT)	Delivered at low blood-flow and effluent rates over 24 hours. Provides gradual solute clearance and controlled ultrafiltration.	Ideal for hemodynamically unstable patients on vasopressors, those with fluctuating MAP, or cerebral oedema where osmotic shifts may worsen intracranial pressure. Enables precise fluid control in septic shock and acute liver failure.
Sustained Low-Efficiency Dialysis (SLED)	Hybrid technique (6–12 hours) using lower blood-flow rates than IHD.	Useful when CRRT is unavailable (Poor man's CRRT). Provides slower solute removal than IHD and is better tolerated by unstable patients. Cost-effective and feasible in resource-limited units while retaining many CRRT benefits.

Anticoagulation for CRRT

- Heparin: Simple to administer and monitor; risk of systemic bleeding and HIT.
- Regional Citrate: Preferred in many ICUs; prolongs filter life and limits systemic anticoagulation. Requires monitoring of ionized calcium and acid–base status, especially in liver dysfunction

5) Dose and Intensity

Increasing dialysis dose does not improve survival. Large multicenter trials, including the RENAL and ATN studies, demonstrated that a CRRT dose of 20 to 25 mL/kg/h provides outcomes equivalent to high-dose therapy (40 mL/kg/h) [26]. Higher effluent volumes increase loss of antibiotics, micronutrients, and amino acids without clear benefit.

The key is to deliver the prescribed dose consistently. Interruptions for procedures, filter clotting, or technical downtime may significantly reduce the delivered effluent dose.

Future Prospective

Research and innovation in AKI are shifting management strategies from reactive organ support toward targeted, proactive, and biologically informed intervention. Several emerging technologies and therapeutic concepts hold promise for improving early detection, individualized treatment, and long-term renal recovery.

1. Real-Time GFR Monitoring

Current practice relies on delayed biochemical surrogates of filtration. New optical and fluorescence-based systems are being developed to measure GFR continuously at the bedside. These technologies may eliminate the diagnostic lag associated with creatinine and could allow clinicians to adjust therapy in real time rather than after irreversible injury has occurred [27,28].

2. Bio-Artificial Kidney Systems

Renal assist devices incorporating human

tubular cells aim to replicate both filtration and essential metabolic functions such as vitamin D hydroxylation, ammoniagenesis, and immunomodulation. Early clinical studies suggested improved haemodynamic tolerance and potential survival benefit, but implementation remains complex due to manufacturing challenges, immune considerations, and circuit durability. Continued development may eventually provide partial biological replacement rather than purely mechanical dialysis [29].

3. Drug Development and Cellular Protection

Pharmacologic research is moving toward preserving mitochondrial integrity, enhancing cellular repair pathways, and reducing apoptosis. Agents targeting PGC-1 alpha–mediated mitochondrial biogenesis and other cytoprotective mechanisms are under evaluation. Although none have demonstrated definitive clinical benefit to date, these pathways represent a plausible route to disease-modifying therapy for intrinsic renal injury [30,31].

4. Artificial Intelligence and Predictive Analytics

Machine learning tools embedded within electronic health records can integrate laboratory trends and physiological data to predict AKI up to 48 hours before diagnostic criteria are met [32,33]. Early identification enables tailored haemodynamic optimization, avoidance of nephrotoxins, and more rational fluid strategies. As accuracy improves and implementation becomes widespread, predictive algorithms may fundamentally alter AKI prevention strategies.

These advances collectively point toward a future in which AKI management is personalized, biologically targeted, and driven by early prediction rather than delayed laboratory recognition [34].

Conclusion

Acute Kidney Injury in the ICU is a heterogeneous syndrome driven by diverse mechanisms rather than simple hypoperfusion. Management has shifted from uniform treatment to structured KDIGO staging, biomarker-guided risk assessment, and phenotype-based decision making. Although no therapy reverses tubular necrosis, outcomes have improved through careful hemodynamic optimization, fluid stewardship, avoidance of overload, nephrotoxin control, and well-timed renal replacement therapy. Future practice will move beyond serum creatinine toward molecular endotypes and early biomarker signals, but until those tools become routine, vigilance and prevention remain the foundation of AKI care in critical illness.

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REVIEW ARTICLE

Still's Disease: Bridging Pediatric and Adult Auto-inflammatory Spectrum

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Abstract

Abstract: Adult-onset Still's disease (AOSD) is an uncommon multisystem autoinflammatory condition that typically manifests with daily high-grade fever spikes, a transient salmon-coloured rash, arthritis, and markedly elevated serum ferritin levels. The disorder is driven by excessive activation of the innate immune pathways, resulting in increased production of key pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-18, and tumour necrosis factor-α[1]. The diagnosis is primarily clinical and relies on meeting the Yamaguchi criteria once infectious, malignant, and other autoimmune causes have been excluded.The management focuses on controlling inflammation, preventing end-organ damage, and minimising glucocorticoid exposure. Non-steroidal anti-inflammatory drugs may suffice for mild disease, whereas IL-1 and IL-6 inhibitors are the preferred first-line agents for moderate to severe disease[2]. Glucocorticoids remain valuable for rapid control of inflammation and treatment of macrophage activation syndrome (MAS). Early initiation of biologic therapy improves remission rates and reduces chronicity. This review summarises the current understanding of pathogenesis, diagnostic approach, and therapeutic strategies in Still's disease with emphasis on modern cytokine-targeted therapy.

Keywords:
Adult-Onset Still's Disease; Autoinflammatory Disorder; Yamaguchi Criteria; Interleukin-1; Interleukin-6; Biologic DMARDs; Macrophage Activation Syndrome; Hyperferritinemia; Cytokine Storm; Glucocorticoids.

Introduction

Adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA) are now recognised as age-related presentations of the same autoinflammatory condition, collectively termed Still's disease. Traditionally, the diagnosis of AOSD was applied to individuals presenting after the age of 16 years, whereas sJIA referred to cases occurring in younger patients. In 2024, the European Alliance of Associations for Rheumatology (EULAR) and the Paediatric Rheumatology European Society (PRES) proposed unifying both under a single disease designation, reflecting their shared clinical and immunological features[3]. The condition is named after Sir George Frederic Still, who first described the paediatric form in the late nineteenth century. AOSD is an uncommon systemic inflammatory disorder of uncertain cause, typically presenting with a distinctive combination of daily or twice-daily fever spikes, a transient salmon-coloured rash, inflammatory arthritis, and involvement of various organ systems.

Epidemiology

Still's disease in adults is rare, with most estimates suggesting an annual incidence of fewer than one

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case per 100,000 individuals. The condition shows a characteristic bimodal age distribution, with an initial peak occurring in late adolescence to early adulthood (around 15–25 years) and a second peak in middle age (approximately 36–46 years). Although less common, cases have also been documented in elderly individuals, including those over 70 years of age[4].

Aetiopathogenesis

The pathogenesis of adult-onset Still's disease (AOSD) is not fully understood, but current evidence indicates that it represents an autoinflammatory disorder driven by excessive activation of the innate immune system. Overactivity of neutrophils and macrophages leads to uncontrolled release of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-18, and tumour necrosis factor-β, which collectively sustain fever, joint inflammation, and systemic illness[5]. IL-1β is central to the development of fever and synovial inflammation, while IL-6 enhances hepatic production of acute-phase reactants, contributing to the marked hyperferritinaemia frequently seen in active disease. Ferritin levels often rise into the thousands, reflecting intense macrophage activation. IL-18 further amplifies the inflammatory cascade by stimulating natural killer cells and promoting interferon-β secretion, and markedly elevated IL-18 concentrations are strongly associated with the development of macrophage activation syndrome, a severe hyperinflammatory complication. Genetic susceptibility may also play a role, with certain HLA alleles reported more frequently in patients with AOSD, while environmental triggers—particularly viral infections such as Epstein–Barr virus, cytomegalovirus, and parvovirus B19—are proposed to initiate disease in predisposed individuals by activating inflammasome pathways and enhancing IL-1β and IL-18 production.

Hyperferritinemia itself may contribute to pathogenesis through altered iron metabolism, low glycosylated ferritin levels, and iron-induced oxidative stress, which may perpetuate cytokine-driven inflammation. Unlike classical autoimmune diseases, AOSD lacks disease-specific autoantibodies, and its inflammatory profile is dominated by the innate rather than adaptive immune system, placing it firmly within the spectrum of autoinflammatory disorders and highlighting its close relationship to systemic juvenile idiopathic arthritis[6].

Clinical Features

The core clinical manifestations of adult-onset Still's disease (AOSD) include high-grade fever, a characteristic rash, and inflammatory joint symptoms such as arthritis or arthralgia. Additional systemic features may include sore throat, hepatomegaly, serositis involving the pleura or pericardium, and abdominal discomfort. A potentially life-threatening complication, macrophage activation syndrome (MAS), although uncommon, requires prompt recognition.

Fever is one of the most prominent symptoms, typically reaching ≥39°C and appearing in a once-daily or twice-daily spike pattern. These fever spikes often precede other clinical signs and, in some patients, may initially present as pyrexia of unknown origin (PUO).

The rash associated with AOSD is usually transient, pink-to-salmon coloured, and macular or maculopapular in appearance. It commonly affects the trunk and limbs but may occasionally extend to the palms, soles, or even the face. The eruption is generally non-itchy and often coincides with fever peaks.

Arthritis and Arthralgia are Universal features of Still's disease in adults, and myalgia is common. Arthritis is mild, transient, and oligoarticular. Most commonly involved joints include the knee, wrist, ankle, elbow, PIP, and shoulder joints. DIP, sacroiliac joints are rarely affected. Fusion of the wrist joint is classic of stills but not specific. Myalgia is common and worsens with fever spikes.

Pharyngitis is severe, non-suppurative. Hepatomegaly is seen in some associated with moderate elevation of hepatic aminotransferases and alkaline phosphatases. Pleurisy,pleural effusion, and pulmonary infiltrates are seen in some. Lymphedema is present in two-thirds of adults, which is typically symmetrical.Splenomegaly is seen in about one-half of adults.Abdominal pain is present is associated with nausea, anorexia, and weight loss.

Rare clinical manifestations include seizures, aseptic meningitis, and reversible posterior

leukoencephalopathy, myocarditis, heart failure, interstitial nephritis, secondary amyloidosis,TTP, DIC, conjunctivitis, episcleritis, uveitis[7].

Investigations

A variety of laboratory abnormalities may support the diagnosis of adult-onset Still's disease (AOSD), although none are pathognomonic. Most patients demonstrate evidence of a systemic inflammatory response, including markedly elevated acute-phase reactants, leukocytosis with predominant neutrophilia, thrombocytosis, anaemia, and raised liver transaminases. Serum ferritin levels are often exceptionally high, sometimes reaching several thousand nanograms per millilitre. Pro-inflammatory cytokines such as IL-6, TNF-α, and interferon-γ may be increased, though these findings are non-specific. In contrast, IL-18 elevations appear more closely associated with AOSD and may correlate with disease activity.

Imaging results vary with disease stage. Early in the course, plain radiographs of the hands may be normal or demonstrate only soft-tissue swelling or joint effusion. Over time, a characteristic nonerosive narrowing of the carpometacarpal and intercarpal joints can occur, occasionally progressing to ankylosis. Cross-sectional imaging such as computed tomography (CT) may reveal hepatosplenomegaly, enlarged lymph nodes, or pulmonary findings. Increased fluorodeoxyglucose uptake on 18F-FDG PET scans has also been described, involving lymph nodes, salivary glands, and other organs.

The diagnosis of AOSD remains clinical and is based on excluding infections, malignancies, and other rheumatologic conditions. The Yamaguchi criteria, introduced in 1992, continue to be the most widely applied diagnostic framework, with reported sensitivity and specificity of approximately 96% and 92%, respectively[8]. Positive diagnosis of Still's disease requires at least 2 major and a total 5 criteria to be fulfilled .

Yamaguchi Criteria:

MAJOR CRITERIA	MINOR CRITERIA
Fever ≥39ºC,> 1 week	Sore throat
Arthritis / Arthralgia lasting >2 weeks	Lymphedanopathy
Typical nonpruritic salmon colored rash	Spleenomegaly
Elevated WBC > 10000 with 80% granulocytes	Negative ANA and RF
	Abnormal liver function tests

Treatment

The management of Still's disease aims to suppress systemic inflammation, prevent organ damage, and minimize drug-related adverse effects. Treatment decisions are guided primarily by disease severity and the presence or absence of macrophage activation syndrome (MAS).

1. Pretreatment Evaluation

Before initiating therapy, infection and malignancy should be excluded, as both can mimic AOSD. Baseline investigations include complete blood count, liver and renal function tests, ESR, CRP, ferritin, D-dimer, and viral serology for hepatitis B and C. Screening for latent tuberculosis is recommended before the use of biologics. Vaccinations should be updated before starting immunosuppressive therapy.

Approach to Initial Therapy

Patients with Mild Disease (without MAS)

For patients presenting with mild systemic symptoms (fever, rash, arthralgia), a short trial of nonsteroidal anti-inflammatory drugs (NSAIDs) is appropriate. Common options include naproxen (500 mg twice daily), ibuprofen (800 mg three times daily), or indomethacin (25–50 mg three times daily). Approximately 15–20% of patients may achieve symptom control with NSAIDs alone.

If no improvement occurs within 1–2 weeks, escalation of therapy is indicated.

Moderate to Severe Disease (without MAS)

Patients with persistent fever, polyarthritis, serositis, or internal organ involvement require initiation of disease-modifying therapy.

First-line therapy: Interleukin-1 (IL-1) inhibition with anakinra (100 mg subcutaneously daily) is preferred. The dose can be increased to 100 mg twice daily in partial responders[9].

Alternatives: If anakinra is unavailable, other IL-1 blockers (canakinumab) or IL-6 inhibitors (e.g., tocilizumab, sarilumab) may be used. Methotrexate may be considered for patients with predominant articular involvement when biologics are not accessible[10].

Rationale: Early use of IL-1 blockade improves remission rates, shortens glucocorticoid exposure, and prevents chronic disease progression.

Role of Glucocorticoids

Glucocorticoids are useful for rapid control of inflammation or when MAS is suspected. Prednisolone is started at 0.8–1 mg/kg/day for active disease, while lower doses (0.2–0.3 mg/kg/ day) are less effective and associated with lower remission rates. Once remission is achieved, tapering should begin gradually.For patients with limited joint disease, intra-articular corticosteroid injections can be considered after excluding septic or Lyme arthritis.

Management of Macrophage Activation Syndrome (MAS)

MAS is a potentially fatal hyperinflammatory complication of Still's disease. Patients with very high ferritin, elevated D-dimer, cytopenias, and rising transaminases should be promptly evaluated. Treatment includes high-dose intravenous methyl prednisolone (1g daily for 1–3 days) combined with high-dose anakinra (up to 100 mg every 6 hours intravenously).

Long-Term Management :

Once systemic inflammation is controlled, glucocorticoids should be tapered and discontinued whenever possible. Maintenance therapy with biologic or conventional DMARDs helps prevent relapse. Regular monitoring of inflammatory markers and liver function is necessary to assess disease activity and detect medication-related toxicity.

Discussion

Adult-Onset Still's Disease continues to challenge clinicians due to its nonspecific presentation and overlap with infections and malignancies. The diagnosis is primarily one of exclusion, guided by clinical features and elevated inflammatory markers. The Yamaguchi criteria remain the most widely accepted diagnostic standard, with high sensitivity and specificity.

Advances in immunopathology have shifted the understanding of AOSD from an autoimmune to an autoinflammatory disorder, emphasizing the central role of IL-1 and IL-6 pathways. This has revolutionized management—biologic disease-modifying agents such as anakinra, canakinumab, and tocilizumab are now preferred for patients with persistent or severe disease. Early biologic intervention not only achieves faster remission but also limits glucocorticoid dependence and long-term complications.

Macrophage activation syndrome (MAS) represents the most serious complication, associated with high morbidity and mortality. Prompt recognition, high-dose corticosteroids, and IL-1 blockade remain the mainstay of therapy. Regular follow-up with monitoring of ferritin, liver enzymes, and inflammatory markers is crucial to detect relapse or toxicity early.

Despite therapeutic advances, several challenges persist, including delayed diagnosis, high treatment costs, and limited access to biologic agents in developing countries. Further research is needed to identify reliable biomarkers for disease activity and to develop cost-effective therapeutic options suitable for resource-limited settings like India.

Conclusion

Adult-Onset Still's Disease is a rare but potentially severe systemic inflammatory condition with diverse clinical manifestations. Timely recognition and prompt initiation of appropriate therapy are

essential to prevent complications such as MAS and chronic arthritis. Cytokine-targeted biologic therapy, particularly IL-1 and IL-6 inhibitors, has transformed the prognosis of AOSD, allowing steroid-sparing remission in a significant proportion of patients. Ongoing research into disease mechanisms may further refine personalized and safer treatment approaches.

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REVIEW ARTICLE

Interpretation of CBC in Elderly

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Abstract

The interpretation of complete blood count (CBC) parameters in elderly patients requires a nuanced understanding of age-related physiological changes alongside pathological processes that commonly affect this population. With global aging trends, healthcare professionals increasingly encounter elderly patients presenting complex hematologic pictures that may deviate significantly from standard reference ranges established primarily in younger adult populations. This comprehensive review examines both physiological and pathological interpretations of core CBC components, including hemoglobin, white blood cells, platelets, and red cell indices, while providing disease-specific examples to contextualize abnormalities in elderly patients.

Age-Related Physiological Changes in CBC Parameters

a. Hemoglobin and Hematocrit Alterations

Age-related changes in hemoglobin levels represent one of the most significant departures from traditional reference ranges in elderly populations. Current World Health Organization criteria define anemia as hemoglobin levels below 130 g/L for men and 120 g/L for non-pregnant women aged 15 years and above. However, these cutoffs may be inappropriate for elderly patients, as evidenced by population-based studies demonstrating that average hemoglobin levels for men beyond age 70 and women beyond age 80 often fulfill WHO criteria for anemia diagnosis.[1]

Large-scale studies have revealed substantial age-related hemoglobin decline. In a comprehensive analysis of 1,724 individuals, approximately 20% of men and women aged 60-69 years were classified as anemic by WHO definition, with these proportions steadily increasing to 63% in females and 76% in males beyond age 90. More precise age-specific reference intervals suggest lower limits of 125 g/L and 116 g/L for males and females respectively over age 60, decreasing further to 108 g/L and 97 g/L for those over 75 years.[2][1]

Hematocrit values similarly demonstrate age-related decline, with studies showing significant decreases in elderly populations. Men aged over 65 years exhibit median hematocrit values of 40.9% compared to 43.2% in younger cohorts, while women show less pronounced but measurable decreases from 40% to 39.6%. These changes reflect multifactorial processes including decreased erythropoietin production, reduced hematopoietic stem cell reserve, and subclinical chronic disease states commonly present in elderly populations.[3]

b. White Blood Cell Count Dynamics

White blood cell counts in healthy elderly individuals generally remain within normal ranges, though subtle changes occur with aging. The normal reference interval for adults is typically 4,500-11,000 cells/ml, with studies showing median WBC counts of 6.3×10ml in 75-year-old men and 5.7×10/ml in women. However, the clinical significance of WBC count changes in elderly populations extends beyond simple enumeration, as these values demonstrate prognostic importance for mortality outcomes.[4]

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Age-related immunosenescence significantly impacts white blood cell function despite maintained absolute counts. Neutrophil function particularly deteriorates with aging, characterized by reduced chemotaxis, impaired priming responses to inflammatory cytokines like GM-CSF, and decreased ability to delay apoptosis in response to infectious stimuli. These functional deficits contribute to increased infection susceptibility in elderly populations, even when absolute neutrophil counts remain within normal ranges.[5]

a. ***Platelet Count and Function Changes***

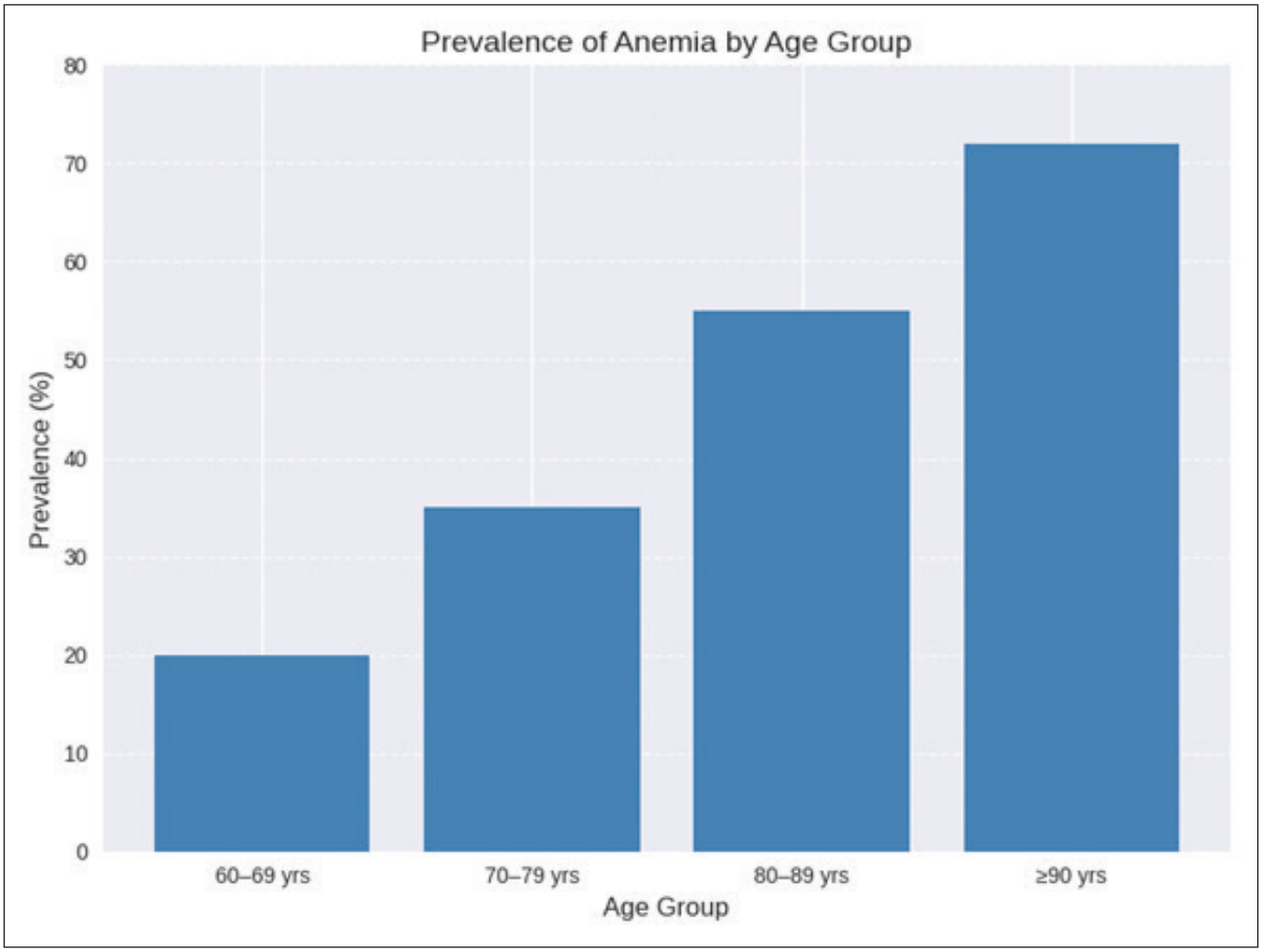
Platelet counts demonstrate complex age-related patterns, with significant sex and age-specific variations requiring adjusted reference intervals. In males, 95% reference intervals decrease with age: 150-300×10^9/L (ages 60-69), 130-300×10^9/L (ages 70-79), and 120-300×10^9/L (ages 80+). Females maintain relatively stable platelet counts across age groups, with a consolidated age-independent 95% reference interval of 165-355×10^9/L.[6]

The age-related decline in platelet count reflects broader hematopoietic changes, with cross-sectional studies demonstrating that platelet count in old age is reduced by 35% in men and 25% in women compared to early infancy. This reduction occurs primarily during childhood and old age, with minimal changes during middle adulthood. Despite numerical decline, elderly platelets may demonstrate increased activation and reactivity, as evidenced by elevated mean platelet volume (MPV) values in patients over 75 years.[7][8]

Red Cell Indices and Their Clinical Significance

a. **Mean Corpuscular Volume and Related Parameters**

Red cell indices, including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), show relatively stable patterns across age groups, though subtle changes occur with clinical significance. Studies



demonstrate that MCV, MCH, and MCHC show less variation across age groups compared to other CBC parameters, with no significant differences observed in MCV and MCH in most elderly populations.[9]

However, age-related changes in MCHC demonstrate statistical significance, with pronounced declines noted in subjects aged 80 years or more. This decline likely reflects both decreased red blood cell levels and lower hemoglobin concentrations characteristic of aging populations. Clinical interpretation must consider that elderly patients with elevated MCV and MCH levels may face increased cardiovascular risks, particularly in non-anemic populations where high MCV and MCH values are associated with major adverse cardiovascular events.[10][9]

b. Red Cell Distribution Width as a Prognostic Marker

Red cell distribution width (RDW) emerges as a particularly important parameter in elderly populations, serving not merely as a diagnostic tool for anemia classification but as a prognostic marker for cardiovascular events and mortality. RDW reflects erythrocyte size distribution and represents anisocytosis, with elevated values associated with diverse pathological conditions including cardiovascular disease, chronic kidney disease, and inflammatory states.[11]

In elderly hospitalized patients with chronic cardiovascular disease, RDW values are significantly elevated, with approximately 59% demonstrating values above the normal upper limit of 14.5%. The most significant factors associated with elevated RDW include acutely decompensated chronic heart failure, atrial fibrillation, and anemia, suggesting that RDW elevation reflects both hematologic abnormalities and cardiovascular pathophysiology involving sympathetic nervous system overactivity.[11]

Physiologic vs. Pathologic CBC Changes in the Elderly

Common Pathological Conditions Affecting CBC in Elderly

a. Iron Deficiency Anemia

Iron deficiency anemia represents the most common nutritional cause of anemia in elderly populations, affecting approximately one-third of older adults with anemia. The presentation in elderly patients often differs from younger populations, with subtle, non-specific symptoms potentially masking the underlying deficiency. Gastrointestinal bleeding accounts for the majority of iron deficiency cases in elderly patients, necessitating comprehensive evaluation including colonoscopy and esophagogastroduodenoscopy.[12]

Diagnostic challenges arise from age-related changes in iron metabolism and chronic inflammation. Ferritin levels, the primary marker for iron stores, increase with age and may remain within normal ranges despite true iron deficiency in the presence of inflammatory conditions. In elderly patients with chronic kidney disease or inflammatory states, ferritin levels up to 100 μg/L, or as high as 300 μg/L with transferrin saturation $<20\%$, may still indicate iron deficiency requiring supplementation.[12]

Management of iron deficiency anemia in elderly patients requires careful consideration of absorption issues, drug interactions, and underlying comorbidities. While oral iron supplementation remains first-line therapy, elderly patients

CBC Component	Physiologic Changes	Pathologic Changes
Hemoglobin/Hematocrit	Gradual decline; mild anemia common in >70 y	Nutritional deficiencies, CKD, MDS, chronic inflammation, occult bleeding
WBC Count	Stable or slight decline; lymphopenia common	Infection, leukemia, myelodysplasia, drug-induced cytopenia
Platelets	Modest decrease (~9×10^9/L per decade); increased MPV	ITP, MDS, reactive thrombocytosis, myeloproliferative neoplasm
RBC Indices	Mild macrocytosis possible; RDW slightly higher	Iron/B12/folate deficiency, MDS, hemolysis

frequently require intravenous iron administration due to malabsorption, medication interactions with proton pump inhibitors or antacids, and gastrointestinal intolerance. Target hemoglobin levels in elderly patients should be individualized, typically ranging from 100-120 g/L to avoid adverse effects associated with overcorrection.

b. Vitamin B12 and Folate Deficiency

Vitamin B12 deficiency affects up to 20% of elderly individuals, with prevalence increasing significantly with advancing age. Age-related changes in gastrointestinal function, including decreased gastric acid production and intrinsic factor secretion, predispose elderly patients to malabsorption. Pernicious anemia, caused by autoantibodies against intrinsic factor and parietal cells, occurs most frequently in adults over 60 years.[13]

Clinical presentation often includes macrocytic anemia with MCV >100 fL, though up to 30% of patients may present with normal MCV values, particularly in the presence of concurrent iron deficiency. Neurological symptoms, including cognitive decline, peripheral neuropathy, and balance disturbances, may precede hematologic abnormalities and can be irreversible if treatment is delayed.

Diagnostic evaluation should include serum B12 levels, though values between 200-300 pg/mL may represent borderline deficiency. Methylmalonic acid levels provide more sensitive detection of functional B12 deficiency, though availability may be limited. Given the low cost and potential benefits, therapeutic trials of B12 supplementation are recommended for borderline cases. Treatment typically involves high-dose oral B12 (1000 μg daily) for patients with normal absorption, while those with malabsorption require parenteral administration.

Folate deficiency has become less common in countries with folate supplementation programs but should be suspected in elderly patients with severe malnutrition or excessive alcohol use. Treatment with 1 mg folic acid daily typically achieves rapid correction, though concurrent B12 deficiency must be excluded to prevent neurological complications.

c. Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) represents a significant cause of anemia in elderly populations, with median age at diagnosis of 70 years. This clonal hematopoietic stem cell disorder is characterized by ineffective hematopoiesis leading to peripheral cytopenias despite hyperplastic bone marrow. The incidence of MDS increases substantially with age, making it a critical consideration in elderly patients presenting with unexplained anemia, particularly when accompanied by other cytopenias.[14]

Clinical presentation typically includes progressive anemia, often transfusion-dependent, with variable thrombocytopenia and neutropenia. Approximately 30% of patients eventually develop acute myeloid leukemia, though mortality often results from complications of cytopenias rather than leukemic transformation. Morphologic dysplasia in blood cells, including macrocytosis, oval macrocytes, and hypogranular neutrophils, provides important diagnostic clues.

The International Prognostic Scoring System (IPSS) stratifies patients into risk categories based on cytogenetics, blast percentage, and number of cytopenias, guiding treatment decisions. Lower-risk disease (low and intermediate-1 categories) focuses on hematologic improvement and symptom management, while higher-risk disease (intermediate-2 and high categories) emphasizes disease modification and survival prolongation.

Treatment options for elderly patients with MDS must consider performance status, comorbidities, and patient preferences. Supportive care including transfusions, iron chelation, and growth factors remains fundamental. Low-intensity therapies such as hypomethylating agents (5-azacitidine, decitabine) and immunomodulatory drugs (lenalidomide for 5q deletion syndrome) offer potential for disease modification while maintaining acceptable tolerance in elderly populations.

d. Chronic kidney disease and Anemia

Chronic kidney disease (CKD) represents a major contributor to anemia in elderly populations, with prevalence increasing substantially as glomerular filtration rate declines. CKD-associated anemia typically develops when eGFR falls below 60 mL/

min/1.73 m^2, with prevalence becoming age-independent when eGFR drops below 45 mL/min/1.73 m^2.[15]

The pathophysiology involves multiple mechanisms including decreased erythropoietin production, reduced hematopoietic response to erythropoietin due to uremic toxins, and functional iron deficiency secondary to chronic inflammation. Hepcidin elevation, common in CKD patients, impairs iron absorption and mobilization from stores, creating iron-restricted erythropoiesis even with adequate iron stores.

Diagnostic evaluation should exclude other causes of anemia while assessing iron status using both serum ferritin and transferrin saturation. In CKD patients with inflammation, iron deficiency may occur at higher ferritin levels than typically recognized, requiring individualized assessment.

Management includes erythropoiesis-stimulating agents (ESAs) and iron supplementation, with target hemoglobin levels of 100-120 g/L recommended to balance symptom improvement against cardiovascular risks associated with higher targets. Intravenous iron administration often proves more effective than oral supplementation in CKD patients due to absorption issues and chronic inflammation.

Drug-Induced Hematologic Abnormalities

a. Polypharmacy and CBC Alterations

Polypharmacy, defined as the concurrent use of five or more medications, affects approximately 95% of elderly patients with cardiovascular disease. The complex medication regimens common in elderly populations create substantial risk for drug-induced hematologic abnormalities, with potential for both direct toxic effects and drug-drug interactions affecting CBC parameters.[16]

Drug-induced thrombocytopenia represents a particularly important concern, with incidence rates of 9% for major bleeding and 0.8% for fatal bleeding reported in affected patients. Heparin-induced thrombocytopenia poses especially high mortality risk due to associated thrombotic complications. Other commonly implicated medications include quinidine, sulfonamides, vancomycin, and nonsteroidal anti-inflammatory drugs.[17]

Mechanisms of drug-induced thrombocytopenia include both immune-mediated and non-immune pathways. Immune-mediated thrombocytopenia involves antibody formation against platelet-drug complexes, while non-immune mechanisms result from direct bone marrow suppression or platelet toxicity. Clinical presentation typically includes rapid platelet count decline within days to weeks of drug initiation, often with severe bleeding complications.

Management requires immediate discontinuation of suspected medications and supportive care including platelet transfusions for severe bleeding. Recovery typically occurs within days to weeks following drug discontinuation, though some cases may require additional interventions such as corticosteroids or intravenous immunoglobulin.

b. Neutropenia and Immunosuppressive Medications

Age-related immunosenescence compounds the risks associated with medication-induced neutropenia in elderly populations. Common medications causing neutropenia include antibiotics (particularly beta-lactams), antithyroid drugs, cardiovascular medications, and psychotropic agents. The combination of drug-induced neutropenia and age-related immune dysfunction creates particularly high infection risk.

Clinical monitoring should include regular CBC assessment for patients receiving potentially myelosuppressive medications, with particular attention to absolute neutrophil counts. Neutropenia severity classification guides clinical management, with severe neutropenia (<500 cells/μL) requiring immediate evaluation for infectious complications and consideration of growth factor support.

Clinical Approach to CBC Interpretation in Elderly Patients

I. Establishing Age-Appropriate Reference Ranges

The evidence strongly supports adoption of age-specific reference ranges for CBC interpretation in elderly populations. Traditional reference ranges, established primarily in younger adults, may lead to overdiagnosis of anemia and other abnormalities in elderly patients while potentially missing clinically significant changes within age-adjusted normal ranges.

Recommended age-specific hemoglobin reference ranges suggest lower limits of 125 g/L for males and 116 g/L for females over age 60, with further reductions to 108 g/L and 97 g/L respectively for patients over 75 years. Similarly, platelet count reference ranges should be adjusted for elderly males, with lower limits decreasing from 150×10^9/L in the 60-69 age group to 120×10^9/L for patients over 80 years.[2][6]

II. Systematic Diagnostic Approach

CBC interpretation in elderly patients requires systematic evaluation incorporating multiple clinical factors. Initial assessment should exclude easily treatable causes including nutritional deficiencies (iron, B12, folate) and thyroid dysfunction. When standard causes are excluded or residual abnormalities persist after treatment, further evaluation for chronic diseases, malignancies, and medication effects becomes necessary.

Red flag signs warrant immediate attention and often require hematologic consultation or bone marrow examination. These include MCV>96 fL, absolute neutrophil count<1000 cells/μL, platelet count $<120\times10^9$/L, family history of hematologic malignancies, abnormal peripheral smear findings, severe anemia <90 g/L, and progressive unexplained worsening of cytopenias.[18]

III. Multidisciplinary Management Considerations

Effective management of CBC abnormalities in elderly populations requires multidisciplinary collaboration incorporating geriatric principles. Treatment decisions must consider life expectancy, functional status, comorbidities, and patient preferences alongside traditional disease-specific factors. Goals of care should emphasize symptom improvement and quality of life rather than normalization of laboratory values when appropriate.

Medication management requires particular attention to drug interactions, dose adjustments for renal function, and monitoring for adverse effects. Regular reassessment of medication necessity and potential for discontinuation helps minimize polypharmacy-related complications while maintaining therapeutic benefits.

Future Directions and Emerging Concepts

a. Unexplained Anemia of Aging

Unexplained anemia of aging (UAA) represents a diagnosis of exclusion in elderly patients with mild anemia after thorough evaluation excludes identifiable causes. This entity may represent the convergence of multiple age-related factors including decreased hematopoietic reserve, chronic low-grade inflammation, and subtle hormonal changes. Recognition of UAA as a distinct clinical entity helps avoid unnecessary interventions while providing appropriate monitoring and supportive care.

b. Biomarker Integration

Emerging research emphasizes the prognostic value of CBC parameters beyond traditional diagnostic roles. RDW, neutrophil-to-lymphocyte ratio, and platelet indices demonstrate associations with cardiovascular events, mortality, and functional decline in elderly populations. Integration of these biomarkers into comprehensive geriatric assessment may enhance risk stratification and guide clinical decision-making.

c. Precision Medicine Approaches

Future developments in CBC interpretation may incorporate genetic factors, epigenetic changes, and personalized reference ranges based on individual patient characteristics. Understanding of age-related clonal hematopoiesis and its clinical implications continues to evolve, potentially informing interpretation of subtle CBC abnormalities in elderly patients.

Conclusion

Interpretation of CBC parameters in elderly populations requires fundamental shifts from traditional approaches established in younger adults. Age-specific reference ranges, recognition of physiological aging changes, and understanding of common pathological conditions affecting elderly patients are essential for accurate diagnosis and appropriate management. The complex interplay between normal aging, chronic diseases, and polypharmacy creates unique challenges requiring multidisciplinary expertise and individualized care approaches.

Healthcare professionals caring for elderly patients must appreciate that CBC abnormalities may represent normal aging variants, treatable conditions, or early manifestations of serious diseases requiring prompt intervention. Systematic evaluation incorporating age-appropriate reference ranges, comprehensive medical history, and multidisciplinary assessment optimizes outcomes while avoiding both overtreatment and under-recognition of significant abnormalities.

The growing elderly population demands increased attention to hematologic changes accompanying aging, with continued research needed to refine diagnostic criteria, establish optimal treatment targets, and develop age-specific management guidelines. Integration of emerging biomarkers and precision medicine approaches holds promise for enhancing care quality while reducing healthcare burden associated with inappropriate interventions based on age-inappropriate reference standards.

As our understanding of aging-related hematologic changes continues to evolve, healthcare systems must adapt to provide comprehensive, age-appropriate CBC interpretation that balances diagnostic accuracy with clinical relevance. This approach ensures optimal outcomes for elderly patients while supporting healthy aging and quality of life maintenance in our increasingly aged society.

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REVIEW ARTICLE

Non-invasive Markers for the Diagnosing Liver Fibrosis

Deepika Kedia

Abstract

Liver diseases with chronicity due to viral hepatitis B or C, alcohol, cholestatic (PBC or PSC) or MASLD/MASH is very common. Liver fibrosis is the strongest histologic predictor of liver related outcomes in chronic liver diseases. Liver biopsy is invasive and has significant sampling and observer variability. Noninvasive markers for the diagnosis of liver fibrosis have become an important tool specially for MASLD/MASH and other chronic liver diseases. It helps in the diagnosis of clinically significant or advanced fibrosis. Current clinical practice includes a simple stepwise strategy which is inexpensive and simple – FIB 4, APRI and NAFLD score or NFS score. This is followed by second line biomarker ELF and elastography for further workup or for referral decisions and in some patients, pharmacotherapy. The newer biomarkers like PRO – C3, M2BPGi, NIS4 and NIS2+1 are blood based, expensive tests and some of them are not available in India yet.

Background

Liver diseases in the form of chronic viral hepatitis B or C, alcoholic liver disease, cholestatic diseases like PBC or PSC and fatty liver renamed MASLD are very commonly encountered by physicians. The incidence of chronic hepatitis B or C has reduced in India due to the use of new sterile syringes, sterile OT equipment and stricter pre blood transfusion checks. Alcohol intake in Gen Z has definitely reduced but the older generations are still drinking too much alcohol and women in India are consuming more alcohol than before. Obesity is on the rise in India and the rest of the world and is a common cause of fatty liver, metabolic syndrome and MASLD/MASH. More than 30% of the population of India is obese.

Diabetes in on the rise all over the world. India is experiencing a massive diabetes epidemic with over 100 million people affected and an additional 136 million prediabetics. This is due to high genetic susceptibility and lifestyle changes. More and more patients are coming to doctors with either an ultrasound of the abdomen with a diagnosis of fatty liver with different grades or abnormal liver function tests done for various reasons.

Doctors have to answer questions like 'is this fatty liver anything to worry about' or 'why do I have an abnormal liver function test'. General Physician or Specialists namely Hepatologist, Gastroenterologist or Endocrinologist have to be able to tell the patient and relatives what is status of the liver and what needs to be done. Liver biopsy which was the gold standard a decade ago

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is hardly done now a days apart from academic research centres and as part of a research protocol. The indications for which one needs to do a liver biopsy is to confirm autoimmune hepatitis or rarely severe drug induced hepatitis and to rule out acute or chronic rejection in post liver transplant patients. Rarely it is also done in liver transplant donor to check the percentage of steatosis in his/her liver.

Liver biopsy has significant morbidity and rarely mortality attached to it. It is invasive, expensive and has significant observer and sampling variability. The patients do not want to get it done and doctors are reluctant to do it especially due to the rising cases of litigations against doctors in case there is any complications due to the procedure. Therefore, there was a need for noninvasive markers for diagnosing liver fibrosis.

Liver Fibrosis is the strongest histologic predictor of liver related outcomes in chronic liver diseases. There is a need to rule-in or rule-out significant liver fibrosis and identify which patients will need further specialist referral, surveillance, pharmacotherapy or lifestyle changes in the form of weight loss and stricter diabetic control.

Change in nomenclature

Patients with fatty liver disease form a significant global burden. These patients are seen in the primary care and endocrinology settings too. That is why there was a need to change the nomenclature to SLD – steatotic liver disease which includes MASLD and MASH. NAFLD has been changed to MASLD and NASH to MASH[2,8]. Because fibrosis progression is slow, the clinical focus is not giving a one time stage assignment to liver fibrosis but identifying those at the highest risk of progression or outcomes and tracking change over a period of time.

Clinical endpoints that biomarkers and elastography try to detect

Blood biomarkers are most often validated against histology for:

- Significant/clinically significant fibrosis: ≥F2
- Advanced fibrosis: ≥F3
- Cirrhosis: F4

Noninvasive markers for liver fibrosis (2021–2026)1-9

In modern pathways, 'noninvasive markers' for fibrosis include blood-based biomarkers/scores + elastography (stiffness) tests + combined (sequential). Major guidelines in this period strongly support stepwise testing to rule out low risk and then confirm/risk-stratify higher risk patients[3].

1. Blood-based (serum) markers

A) Simple, widely available scores (first-line triage)

- FIB-4 (age, AST, ALT, platelets)
  FIB-4 <1.3 is used as a rule-out threshold for advanced fibrosis in clinical practice, and is recommended moving to elastography and/or patented serum tests if FIB-4 >1.33.
- APRI (AST/platelets) and NFS
  (NAFLD Fibrosis Score)-APRI is still used for triage/risk stratification, along with FIB-4 in primary care, endocrinology or community based pathways2.
- NFS – this is NAFLD score which is calculated online putting in the values of the patient. It consists of age, BMI, AST/ALT ratio, platelets, albumin, glucose/diabetes status.
- Scores between ≤ 1.455 to ≤ 0.675 are indeterminate. Scores > 0.675 suggest high risk of fibrosis (positive predictive values of 82%- 90%)

Recent 2025–2026: performance of simple scores can vary in high-metabolic-risk subgroups[5].

B) Patented/'specialty' fibrosis panels (second-line)

- **ELF (Enhanced Liver Fibrosis)** = hyaluronic acid + PIIINP(Procollagen IIIN -terminal peptide) + TIMP-1 (Tissue Inhibitor of Metalloproteinase -1) EASL 2021 includes **ELF <9.8** as a rule-out option for advanced fibrosis in NAFLD, used particularly as a second-step test when first-line scores are elevated/indeterminate. AASLD's 2025 blood-based guideline covers these panels as part of evidence-based recommendations. ELF is expensive and not available in India apart from academic research centres.

C) 'Active fibrogenesis /ECM turnover' biomarkers (fast growth area)

- **PRO-C3** (type III collagen formation marker) and **ADAPT** (age + diabetes + PRO-C3 + platelets) Recent reviews highlight ADAPT/PRO-C3 as strong noninvasive markers for advanced fibrosis assessment in MASLD patients.
- **M2BPGi** (Mac-2 binding protein glycosylation isomer) 2025 expert consensus summaries support M2BPGi for fibrosis assessment and prognostic stratification across etiologies (HBV/HCV and emerging MASLD data), while emphasizing that cutoffs can vary by population/etiology 4.

  PRO – C3 is available in some labs in India but is expensive.

D) 'At-risk MASH' blood panels (activity + fibrosis; mostly trial-to-clinic)

- **NIS4** (at-risk NASH/MASH identification)
- **NIS2+** (optimization of NIS4; evidence for serial monitoring emerging)

  These tests are yet to be available in India

2) Elastography (imaging-based 'stiffness' markers)

A) VCTE / FibroScan (Transient elastography)

- Measures **liver stiffness (kPa)** as a surrogate for fibrosis and in advanced disease, portal hypertension risk.
- **VCTE LSM <8 kPa** - a rule-out threshold for advanced fibrosis.

LSM 9 -12 kPa – F3 - advanced fibrosis or precirrhotic

LSM ≥ 12.5 kPa – F4 or cirrhosis. If the reading is much higher and if the portal hypertension is treated or if the sugar levels are well controlled or an obese cirrhotic loses weight by eating less calories and exercising, the stiffness becomes much better. 4 hours of fasting is a must for transient elastography.

Portal hypertension:

Baveno VII formalized noninvasive criteria using **VCTE + platelet count** to estimate clinically significant portal hypertension (CSPH) and guide endoscopy/NSBB(nonselective betablockers) decisions6.

LSM ≤15 kPa + platelets ≥150×10⁹/L - to rule out CSPH

LSM ≥25 kPa to rule in CSPH in specific compensated patients.

B) Shear-wave elastography (SWE)

- **pSWE (point shear-wave / ARFI)** and **2D-SWE** are ultrasound-based stiffness methods increasingly used where FibroScan or MRE access is limited.
- AASLD's imaging guidelines reviews TE, SWE methods, and MRE across etiologies, noting that accuracy generally improves from detecting ≥F2 to ≥F3/≥F4.

C) MRE (Magnetic Resonance Elastography)

- MRE is the most accurate stiffness method especially for staging across fibrosis ranges. This is not easily available and is costlier, so commonly used in referral centres and research pathways.

3) Combined markers that became prominent (2021–2026)

A) Stepwise clinical pathways

EASL 2021 explicitly recommends: **if FIB-4 >1.3** → use **VCTE and/or patented serum tests** to rule out/in advanced fibrosis rather than relying on one test alone. EASL–EASD–EASO 2024 MASLD guidelines recommend noninvasive tests in people with cardiometabolic risk factors.

B) FibroScan-derived composite scores (specially in MASLD/MASH)

- **FAST score** = FibroScan LSM + CAP + AST (targets fibrotic, active steatohepatitis, at-risk MASH). CAP score is in dB/m and is indicative of steatosis, that is, the percentage of liver cells which have fat in them10.

  Normal < 238 dB/m - S0, upto 4% liver cells have fat in them

  S1 – 238 – 260 dB/m, 5 - 33% liver cells have fat in them

  S2 – 260 – 290 dB/m, 34 - 66% have fat in them

  S3 > 290 dB/m, more than 67 – 100 % liver cells have fat in them
- **Agile 3+ (advanced fibrosis)** and **Agile 4 (cirrhosis)** = VCTE + routine labs; developed/validated to improve rule-in performance vs LSM alone. These are online calculators mainly used patients with MASLD. Agile 4 includes

LSM, AST/ALT ratio,platelets, sex and diabetes status. Agile 3+ includes LSM, AST, ALT, platelets, sex, diabtetes status and age7.

C) MRE + blood-score combinations (prognosis-focused)

- **MEFIB = MRE ≥3.3 kPa + FIB-4 ≥1.6** is considered as a strong 'rule-in' for significant fibrosis and is associated with outcomes in MASLD cohorts.

Practical takeaways

1. **Core first-line markers:** FIB-4/APRI (triage) → **VCTE (FibroScan)** or **ELF** as second step.
2. **Elastography expanded beyond fibrosis staging** to **portal hypertension risk** - Baveno VII criteria using VCTE + platelets. There is a growing role for spleen stiffness. Some centres in India perform splenic stiffness. It measures splenic tissue stiffness and is used for assessing portal hypertension and esophageal varices. If the values > 32.8 kPa, it indicates high risk for varices6.
3. **MASLD/MASH-focused composite tools** (FAST, Agile 3+/4, MEFIB) are the most notable 'new' clinical-research bridge tools since 2020–2024, with multiple validations through 20257.
4. **Biology/turnover biomarkers** (PRO-C3/ADAPT; M2BPGi) are increasingly discussed for refining risk and potentially tracking disease activity—still with ongoing work on cutoffs and real-world implementation.

Table 1. Key noninvasive fibrosis markers used in the last 5 years (2021–2026)1-10

Category	Test/marker	What it measures	Typical role in pathways	Notes (2021–2026 focus)
Simple blood scores	FIB-4, APRI, NFS	Indirect signals (injury + platelet changes)	Step 1 triage (rule-out emphasis)	Recommended as first step; many patients need step-2 testing.
Patented serum panel	ELF	ECM turnover (HA, PIIINP, TIMP-1)	Step 2 confirmation / risk stratification	FDA-authorized (US) for prognostic use in advanced fibrosis due to NASH; used broadly as second-line test elsewhere.
Fibrogenesis biomarkers	PRO-C3, ADAPT	Collagen formation (active fibrogenesis)	Adjunct/2nd-line; research-to-clinic	Growing evidence base in MASLD; focus on biology + outcomes.
Glycoprotein marker	M2BPGi	Glycosylation isomer linked to fibrosis	Adjunct fibrosis/ prognosis	2025 consensus supports usefulness; ongoing cutoff standardization.
At-risk MASH panels	NIS4, NIS2+	Multi-marker panels (activity+fibrosis intent)	Trial enrichment; emerging monitoring	NIS4 validated for at-risk NASH/MASH; NIS2+ explored for serial monitoring.
Elastography	VCTE (FibroScan)	Liver stiffness (kPa)	Step 2 rule-in/ risk; portal HTN stratification	Expanded use for CSPH risk via Baveno VII framework.
Elastography	2D-SWE / pSWE	Ultrasound stiffness (vendor-dependent)	Alternative to VCTE in many settings	2025 studies/meta-analyses support strong performance; standardization remains key.
Elastography	MRE	MRI stiffness	High-accuracy staging in referral centres	Often paired with FIB-4 as MEFIB for rule-in/out and outcome association.

Limitations: indeterminate zones, inflammation effects, population/etiology differences, need for sequential testing.

This table has been made with the help of AI taking information from all the references cited and from guidelines of AASLD, INASL, EASL and APASL.

5. Conclusions

Noninvasive markers for the diagnosis of liver fibrosis is a very dynamic field and newer tests are being validated still for clinical use. In India, NAFLD, now MASLD has been included in the National program for the prevention and control of and control of cancer, diabetes, cardiovascular diseases and stroke in Feb 2021.

In India, the health care workers know as Asha workers goes to the villages where they are assigned and get information about who has diabetes, hypertension, obesity, dyslipidemia etc. She puts all this information into a tab and the at-risk people go through blood tests. FIB4 and APRI are calculated in the community by doctors and those people who they think need ultrasound of the liver are referred to district hospitals and these patients go through further testing like elastography if need arises. In urban India, usually the general physicians, intensivists or endocrinologist get a report of ultrasound of the abdomen which reports fatty liver and then they do blood tests and calculate FIB4 and decide who needs to be referred to a Specialist like Hepatologist or Gastroenterologist for further testing like elastography or care.

Noninvasive biomarkers help the clinician to rule out or rule in clinically significant or advanced liver fibrosis. The step wise pathway for liver fibrosis has to be developed locally by the doctors as to what is available and affordable by their patients. Once the patient develops cirrhosis, there is significant morbidity and mortality attached to it. There is also huge expenditure for the patient and the family, if complications develop. It is therefore important to identify the at-risk patients and treat the causative reason for their liver fibrosis. If it is chronic hepatitis B or C, then we have to give them the medicines to clear the virus. If alcohol is the cause, then we have to counsel the patient to stop drinking. They also need a lot of psychological help or referral to a psychiatrist. Metabolic clinics are the best way to work as a team and look after obese or patients with metabolic syndrome and with MASLD or MASH. There is a liver specialist, endocrinologist, dietitian, physical trainer if possible, working as a team and helping patients to lose weight, control their diabetes and other aspects of their metabolic syndrome, liver fibrosis is stratified and all efforts are taken to reverse back the liver fibrosis in conjunction with the patient and family.

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REVIEW ARTICLE

In Vitro Fertilization Pregnancies— Possible Complications

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Abstract

Several complications may arise during ART (Assisted Reproductive Technology) and IVF (In Vitro Fertilization) procedures and in the resulting pregnancies.These include miscarriages, preterm labours, multifetal pregnancies, hypertensive disorders in pregnancy, geatational diabetes mellitus, increased Caesarean Section rates, Postpartum Haemorrhage(PPH) and birth defects. It is necessary to properly envisage and deal with these complications as and when they arise. Intra Cytoplasmic Sperm Injection (ICSI). Cryopreservation and Preimplantation Genetic Testing (PGT) are modern advancements in ART and have their own benefits and drawbacks.

Keywords:

Assisted Reproductive Technology, In Vitro Fertilization, Intra Cytoplasmic Sperm Injection, Cryopreservation, Preimplantation Genetic Testing, Pregnancy complications.

Introduction

Despite the scourge of population explosion affecting various countries over the years, the problem of infertility faced by a certain section of the population remains significantly impactful and warrants appropriate corrective measures. The incidence of infertility is steadily on the rise because of several reasons like ovulation disorders, endocrinopathies, Fallopian tubal factors, endometriosis, pelvic inflammatory diseases, genetic defects, congenital uterine anomalies, abnormal sperm parameters, lifestyle factors like substance abuse and environmental changes. Concomitantly, of course, there have been tremendous advances in the methodology of infertility treatment, the most striking example being ART, IVF, ICSI, Cryopreservation of embryos and gametes and PGT. Side effects and complications are frequently encountered in ART procedures and pregnancies resulting therefrom. The aim of this article is to emphasize the anticipation, recognition and proper management of such complications.

IVF may be required in many of the conditions that cause infertility but the tilt towards IVF increases with rising maternal age and poor egg quality and when no cause of infertility can be found ('unexplained infertility'). IVF is also considered when pregnancy is sought to be delayed and eggs cryopreserved for social reasons or when cancer treatment in the form of chemotherapy or radiotherapy is being carried out.

Epidemiology

Globally approximately one-sixth of the

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reproductive age population is affected by infertility.1

It has been reported that there is twice as high a risk of major birth defect after ICSI or IVF compared to natural conception.2 The incidence of ectopic pregnancy after IVF is 2 – 8% higher than after natural pregnancy. The risk of developing OHSS (Ovarian Hyperstimulation Syndrome) at IVF is less than 5% but can have serious implications like massive ascites, respiratory distress and thromboembolism. The incidence of miscarriages after IVF exceeds that after natural pregnancy in women above 40 years of age. There is also an increased chance of multifetal pregnancies, preterm labour and birth defects (particularly cardiac, facial and genitourinary). Multifetal pregnancies present their own set of risks in the form of gestational diabetes mellitus, pre-eclampsia, preterm labour, placenta praevia, placental abruption, emotional stress and birth defects.3

With ART the risk of twins and higher order births is significantly higher as compared to the 1 in 80 chance of twin pregnancies in natural conception.4

In a retrospective cohort study the incidence of birth defects in the ART population was found to be 1.55 times higher than in the non – ART population. Specifically, gastrointestinal, cardiovascular and musculoskeletal abnormalities were found to be higher in incidence. Counselling offered while treating infertile couples must include information regarding the increased possibility of birth defects.5

Aetiopathogenesis

The process of ovum pick-up at IVF may itself give rise to some serious complications like injury to adjacent structures like bowel and urinary bladder, significant bleeding, infection and ovarian abscess.

Age, parity and the underlying cause of infertility play an important role in the causation of pregnancy complications.6 The outcome of IVF pregnancy is definitely influenced by the day of embryo development on which embryo transfer is done. A single good quality vitrified embryo transferred on Day 5 and Day 6 results in improved live birth rate and birth weight as opposed to Day 3 transfer.7 Emotional and mental issues also arise in IVF pregnancies springing from long waiting periods, uncertainty, complications and failures.3

IVF pregnancies involving ovum donation (OD) are prone to more complications as the embryo is immunologically different to the mother leading to placental maldevelopment. OD is an independent risk factor for hypertensive disorders in pregnancy and PPH.8

Clinical Features

Pregnancy after IVF-ET (IVF – Embryo Transfer) is classified as High-Risk because the patients are elderly and have co-morbidities and also because of the known complications. There is an increased risk of prematurity, low birth weight, Induction of labour and Caesarean Section which cannot be attributed solely to a higher rate of multifetal pregnancy. Biochemical pregnancy loss (very early loss with positive serum beta-hCG (human Chorionic Gonadotrophin) but no evidence of pregnancy on Trans Vaginal Sonography) has also been reported. The rate of ectopic and heterotopic pregnancy is also increased.9

In vitro fertilization is associated with an increased risk for adverse perinatal outcomes primarily caused by the increased risks of prematurity, gestational diabetes mellitus, and hypertensive disorders. Infertility can be caused by a variety of factors, including both male and female factors, and in some cases, the cause remains unknown. The underlying cause may influence the nature of complications arising in IVF pregnancies.

Prematurity, gestational diabetes mellitus and hypertensive disorders are some of the complications which may arise in IVF pregnancies and these may in turn lead to perinatal complications inherently associated with them. For example, prematurity may lead to low birth weight, birth asphyxia and neonatal respiratory distress syndrome, gestational diabetes mellitus may result in miscarriage, pre-eclampsia, preterm labour, birth defects, macrosomic babies, birth trauma, shoulder dystocia and future risk of diabetes mellitus for both the mother and the baby and hypertensive disorders in pregnancy may lead to fetal growth restriction, placental abruption, preterm labour, eclampsia and multi-organ failure. As IVF patients are usually elderly and may already

be having one or more comorbidities, the overall incidence of complications in IVF pregnancies naturally increases.10

Prematurity (delivery before 37 weeks of gestation) may be moderate or late preterm (between 33 and 36 weeks), very preterm (28 to 32 weeks) and extremely preterm (less than 28 weeks) with greater morbidity and mortality with increasing severity of prematurity. IVF is an identified risk factor for prematurity and one way to address it is by lowering the number of embryos transferred. Twin pregnancy rate is higher when 2 embryos are transferred as opposed to single embryo transfer. Again, advanced maternal age is an independent risk factor for multiple pregnancy adding to the risk posed by IVF.10

Frozen embryo transfers are done a significant time later than ovarian stimulation so the process mimics natural conception more and therefore the implantation rates and live birth rates are better and the incidence of OHSS lesser. Also, there is lower rate of miscarriage and preterm labour.11

Pregnancy hypertensive disorders may appear in the form of gestational hypertension (hypertension after 20 weeks of pregnancy but with no proteinuria) or pre-eclampsia (hypertension after 20 weeks of gestation with proteinuria).

Investigations

Routine blood, urine and ultrasonographic (including Doppler waveform velocimetry and fetal echocardiography) studies are employed to screen for and detect various pregnancy complications. A fetal Fibronectin (fFN) test carried out on cervicovaginal secretions between 22 and 35 weeks of gestation can indicate or rule out the possibility of preterm labour. In recent times, modern laboratory techniques have become available to screen embryos for specific genetic defects before embryo transfer. These techniques fall under the broad topic of Preimplantation Genetic Diagnosis (PGD) or Preimplantation Genetic Testing (PGT). They may be applied for Monogenic diseases (PGT-M) or single gene disorders such as Thalassaemia. Sickle Cell Anaemia, Cystic Fibrosis and Tay-Sachs Disease or for chromosomal Structural Rearrangements (PGT-SR) as in chromosomal translocations or inversions which may lead to aneuploidies. The genetic analysis is carried out on cells obtained by embryo biopsy at the blastocyst stage. PGT may be performed when there is a family history of hereditary diseases like Huntington's disease, Muscular Dystrophy or fragile X syndrome and also in cases of Recurrent Pregnancy loss or IVF failures.

An Endometrial Receptivity Assay (ERA) test helps in identifying the best time for ET for optimizing results.11

Treatment

The treatment of complications of IVF pregnancies should be on the same lines as for complications arising in natural conception pregnancies, only that surveillance should be more rigorous and pro-active. OHSS must be treated in its own right, stressing on pain relief, maintenance of electrolyte and fluid balance, thromboprophylaxis and abdominal paracentesis when required. Most of the complications can be prevented if anticipated, properly screened for and preemptively treated. Luteal Phase support with progesterones is important to support early pregnancy. For oocyte recipients and for Frozen-Thawed Embryo Transfer cycles, progesterone plus oestrogen support is required.

PGT and transfer of healthy embryos leads to a lowering of miscarriage rate and also does away with the traumatic experience of having to have therapeutic abortion in case a serious fetal condition is detected in later prenatal diagnostic tests like chorionic villus sampling and amniocentesis. Although there is a small risk of damage to the embryo during embryo biopsy, the technique itself is largely safe and the results are highly accurate.

The support of psychologists and peer support groups plays an important role in mitigating emotional and mental issues.3

Discussion

It is a stark and cognizable reality that infertility is a serious concern for a section of the population and needs proper redressal. Although population explosion is a worrisome scourge in many countries, infertility is no less of a concern in affected couples and the incidence of infertility and consequently of IVF attempts and pregnancies is steadily on the

rise.10 Modern techniques pertaining to ART have brought hope to innumerable infertile couples but one must not lose sight of the additional complications posed by these techniques and the couples must be counseled accordingly and appropriate management protocols must be put in place. The safest treatment strategies must always be selected to minimize the risks.

Conclusions

Modern technology often comes with unprecedented benefits but the flip side in the form of possible complications must be kept in mind. While embracing modern technology one must safeguard against serious drawbacks which may sometimes arise. The benefits of IVF must be offered to deserving couples but they must be protected against serious complications which may affect both the mother and the child.

Conflicts of Interest

None to declare.

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REVIEW ARTICLE

P-QRS Relationship in Premature Ventricular Complex (PVC) & Interpolated PVC

Mainak Mukhopadhyay[1]
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Abstract

Premature Ventricular Complexes (PVCs) are a commonly observed phenomenon that are best evaluated with a thorough history and physical examination and 12-lead electrocardiography. This article deals with the P-QRS relationship in PVC, along with the understanding of the interpolated PVC and concealed conduction.

Keywords

PVC: Premature ventricular complex, Retrograde P, Concealed conduction, P-QRS relationship, Compensatory pause, Interpolated PVC.

Introduction

PVCs are often commonly found in the ECG, mostly when the monitoring is done for a longer period. The relationship between the P wave and the QRS complex in the PVC is often varying and confusing. Interpolated PVCs are unique, and understanding theirelectrical pathogenesis is indeed complex.

Premature Ventricular Complex (PVC)-Definition

Ectopic impulses from the ventricles that disrupt the regular cardiac rhythm.

ECG Character of PVC

- Broad QRS complexes (≥120 ms)
- Abnormal QRS morphology
- No preceding P wave
- Discordant T wave
- Usually a compensatory pause (Not in interpolated PVC)

Electrical Basis of PVC

Ectopic firing of a focus within the ventricles bypasses the His-Purkinje system and depolarises the ventricles directly. This disrupts the normal sequence of cardiac activation, leading to asynchronous activation of the two ventricles. The consequent interventricular conduction delay produces QRS complexes with prolonged duration and abnormal morphology.

Retrograde Atrial Capture-P QRS Relationship

- The ectopic impulse generating the PVC is also conducted retrogradely through the AV node, producing the atrial depolarisation from below up.

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- This is visible on the ECG as an inverted P wave (retrograde P wave), usually occurring after the QRS complex. (Fig 1) As this retrograde P resets the sinus node, the next sinus P will come later, leading to the post-PVC compensatory pause.

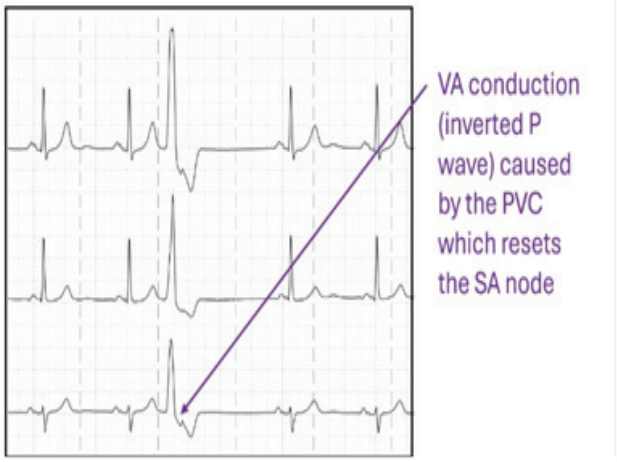

Fig. 1 Retrogradely conducted (VA conduction) P wave .(Retrograde P) noted just after the QRS complex

- Sometimes the retrograde P is timed such that it is buried inside the T wave and can't be found clearly in the ECG. In such a possible scenario, using an ECG ruler or scale to assess the P-P interval and projecting it over the PVC will help to understand the completely buried retrograde P inside the T wave. (Fig 2)

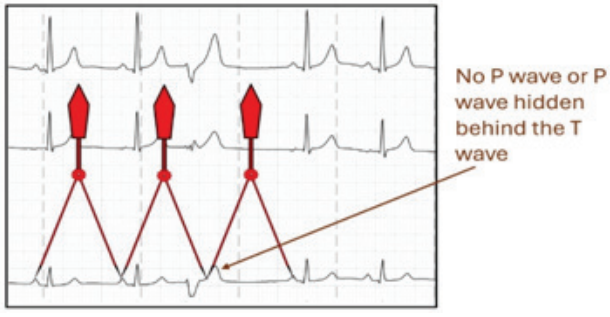

Fig. 2 Retrogradely conducted (VA conduction) P wave buried inside the QRS-T waves that can only be traced out using the ECG ruler/scale.

- Interestingly, it is also possible to have a sinus P wave before a PVC. After the generation of a sinus P wave, normally the wave of depolarisation travels down the AV junction and depolarises the ventricles, generating the QRS complex in the ECG. Rarely, before the current gets conducted through the AV junction, a PVC may be generated inside the ventricular myocardium, in which case there will be a sinus P before that PVC. In this condition, the P-PVC onset (Q or R wave) interval will be less than the normal sinus PR interval. (Fig 3) This is a close differential diagnosis of sinus P conducted aberrantly with underlying bundle branch block where the PR/PQ interval may not always be shorter, or sinus P conducted through an accessory pathway where the PR/PQ interval will be shorter but with a possible positive or negative delta wave, or a premature atrial contraction with aberrant conduction where the P wave will be prematurely occurring with different morphology with respect to the sinus P.

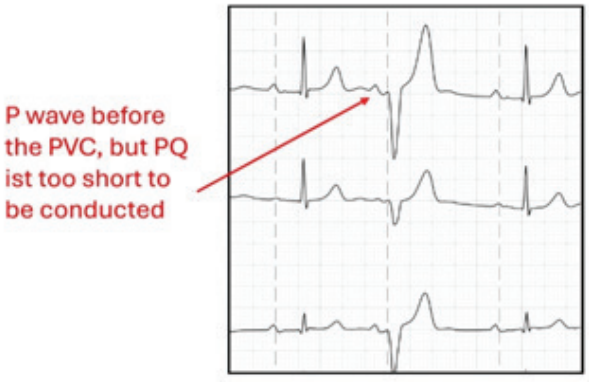

Fig. 3 Sinus P before a PVC. Noteworthy is the narrowed PQ interval of the PVC with respect to the normal sinus PR interval.

- This retrograde capture is absent in the interpolated VPC.

Interpolated PVC

- Definition: Occurs between two consecutive sinus beats without a compensatory pause; the sinus node is not reset.
- Clinical importance: Higher risk of PVC-induced cardiomyopathy; interpolation may increase overall ventricular ectopy burden.

ECG Pattern Of Interpolated PVC

- A normal sinus beat.
- An early, wide, and bizarre PVC that is not preceded by a P wave.
- No compensatory pause following the PVC.
- The next sinus beat (with its P wave) occurs on schedule.

- A prolonged PR interval for the sinus beat immediately following the PVC, due to the phenomenon of concealed conduction. (Fig 4)

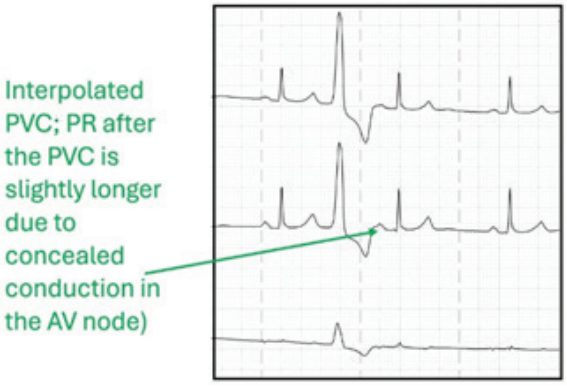

Fig. 4 Interpolated PVC and concealed conduction.

Interpolated PVC – The Electrical Basis

An interpolated PVC occurs due to a unique timing sequence involving the sinus node, the atrioventricular (AV) node, and the ectopic ventricular focus.

1. Ectopic ventricular firing.
2. Lack of retrograde conduction: For the PVC to be interpolated, the ventricular impulse must not travel backwards (retrograde) up the heart's electrical system to the sinoatrial (SA) node and reset its timing. This can happen because:
   - The impulse blocks as it travels retrogradely towards the AV node, meaning it is not conducted to the atria.
   - The ectopic impulse collides with the normal sinus impulse either in the AV node or the ventricles, preventing it from resetting the SA node.
3. Antegrade conduction of the next sinus beat: Because the PVC did not reset the SA node, the next sinus impulse travels down the atria as scheduled.
4. AV nodal recovery and concealed conduction: The timing of the interpolated PVC is critical. The PVC must occur during a window of opportunity where the AV node has had sufficient time to recover from the previous sinus beat but remains slightly refractory when the PVC occurs.
   - Concealed conduction: The retrograde electrical signal from the PVC penetrates the AV node but does not travel all the way through. This "concealed" conduction can make the AV node more refractory.
   - Delayed antegrade conduction: When the next normal sinus impulse arrives at the partially refractory AV node, its conduction is delayed. This causes the PR interval of the beat following the PVC to be longer than the normal PR interval.

Conclusion

A systematic approach is necessary to understand the P wave and the QRS relationship in PVC, with special importance to the interpolated PVCs and concealed conduction.

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QUIZ

Medical Quiz

K K Perumal

Basic Sciences Questions

1. When evaluating a patient with isolated enlarged inguinal lymph nodes, which one of the following areas is the LEAST likely site that warrants thorough examination?

A. Perinium
B. Testes
C. Uterus
D. External Genitalia
E. Feet

2. Abnormal apoptosis is least implicated in the pathogenesis of which one of the following conditions?

A. Systemic lupus erythematosus
B. Alzheimer's disease
C. Ischaemic heart disease
D. Lung Caner
E. Myelodysplastic syndrome

Cardiology Questions

1. Which one of the following statements BEST describes primary pulmonary hypertension?

A. The familial form is inherited as sex-linked recessive
B. Chronic thromboembolic disease can be identified in 30% of primary cases
C. Spontaneous remission is the rule in more than half the cases
D. Cannabis inhalation may induce similar disease
E. The mean pulmonary artery pressure is more than 25 mmHg at rest

2. Paradoxical splitting of the second heart sound is not a feature in which one of the following conditions?

A. Atrial septal defect (ASD)
B. Aortic stenosis
C. Left bundle branch block (LBBB)
D. Type B Wolff-Parkinson-White syndrome (WPW)
E. Patent ductus ateriosus (PDA)

Endocrinology and metabolic disorders Questions

1. Which one of the following statements is incorrect regarding phaeochromocytoma?

A. Bilateral in 10% of cases
B. Malignant in 10% of cases

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C. Extra-adrenal in 10% of cases
D. Extra-adrenal phaeochromocytomas secrete adrenaline
E. Familial cases almost always arise from the adrenal medulla

2. In patients with hypertension, the presence of hypokalaemia should prompt investigations of each of the following disorders EXCEPT?

A. Renal artery stenosis
B. Liddle's syndrome
C. Conn's syndrome
D. Cushing's syndrome
E. Bartter's syndrome

Gastroenterology Questions

1. Which one of the following statements BEST describes a person with irritable bowel syndrome (IBS)?

A. Characterized by nocturnal diarrhoea
B. If there is nausea and vomiting the diagnosis should be reconsidered
C. Weight loss becomes more evident as the disease runs a chronic course
D. Sigmoidoscopy findings are often diagnostic
E. High fiber diet is often prescribed for the treatment of the syndrome

2. Which one of the following pathological changes favors ulcerative colitis over Crohn's disease?

A. Ileal involvement
B. Crypt abscesses
C. Transmural involvement
D. Cranulomas
E. Skip lesions

Clinic Pharmacology and Toxicology Questions

1. Which one of the following features is MOST characteristic of lead poisoning?

A. Predominately sensory peripheral neuropathy
B. Posterior uveitis
C. Punctuate basophilic stippling on peripheral blood film examination
D. Membranous glomerulonephritis as the primary kidney lesion
E. A gingival blue line in children

2. A 31-year old pregnant woman, was found by her husband in the garage cyanosed and agitated. Apparently she left the car engine running while she was clearing the garage before driving to her maternity hospital appointment.

She smokes heavily but has no previous medical problems.

She was rushed to the accident and emergency department. On arrival it was thought that she had carbon monoxide (CO) poisoning. Which one of the following statements is not true?

A. The baseline CO may exceed 15% in smokers as compared with 1-3% non smokers
B. The affinity of haemoglobin for CO is 200-250 times as great as its affinity for oxygen
C. The final CO level in the fetus may significantly exceed the levels in the mother
D. Venous blood samples are adequate for measurements of CO in the blood
E. CT scan of the brain identifies hypedense periventricular lesions characteristic of CO poisoning

CASE REPORT

True Endometrial Vascular Dystrophy in a Patient undergoing IVF Treatment

***Monika Kumari*[1], *Sudip Basu*[2]**
***Ranajay Ghosh*[3]**

Introduction

Endometrial vascular dystrophy is an extremely rare hysteroscopic finding and is scarcely described in the medical literature. Hamou (1) first characterized it as the presence of abnormally dilated, tortuous, and often thrombosed blood vessels within the endometrial cavity, typically observed during the secretory phase or in women receiving progestogens. Most reported cases suggest this entity represents a benign or exaggerated variant of secretory endometrium rather than a true vascular pathology. We report a rare case of true endometrial vascular dystrophy diagnosed hysteroscopically and confirmed histopathologically in a patient undergoing in vitro fertilization (IVF).

Case Description

A 34-year-old woman underwent IVF treatment and conceived a viable twin pregnancy, which unfortunately ended in spontaneous miscarriage at six weeks of gestation. The miscarriage was complicated by profuse vaginal bleeding, requiring emergency suction evacuation and transfusion of three units of blood. After a few months, frozen embryo transfer using the remaining embryos was attempted but failed to achieve pregnancy.

Prior to planning another IVF cycle, diagnostic hysteroscopy was performed to evaluate the uterine cavity. Saline vaginoscopy followed by saline hysteroscopy was performed on day 18 of the menstrual cycle using a 2.9-mm, 30° hysteroscope under a no-touch technique. The procedure was carried out under intravenous sedation after obtaining informed consent. No cervical priming with misoprostol was used.

Hysteroscopic evaluation revealed an unusual and striking vascular pattern within the endometrial cavity. A complex meshwork of multiple dilated, markedly tortuous, and thrombosed blood vessels was observed involving the fundus and both lateral walls of the uterine cavity. The vessels appeared serpiginous and prominently engorged, projecting into the cavity. Notably, there was no blanching of these vessels even on increasing the intrauterine distension pressure, suggesting true vascular involvement rather than superficial endometrial

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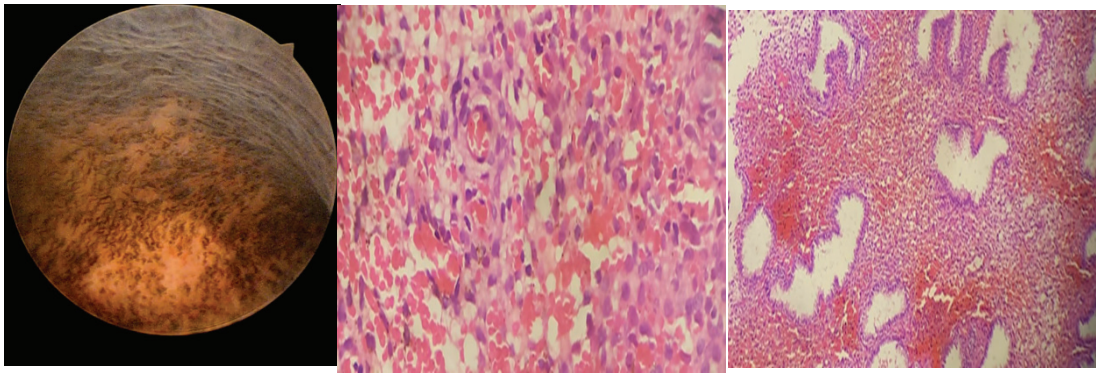

Fig. 1 (a) (b) (c)

congestion. The remaining endometrial surface appeared otherwise unremarkable. (fig-a).

Endometrial biopsy was obtained for histopathological evaluation. In view of the unusual hysteroscopic vascular findings, the senior pathologist was informed in advance about the macroscopic appearance observed during hysteroscopy, particularly in the context of failed IVF treatment, to facilitate focused histopathological assessment.

Endometrial biopsy (fig-b,c) showed secretory endometrium with numerous congested thick- and thin-walled blood vessels and scattered stromal hemorrhagic areas, confirming endometrial vascular dystrophy. The differential diagnoses considered for the abnormal hysteroscopic vascular appearance included:

1. **Abnormal endometrial angiogenesis, particularly in the secretory phase**
2. **Endometrial arteriovenous malformation (AVM)**
3. **Chronic endometritis with associated vascular proliferation**

The patient was recalled for follow-up to assess any clinical correlation with the histopathological findings. She denied any history of menorrhagia or abnormal uterine bleeding. Color Doppler ultrasonography of the endometrium was performed to evaluate for the presence of arteriovenous malformations; however, no abnormal vascular flow was detected. An extensive review of the available literature was undertaken, and opinions were sought from experienced gynecologist endoscopic surgeons across India. Based on the collective clinical, hysteroscopic, and histopathological findings, a provisional diagnosis of endometrial vascular dystrophy was made. The patient was commenced on cyclical estrogen–progesterone therapy for a duration of three months, following which repeat hysteroscopic evaluation was planned. Repeat hysteroscopy demonstrated complete resolution (fig-d) of the vascular abnormalities, and the patient was reassured and prepared for a subsequent IVF cycle.

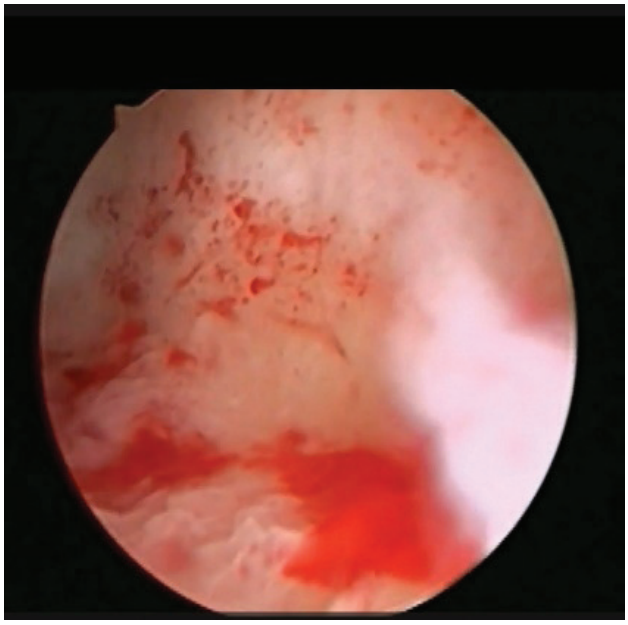

Fig. 1 (d)

Discussion

Similar hysteroscopic appearances have been reported previously in the literature (1-3), with approximately 12 documented cases of so-called endometrial vascular dystrophy. These reports describe the condition as benign, with spontaneous resolution or resolution following a few cycles of cyclical estrogen and progesterone therapy.

In most previously reported cases, histopathological examination revealed secretory

endometrium. The structures that appeared hysteroscopically as curved or dilated blood vessels were subsequently identified as secretory-phase endometrial glands, occasionally containing red blood cells within the glandular lumina. True vascular involvement was not demonstrated in these cases. In contrast, although the hysteroscopic appearance in our patient was macroscopically similar to those described in the literature, histopathological evaluation clearly demonstrated genuine vascular pathology, with involvement of both thin- and thick-walled congested blood vessels and associated hemorrhagic areas. This distinct histological finding has not been previously documented, thereby questioning the appropriateness of the term "endometrial vascular dystrophy," which may represent a misnomer in most reported cases.

Notably, to our knowledge, this is the first reported case of such a condition identified in an infertile patient with a history of failed IVF treatment. Previously reported cases were largely associated with endometrial polyps, isthmocele, menorrhagia, or prior progesterone exposure rather than infertility or assisted reproductive failure. This observation raises an important question regarding the potential impact of true endometrial vascular pathology on endometrial receptivity and implantation. While the condition appears clinically benign and reversible, its possible long-term molecular and functional implications on endometrial receptivity and IVF outcomes remain unclear. Further research is warranted to better understand this rare entity and its relevance in reproductive medicine.

Conclusion

True vascular involvement of the endometrium is exceptionally rare. While traditionally described endometrial vascular dystrophy is considered a misnomer and a variant of secretory endometrium, our case demonstrates genuine vascular pathology confirmed histologically. Whether this condition contributed directly to the miscarriage remains uncertain, warranting further study.

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CASE REPORT

Chronic Liver Disease in Systemic Lupus Erythematosus: A Diagnostic Dilemma

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***Soumodip Saha*[3]**

Abstract

Abstract: Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease that may occasionally present with unusual organ involvement, making diagnosis difficult. Liver dysfunction in SLE is usually attributed to infection, drug-induced injury, or autoimmune overlap, while chronic liver disease (CLD) as a primary manifestation remains uncommon.

We describe a young female who presented with features of decompensated CLD, including jaundice, oedema, ascites, and altered sensorium. Initial investigations revealed cytopenia, coagulopathy, and raised liver enzymes, but viral and autoimmune hepatitis panels were negative. Further evaluation demonstrated strong serological evidence of SLE, including positive ANA, anti-dsDNA, and anti-Smith antibodies with low complement levels, thereby establishing the diagnosis. Supportive management led to stabilization, and the patient was subsequently planned for immunosuppressive therapy.

This case draws attention to the rare but significant presentation of CLD in SLE. It underscores the importance of considering autoimmune aetiologies in young females with unexplained hepatic dysfunction and highlights the role of timely immunological workup in guiding management.

Keywords:
SLE – Chronic Liver Disease – Diagnostic – Dilemma

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the production of autoantibodies and immune complex deposition, leading to widespread organ involvement. The liver is not classically considered a primary target organ in SLE; however, hepatic abnormalities are increasingly recognized. Reported hepatic manifestations range from mild, asymptomatic biochemical alterations to severe forms such as autoimmune hepatitis, hepatic steatosis, drug-induced liver injury, and chronic liver disease (CLD).

Chronic liver disease in the setting of SLE poses a unique diagnostic challenge, as it may be attributed to multiple aetiologies, including viral infections, overlapping autoimmune disorders, or drug toxicity. In rare instances, CLD may precede or obscure the diagnosis of SLE, leading to diagnostic dilemmas. Hepatic encephalopathy, a serious complication of advanced CLD, can further complicate clinical presentation by producing neuropsychiatric symptoms such as confusion, irritability, or coma.

Early recognition of CLD in SLE is crucial, as timely diagnosis and management can significantly alter disease outcomes and reduce morbidity.

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Here, we present a case of a young female who initially presented with features of decompensated chronic liver disease, later diagnosed as systemic lupus erythematosus. This case highlights the importance of considering SLE in the differential diagnosis of unexplained chronic liver disease, especially in young females.

Case Report

A 22-year-old female presented to the Emergency Department with altered sensorium and irritability for three days. She reported gradual swelling of face and both lower limbs for 7 days associated with one to two episodes of black stool in past7 days. She also complained of gradual swelling of the abdomen since last 21 days. She a reported generalized fatigue, intermittent fever, yellowish discoloration of eyes and urine for last 5months.

She was treated primarily with traditional methods during first 3 month. Her first admission was in a local hospital during a flare two and half months ago and treated conservatively. Her symptoms improved gradually except the presence of abdominal fullness, bloating, nausea, occasional pain abdomen and low-grade jaundice during this time. From then she was on regular check up to a local physician.

She denied any history of rash, anemia, easy bruising, joint pain, alopecia, oral ulcer, miscarriage or prior blood transfusion. She had no prior surgeries except an uneventful single child birth at term two and half year ago. She had no known allergies and no significant other past medical illness. She denied using alcohol, tobacco, or any other illicit substances. No significant family history was present.

On examination, patient was conscious, disoriented, irritable, anemic, icteric and bilateral pedal edema was present. Her vitals were blood pressure 98/60 mmHg, pulse 102 beats/min, respiratory rate 20/min, temperature 98.8°F and capillary blood glucose was 110mg/dl. Chest auscultation revealed bilateral decreased vesicular breath sound Her abdomen was distended but non-tender. Other systemic examination was unremarkable.

Laboratory evaluation revealed anemia (Hemoglobin 6.7gm/dl), total leucocyte count 13500/cmm, thrombocytopenia (68000/cmm), elevated reticulocyte count (3.86%), increased lactate dehydrogenase (695U/L), hypoproteinemia (total protein 5.1 gm/dl, albumin 1.9gm/dl), hyperbilirubinemia (total bilirubin 5mg/dl), and elevated transaminases (serum glutamate pyruvic transaminase (SGPT) 440U/L,serum glutamic oxaloacetic transaminase (SGOT) 1090U/L). Coagulopathy (prothrombin time 32.2 seconds, activated partial thromboplastin time 76.2 seconds, international normalized ratio 2.19) was noted. Serum ceruloplasmin was reduced, and 24-hour urinary copper was mildly increased (95.57μg/day), though Kayser–Fleischer rings were absent. Direct Coombs test was negative. Ascitic fluid analysis showed cell count 2-5cells (polymorphonuclear 10%, mononuclear 90%), albumin o.2gm/dl, adenosine deaminase (ADA) 2.3U/L, serum-ascites albumin gradient (SAAG) >1.1, while serum ammonia was elevated (82.9μmol/L). Viral and autoimmune hepatitis panels were negative.

Immunological workup showed strongly positive antinuclear antibody (ANA, 1:160, 4+ homogenous), positive anti-dsDNA, anti-Sm, and anti-RNP antibodies, along with low complement levels (C3, C4). Lupus anticoagulant was moderately present (1.63), but antiphospholipid antibody profile was negative. Thrombotic profile for protein C, protein S, anti-thrombin III and factor V was negative.

Imaging studies included abdominal ultrasound and contrast-enhanced CT, which demonstrated features of chronic liver disease with coarse echotexture, irregular margins, splenomegaly, gross ascites, and engorged spleno-portal vein. Upper GI endoscopy and MRI brain were unremarkable.

She was managed with intravenous fluids, diuretics, high-grade antibiotics, lactulose, albumin infusion, and blood transfusions. After stabilization, she was planned for initiation of corticosteroid therapy and discharged in stable condition with follow-up in the Rheumatology clinic.

Discussion

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder characterized by the production of a variety of autoantibodies and immune complex deposition, leading to

multisystem involvement. While the liver is not classically considered a primary target organ in SLE, hepatic manifestations are increasingly being recognized in clinical practice. Reported prevalence of liver involvement in SLE varies widely, from 9% to 60%, depending on the study population and diagnostic criteria used [1].

Liver dysfunction in patients with SLE may arise from diverse causes, including lupus hepatitis, autoimmune overlap syndromes, drug-induced hepatotoxicity, infections, and, rarely, chronic liver disease (CLD) [2]. Distinguishing between these entities is challenging, as clinical and biochemical profiles often overlap. Histological examination remains the gold standard for differentiation but is not always feasible, especially in patients with coagulopathy or decompensated liver disease, as seen in our case.

In the present case, the patient presented with decompensated CLD and hepatic encephalopathy as initial manifestations. Common causes of liver dysfunction, such as viral hepatitis and autoimmune hepatitis, were excluded through serological testing. The strong positivity for ANA, anti-dsDNA, and anti-Smith antibodies, along with low complement levels, fulfilled the EULAR/ACR classification criteria for SLE, suggesting that the chronic liver dysfunction was likely lupus-related rather than coincidental. Similar findings have been reported, where SLE-associated hepatitis or CLD occurred as a primary presentation of lupus in the absence of other etiologies [3].

Liver biopsy could have provided histological confirmation of lupus hepatitis, nodular regenerative hyperplasia, or other autoimmune features. However, it was contraindicated due to coagulopathy. Wilson's disease was also considered because of low ceruloplasmin and mild copper elevation, but the absence of Kayser–Fleischer rings and strong lupus serology made this less likely. Runyon et al. emphasized that hepatic abnormalities in lupus can mimic other conditions, underscoring the importance of detailed immunological assessment to establish the diagnosis [1].

The management of hepatic involvement in SLE requires an integrated approach, addressing both the hepatic and systemic autoimmune components. Corticosteroids and immunosuppressive agents are the mainstay of therapy once infectious and drug-induced causes are excluded [4]. Efe et al. reported that timely initiation of immunosuppressive therapy in lupus-associated autoimmune hepatitis or overlap syndromes significantly improves hepatic outcomes [5]. In our patient, supportive management with diuretics, albumin, and antibiotics stabilized hepatic function, and corticosteroid therapy was planned to control lupus activity.

Early recognition of lupus-related liver involvement is crucial, as hepatic dysfunction in SLE has been associated with increased morbidity and mortality [3]. Therefore, in young females presenting with unexplained CLD, SLE should be considered after excluding other common causes. This case highlights the diagnostic challenge and the importance of a comprehensive immunological work-up for appropriate management.

Conclusion: Chronic liver disease is an uncommon but important presentation of systemic lupus erythematosus. In young females with unexplained hepatic dysfunction, SLE should be considered after excluding common etiologies. Early recognition and appropriate management are vital for favorable outcomes. This case highlights the diagnostic challenge and the importance of comprehensive immunological evaluation.

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CASE REPORT

Auto inflammatory Disease with Systemic Lupus Erythematosus Presenting as Fever of Unknown Origin: A Diagnostic Challenge

Avilash K. Tiwari

Abstract

Fever of unknown origin (FUO) remains a challenging clinical entity, often requiring extensive evaluation to identify underlying infectious, inflammatory, autoimmune, or malignant causes. We report a case of a middle-aged woman who presented with prolonged fever, systemic symptoms, and cytopenias, in whom extensive infectious and malignant work-up was negative. Subsequent immunological evaluation revealed features suggestive of an autoinflammatory disorder with evolving systemic lupus erythematosus (SLE). This case highlights the importance of considering autoimmune and autoinflammatory overlap syndromes in FUO and emphasizes the role of longitudinal reassessment and clinical judgment.

Keywords:

Fever of unknown origin; Autoinflammatory disease; Systemic lupus erythematosus; PUO; Autoimmune overlap

Introduction

Fever of unknown origin is traditionally defined as a documented fever exceeding 38.3°C on several occasions lasting for more than three weeks, with no diagnosis despite appropriate evaluation. Autoimmune and inflammatory conditions account for a significant proportion of FUO cases, particularly in regions where infectious causes have been reasonably excluded. Systemic lupus erythematosus can rarely present initially as isolated FUO, posing a diagnostic challenge. We describe such a case with overlapping autoinflammatory features.

Case Presentation

A A middle-aged female patient presented with a history of high-grade intermittent fever lasting several weeks, accompanied by malaise, myalgia, and arthralgia. There were no localised symptoms indicative of a focal infection. Three months prior, she underwent a total knee replacement at a hospital. Since then, she has experienced persistent fever. She has been evaluated by multiple physicians, with investigations including HIV, tuberculosis, and other common infections such as typhoid, malaria, brucella and dengue. Blood cultures, X-rays, and sonography were performed, and empirical

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antibiotic therapy was administered without any improvement. Radiological examination of the knee replacement site was inconclusive. Upon admission, it was noted that she developed white spread stomatitis, impairing her ability to eat. She also reported a 18 week history of Generalised joint pain . Her chikungunya antibody tests returned negative. She complained of severe fatigue . Many years ago she had alopecia areata that recovered spontaneously.Review of her blood investigations revealed persistent leukopenia. She is currently taking levothyroxine for hypothyroidism, which is well-controlled.She has no significant past medical history and no recent travel or exposure history.she denied on any other treatment

Clinical Examination

On examination, the patient was febrile and appeared unwell. Vital signs were stable apart from fever. Systemic examination did not reveal lymphadenopathy, organomegaly, rash, or focal neurological deficits. No skin rash

Investigations and Diagnostic Work-up

Initial laboratory investigations revealed anemia and leukopenia with elevated inflammatory markers. Blood and urine cultures were repeatedly sterile. Extensive infectious work-up including viral serologies and molecular assays was negative. Imaging studies including ultrasonography and cross-sectional imaging did not reveal any occult source of infection or malignancy.

Autoimmune evaluation demonstrated positive antinuclear antibodies, positive sm antibody with low level of c3 .with immunological markers supportive of systemic lupus erythematosus. Serum ferritin levels were markedly elevated, raising suspicion of an autoinflammatory process. IGRA was negative, histone ab was negative,

Differential Diagnosis

Differential diagnoses considered included occult infection, hematological malignancy, adult-onset Still's disease, and connective tissue disease. Sequential investigations and clinical evolution favored an autoimmune etiology.

Final Diagnosis

A final diagnosis of autoinflammatory disease with systemic lupus erythematosus presenting as fever of unknown origin was made.

Management and Outcome

The patient was initiated on immunomodulatory therapy (prednisolone 40 mg, weekly methotrexate 10 mg, hydroxy chloroquine)tailored to disease severity. Following treatment, there was prompt resolution of fever and improvement in laboratory parameters. The patient remains under regular follow-up with sustained clinical improvement.

Discussion

This case underscores the diagnostic complexity of FUO and the importance of considering autoimmune and autoinflammatory overlap syndromes. SLE may initially manifest with nonspecific systemic features before classical organ involvement becomes evident. Elevated ferritin and cytopenias should prompt consideration of inflammatory disorders once infection and malignancy have been excluded.

Learning Points

- FUO requires systematic and repeated reassessment.
- Autoimmune diseases, including SLE, can present initially as isolated fever.
- Elevated ferritin may indicate an autoinflammatory process.
- Longitudinal follow-up is crucial in diagnostically challenging cases.

Patient Consent and Ethics

Informed consent was obtained from the patient for publication of this case report. Ethical principles were adhered to throughout.

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QUIZ

Medical Quiz (Answers)

K K Perumal

Basic Sciences Answers

1. Testes

The superficial inguinal lymph nodes drain the tissues of the following structures
Lower limb
Lower abdominal wall
External genitalia
Perineum
Lower part of the anal canal
Uterus by means of lymphatics that follow the round ligament
The testes lymphatic are drained to the abdominal and para-aortic lymph nodes.

2. Ischaemic heart disease

Apoptosis is defined as 'programmed cell death' which occurs in isolated cells with no inflammatory reaction as opposed to necrosis.
In ischaemic heart disease the pathogenesis involves cell death due to necrosis and is associated with local inflammatory reaction

Cardiology Answers

1. The mean pulmonary artery pressure is more than 25 mmHg at rest

One of the diagnostic criteria includes a mean pulmonary artery pressure of more than 25 mmHg at rest or more than 30 mmHg with exercise. Recent improvement in diagnosis and newer forms of treatment have improved the survival and most patients gradually succumb to progressive right-sided heart failure.

2. Atrial Septal defect (ASD)

Endocrinology and metabolic disorders Answers

1. Extra-adrenal phaeochromocytomas secrete adrenaline
2. Bartter's syndrome Hypertension in association with hypokalaemia is encountered in the following conditions:
   Renovascular disease
   Renin secreting tumors
   Mineralocorticoid and glucocorticoid excess, Cushing's syndrome
   Hypertension is not a feature of Bartter's syndrome.

Gastroenterology Answers

1. High fiber diet is often prescribed for the treatment of the syndrome and high fiber diet is frequently used to improve intestinal motility.

2. **Crypt Abscesses**

   Crohn's disease may involve any segment in the alimentary canal. The distal ileum involvement is characteristic.
   The inflammation is confined to the mucosa and lamina propria with crypt abscesses formation.
   In ulcerative colitis there is diffuse, continuous involvement of the colon with proctitis as an early feature in 90% of cases.

Clinic Pharmacology and Toxicology Answers

1. Punctuate basophilic stippling on peripheral blood film examination.
   Lead interferes with the variety of red cell enzymes leading to red cell abnormalities which include punctate basophilic stippling and clover leaf morphology. The peripheral neuropathy, which is seen in adult patients, is almost always exclusively motor. Interstitial nephritis is the characteristic lesion in the kidneys. A gingival blue-black or grey line is found in up to 20% of adult patients but is infrequent in children.

2. CT scan of the brain identifies hypo dense periventricular lesions characteristic of CO poisoning.
   CO poisoning in pregnancy has an especially deleterious effect on the fetus because of the greater sensitivity of the fetus to the harmful effect of the gas.

NOTES

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